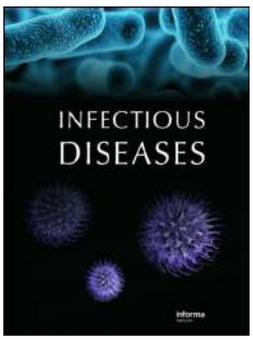

Infectious Diseases

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/infd20

Exosomes: from biology to immunotherapy in infectious diseases

Velia Verónica Rangel-Ramírez, Hilda Minerva González-Sánchez & César Lucio-García

To cite this article: Velia Verónica Rangel-Ramírez, Hilda Minerva González-Sánchez & César Lucio-García (2022): Exosomes: from biology to immunotherapy in infectious diseases, Infectious Diseases, DOI: 10.1080/23744235.2022.2149852

To link to this article: https://doi.org/10.1080/23744235.2022.2149852

Published online: 23 Dec 2022.

Taylor & Francis
Taylor & Francis Group

INFECTIOUS DISEASES,
2023; VOL. 00,
NO. 0, 1–29

https://doi.org/10.1080/23744235.2022.2149852

REVIEW ARTICLE

Exosomes: from biology to immunotherapy in infectious diseases

Velia Verónica Rangel-Ramírez[a*], Hilda Minerva González-Sánchez[b*] and César Lucio-García[c]

[a]Centro de Biociencias, Universidad Autónoma de San Luis Potosí, San Luis Potosí, México; [b]CONACYT-Centro de Investigación sobre Enfermedades Infecciosas, Instituto Nacional de Salud Pública, Cuernavaca, México; [c]Centro de Investigación sobre Enfermedades Infecciosas, Instituto Nacional de Salud Pública, Cuernavaca, México

ABSTRACT

Exosomes are extracellular vesicles derived from the endosomal compartment, which are released by all kinds of eukaryotic and prokaryotic organisms. These vesicles contain a variety of biomolecules that differ both in quantity and type depending on the origin and cellular state. Exosomes are internalized by recipient cells, delivering their content and thus contributing to cell–cell communication in health and disease. During infections exosomes may exert a dual role, on one hand, they can transmit pathogen-related molecules mediating further infection and damage, and on the other hand, they can protect the host by activating the immune response and reducing pathogen spread. Selective packaging of pathogenic components may mediate these effects. Recently, quantitative analysis of samples by omics technologies has allowed a deep characterization of the proteins, lipids, RNA, and metabolite cargoes of exosomes. Knowledge about the content of these vesicles may facilitate their therapeutic application. Furthermore, as exosomes have been detected in almost all biological fluids, pathogenic or host-derived components can be identified in liquid biopsies, making them suitable for diagnosis and prognosis. This review attempts to organize the recent findings on exosome composition and function during viral, bacterial, fungal, and protozoan infections, and their contribution to host defense or to pathogen spread. Moreover, we summarize the current perspectives and future directions regarding the potential application of exosomes for prophylactic and therapeutic purposes.

KEYWORDS
Exosomes
microvesicles
human pathogens
exosomes cargo
vaccines
biomarkers

ARTICLE HISTORY
Received 26 August 2022
Revised 12 November 2022
Accepted 15 November 2022

CONTACT
Hilda Minerva González-Sánchez
hilda.gonzalez@insp.mx
Instituto Nacional de Salud Pública, Av. Universidad 655., Col. Santa María Ahuacatitlán C.P. 62100, Cuernavaca, Morelos, México

*These authors contributed equally to this work.

Introduction

Cells from all living systems can release bioactive vesicles into biological fluids that allow intercellular communication [1,2]. Among these extracellular vesicles, exosomes have been the subject of increasing interest in the past few years [3]. Exosomes are endosome-derived vesicles of 30–100 nm which were first discovered in reticulocytes [4–6]. For a long time, their secretion was thought to be a mechanism to dispose cellular waste [6,7], however, now the increasing research in the exosomes field has shown that they can transfer a wide variety of biomolecules allowing cell-to-cell communications [8]. Moreover, exosomes can be secreted by a wide variety of mammalian cells including lymphocytes, dendritic cells (DC), stem cells, astrocytes, epithelial cells and hepatocytes [9–11], and can act either locally or by distant signaling being released in body fluids [10,12,13]. In humans, they have been implicated in normal conditions such as neuronal function, lactation, and immune response, and during diseases like cancer, neurodegenerative diseases, infections, liver disease, etc. [7,9,11,13–16].

As the process of exosome secretion seems to be evolutionary conserved among different eukaryotes and prokaryotes organisms [1,10,17], during an infection host- and pathogen-derived exosomes are released into the extracellular milieu [18]. The content of these vesicles will transmit messages that can either limit or disseminate the infection [19]. Recently, the exosome-dependent pathways of infection of important human pathogens such as the human immunodeficiency virus (HIV) [11,20], Ebola virus [21] and *Mycobacterium tuberculosis* [22], among others have been characterized. This reflects the importance of the exosome study in microbial pathogenesis. Moreover, the specific composition of these vesicles derived from pathogens or infected cells can be a hallmark of the infection and used as a potential biomarker [23,24]. Furthermore, the hijacking of exosomes by some pathogens has shown the carrying capacity of these vesicles, which can be harnessed for vaccine development [25–29]. This review attempts to summarize the current findings on exosome composition and function during viral, bacterial, fungal and protozoan infections, their contribution to host defense or to pathogen spread, and provide an insight into the potential application of exosomes in biomedical research.

Exosomes structure and composition

All extracellular vesicles are limited by a lipid bilayer which wraps a particular cargo of molecules [30]. Among these vesicles, canonical exosomes are identified by a size of 30–100 nm, a density of 1.13–1.19 g/mL in sucrose gradients, and sedimentation at 100,000 g [31,32]. Due to their small size, exosome morphology is analyzed by transmission electron microscopy where they are usually described as cup-shaped vesicles, however, the more sophisticated technique of cryo-electron microscopy has revealed its rounded shape indicating that the cup-shape may be an artifact generated during sample processing [10,33]. Exosomes are also distinguishable from other secreted vesicles because of their intracellular origin (endosome membranes versus plasma membrane) and lipid composition [34].

Exosome composition may include all kinds of biomolecules (proteins, lipids, carbohydrates and nucleic acids) and differs both in quantity and type of molecules depending on the origin and cellular state [16,18]. Some components of the exosomes are constitutive since they are required for their biogenesis and trafficking, while others reflect the cell of origin [2,5]. Among the components that are typically found in mammalian exosomes are cytoskeletal proteins including actin, tubulin and myosin; tetraspanins including CD9, CD63, CD81 and CD82; adhesion proteins (integrins) as well as proteins related to the multi-vesicular body biogenesis as clathrin, Alix and ubiquitin; membrane trafficking proteins (e.g. Rabs and annexins); metabolic enzymes, heat shock proteins and antigen presentation molecules [2,35–37]. Some of these proteins are currently used as conventional exosome markers [38–40].

The mammalian exosomal lipid membrane has been described as enriched in sphingomyelin, saturated fatty acids, phosphatidylserine, and cholesterol compared with the composition of the plasma membrane [5,36,37]. Lysophosphatidic acid which is key for exosome biogenesis [39], the ganglioside GM3, ceramide and lipid raft microdomains containing glycosphingolipids, cholesterol, and some proteins have also been reported in the exosomal membrane [5,37]. Exosomes also contain a specific signature of nucleic acids including a variety of mRNAs, fragments of tRNAs, microRNAs, Y-RNAs, small nuclear RNA, small nucleolar RNAs, piwi-interacting RNAs, vault-RNAs and long non-coding RNAs [35]. In addition, the presence of oncogenes and transposable elements of DNA has been reported [41,42], whereas the presence of ribosomal RNA and mitochondrial DNA in the exosomes has been associated with cell death during the sample preparation [37,43,44]. Although many reports on exosomal proteomics and nucleic acid contents have been issued, very little is known about the composition of carbohydrates in exosomes. N-glycans including paucimannosidic,

high-mannose and complex type glycans have been identified in exosomes from human urine samples [45–47].

During infection, exosomes undergo alterations in number, content and membrane structure [48], below we describe some of these changes associated with pathogen infections. Additionally, the specific contents of exosomes and other extracellular vesicles in different settings are available in databases such as Exocarta (http://www.exocarta.org/), Vesiclepedia (http://microvesicles.org/), and EVpedia (http://evpedia.info) [49–51].

Biogenesis of exosomes

Multiple stimuli, such as cell differentiation, activation, hypoxia and infections are responsible for inducing cell vesiculation [35]. In this process, cytosolic components and membrane-associated molecules are enclosed within endosomes, whose main fate is to degrade their content by fusing with lysosomes [48]. However, the components bearing some specific hallmarks of late endosomes such as the major histocompatibility complex class II (MHC-II) or the tetraspanin CD63 can release their content to the extracellular space [40]. Mammalian exosome biogenesis begins in the late endosomes with the formation of small vesicles called intraluminal vesicles which are generated by the inward budding of the late endosomal membrane [35,52]. These vesicles accumulate within large multivesicular bodies, which can then fuse with lysosomes or with the plasma membrane to release the content in form of exosomes [37]. Although the process of exosome generation has not been completely elucidated and is presumably to be cell-specific, two kinds of mechanisms for exosome biogenesis have been proposed [53,54]. The mechanism that requires the recruitment of the Endosomal Sorting Complex Required for Transport (ESCRT), composed of four separated complexes (0-III) plus associated proteins, has been extensively described [55–57]. ESCRT-0 through II recognize ubiquitinated proteins for cargo sorting, whereas ESCRT-I and II plus additional factors induce endosomal membrane budding. Subsequently, ESCRT-III binding to ESCRT-I results in cargo deubiquitination and vesicle scission [58].

Alternative ESCRT-independent mechanisms for exosome biogenesis have also been identified. These pathways involve raft-based microdomains of lipids, tetraspanins or heat-shock proteins [40]. Endosomal membranes are enriched in sphingolipids and sphingomyelinases, which convert sphingolipids to ceramide [59]. It is thought that the cone-shaped ceramide induces endosomal membrane budding [52]. Another ESCRT-independent manner of exosome biogenesis through tetraspanin-enriched microdomains has been suggested to be specific for sorting certain receptors and signaling proteins into exosomes [60]. Apparently, different specialized mechanisms for exosome biogenesis may occur depending on the cellular origin [52].

Characterization and analysis of exosomes

Exosomes are identified by their physical characteristics (e.g. size, density, sedimentation, morphology) and the presence of exosome marker proteins (e.g. CD63, CD9, Alix, HSP70, etc.) [35,40,48]. Several techniques and protocols have been described for the isolation and characterization of exosomes obtained from different sources [31,33,45,61,62]. Ultracentrifugation is the golden standard method for exosome isolation, they can be obtained with high purity from cell culture media using this method, however, it is not convenient when working with more complex matrices like body fluids [52]. For such applications, size exclusion methods are more recommendable since chromatography can better preserve the integrity of exosomes present in physiological samples [52]. Immune affinity capture using magnetic beads can also isolate exosomes with high specificity but with low yields [63]. Newly developed techniques including commercial kits, microfluidic technologies, field flow fractionation and contact-free sorting can enable high-throughput analysis with high sensitivity [52,64].

Characterization of exosomes is usually performed by transmission electron microscopy, dynamic light scattering and nanoparticle tracking analysis. Nevertheless, other methods including flow cytometry, surface plasmon resonance, tunable resistive pulse sensing and single extravesicular analysis are also available (Details: [64, 65]). Finally, for a more comprehensive characterization of exosome content, mass spectrometry is the conventional technique used for the analysis of proteins, carbohydrates and lipidic cargo of exosomes, while PCR is used to study nucleic acids [52,61,64,66–68]. In Table 1 we summarized the methods currently available for the purification and characterization of exosomes.

Although, the exosomes field is relatively new, efforts to homogenize the nomenclature, size, morphology and isolation, have been made since 2013 [69,70]. For instance, the International Society of Extracellular Vesicles has urged researchers to describe the methods employed for extracellular vesicles isolation, in order to allow others to replicate and interpret their findings. As a result of international consensus, the 'Minimal information for

Table 1. Exosome purification and characterization methods. Abbreviations: HPLC, high performance liquid chromatograpy; HSP70, heat shock protein 70; LSRP, localized surface resonance plasmon; PCR, polymerase chain reaction; TSG101, Tumor susceptibility gene 101 [52,61,64,66–68].

Isolation	Characterization	Cargo analysis
*Ultracentrifugation, density-gradient ultracentrifugation *Size exclusion (filtration, chromatography) *Immune affinity capture (beads, ELISA, flow cytometry, ExoCap kit) *Co-precipitation or polymer-based (ExoQuick) *Microfluidic technologies *Field flow fractionation *Contact-free sorting	*Microscopy-based methods (Scanning electron microscopy, transmission electron microscopy, cryo-electron microscopy, atomic force microscopy) *Dynamic light scattering *Nanoparticle tracking analysis *Tunable resistive pulse sensing *Single extravesicular analysis method *Surface plasmon resonance *Flow cytometry (typical markers: CD63, Alix, TSG101, HSP70, CD9)	*Proteins: Western blot and ELISA Mass Spectrometry Small Particle Flow Cytometry Micronuclear Magnetic Resonace Surface Plasmon Resonance Integrated magnetic-electrochemical exosome sensor ExoScreen *Nucleic Acids: Conventional PCR Droplet PCR Microfluidics for On-Chip extraction and detection Ion-exchange nanodetector LSRP-based assay *Lipids: Mass spectrometry Ultra-high HPLC Cholesterol content analysis *Carbohydrates: Glycomic microarrays Mass spectrometry HPLC Nuclear magnetic resonance

studies of extracellular vesicles' was first published in 2014 [70] and updated in 2018 [71]. Recently, reports indicate that these guidelines have being widely accepted by the scientific community specialized in the field [72], demonstrating a promising future.

Exosomes released from infected cells

Exosomes have emerged as key players in the intercellular transport of substances, information and communication between eukaryotic cells to maintain the body homeostasis of living organisms to different cell stimuli [2]. Once released, exosomes usually bind to target cells and exert their functional effects, whether in the local environment or at distant sites [73]. Furthermore, these vesicles can cross natural host barriers and have specific cell targeting effects as well as stability in circulation due to their contents [74]. These characteristics are advantageous since exosome analysis can be used as a sensitive and non-invasive method for detection in real-time and at different stages of the disease [75–78]. However, these exosome properties can also be deleterious. As is well-known, viruses can adopt many mechanisms to evade immune system recognition to survive [79] and exosomes may play an important role in this process. Exosomes released from infected cells can regulate the immune response and therefore contribute to the spread of infection [35]. Thereby, these vesicles may allow the escape of cells in any stage of infection and hide them from the immune system [80–83]. Many pathogens utilize the exosome pathway to efficiently transfer virulence factors and host components from infected cells to naïve cells [84–88]. Besides, enclosure in these vesicles seems to be fundamental to it. In the following paragraphs, we describe exosome cargo for different infectious agents (Figure 1).

Viral cargo in exosomes and their potential effects during viral infections

Studies have demonstrated that exosomes are involved in the intercellular transportation of substances and information exchange among cells during viral infections [89–91]. On one hand, exosomes can be advantageous to the virus by facilitating infection and spreading [80,92], as well as cancer progression and metastasis [84]. Because of this, exosomes are called the Trojan Horses of viruses and cancer [93]. When virions (and their components) are released through the exosomes, this mechanism offers an alternative route that avoids cellular damage, such as lysis, and exerts protection from circulating neutralizing antibodies [80,85,94]. Some viral and host components carried on exosomes might also contribute to pathogenesis, like in the case of pathogen miRNAs and viral nucleic acids [84,95,96]; as well as tenascin-C involved in fibrosis during COVID-19 [97].

Furthermore, oncogenic viruses which are responsible for approximately 15% of human tumors [98] take

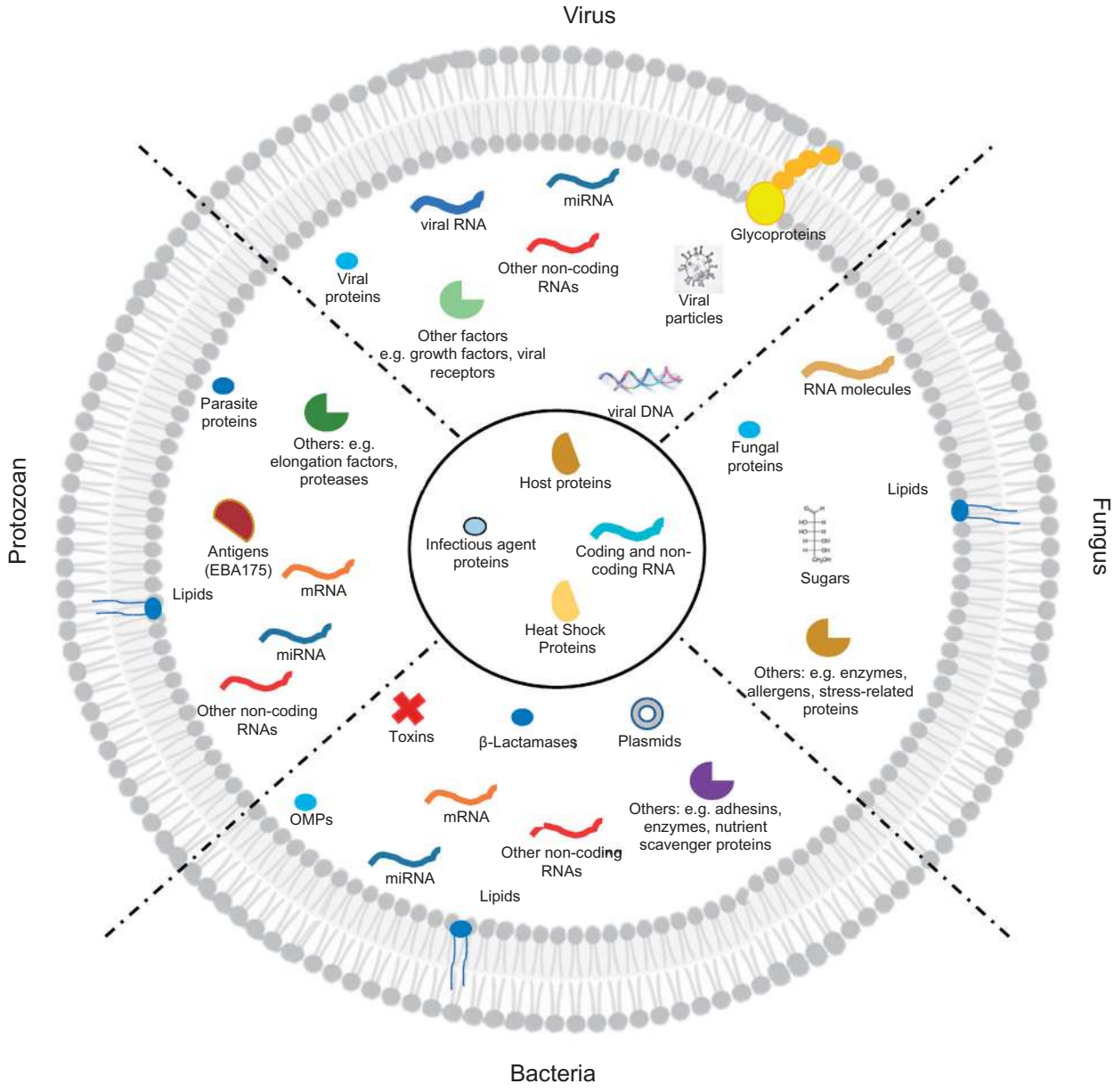

Figure 1. Overall composition of exosomes and exosome-like extracellular vesicles derived from human pathogens.
Schematic representation of the biomolecules cargo in exosomes. Note that the composition can vary depending on the species of microorganisms (for details see Tables 2–5). Other non-coding RNAs may include transfer RNA, ribosomal RNA, small interfering RNA, small nuclear RNA, long non-coding RNA, etc. Abbreviations: EBA175, Erythrocyte binding antigen 175; miRNA, microRNA; mRNA, messenger RNA; OMPs, outer membrane proteins.

advantage of exosomes to enhance viral pathogenesis. Oncogenic viral molecules (such as oncoproteins and RNAs) encapsulated into exosomes have been demonstrated to possess tumorigenic characteristics, such as Epstein Barr Virus latent membrane proteins, and Kaposi's sarcoma herpesvirus miR-K12 which can be detected in all individuals infected by those oncogenic viruses and in virus-associated cancer cells [99,100]. Notably, exosomes that carry some oncogenes molecules can promote tumor development [101]. Accumulated evidence has shown that exosomes derived from oncogenic virus-associated tumors evade immune system recognition helping viruses to survive and accelerating cancer progression, possibly by delivering biologically active molecules that remodel the cellular microenvironment [79]. In this context, exosomes can be a valuable tool as biomarkers for the diagnosis and tracking of disease progression [12,75,78].

On the other hand, some of the exosomes-associated molecules can activate the innate antiviral immune response, showing that they can also have pro-host effects. For instance, herpes simplex virus 1 (HSV-1) encodes genetic material that restricts the transmission of viruses from one cell to another [102]. Moreover,

Table 2. Exosomes released in viral infections and their possible effect on viral-host interaction.

Virus	Viral cargo reported in exosomes	Potential effect of viral exosomes	References
BK virus	Viral miRNA (miR-B1-5p)	Potential biomarkers of kidney disease	[75,76]
Cytomegalovirus	Viral antigens like glycoprotein B (UL55), lectin, DC-SIGN, IFI16	Exacerbate transplant rejection; infection of myeloid DC; viral persistence	[119,120]
Dengue virus 2 and 3	Viral RNA and proteins	Inhibition of RNAi machinery; downregulation of Drosha and DGCR8 increasing viral replication	[90,121]
Ebola virus	Viral matrix protein VP40	Protect RNA from degradation, viral dissemination; induction of cell death in uninfected T-cell and monocyte population; downregulation of miRNA machinery in naïve recipient T-cells, regulation of cell cycle and biogenesis of extracellular vesicles	[21,81,122,123]
Epstein–Barr virus	Viral BART miRNA, viral proteins: LMP1, LMP2A, glycoprotein 350; FGF-2, HIF-1α, IFI16, EGFR, FasL, Galectin-9, EBERs, dUTPase, non-coding RNAs	Proliferation, apoptosis, increase cytokine expression in target cells; modulation of tumor microenvironment, enhance viral efficiency, tumorigenesis promotion; viral reactivation, immune modulation, regulation of downstream signaling, transformation of recipient cells, promote pre-malignancy and tumor angiogenesis, epithelial–mesenchymal transition, angiogenesis, antagonism to innate antiviral immunity, and apoptosis	[77,99,108,109,116,117,124–132]
Enterovirus 71	miR-146a and miR-30a, viral particles	Suppression of type I interferon response; viral dissemination and replication	[91,133–136]
Hepatitis A virus	Viral particles	Immune evasion; enhance transmission of the virus	[114,137]
Hepatitis B virus	Viral DNA, viral RNA, viral proteins (HBsAg, HBeAg, core protein, large envelope protein, protein and HBx protein), viral miRNA (miR-3)	Immune evasion, improve transmission efficiency, promote antiviral immune response, suppressing immune responses	[106,110,111,138,139]
Hepatitis C virus	Structural proteins (E1 and E2); core proteins of the virus, positive and negative sense viral RNA, miR-122 and miR-19a, miR-192, Ago2 and HSP90	Viral pathogenesis, viral RNA replication and productive infection; immune evasion	[89,94,114,140–150]
Hepatitis E virus	Viral RNA and proteins	Viral dissemination and immune evasion	[80,151]
Human Herpes virus 6	Mature virions, viral envelope glycoproteins (gB and gM)	Relevant for viral dissemination	[107]
Human immunodeficiency virus type 1	Viral proteins (Nef, Gag), viral RNA, unspliced RNA, viral miRNAs (vmiR88, vmiR99, vmiR-TAR); viral receptors (CCR5 AND CXCR4), APOBEC3G molecules, cGAMP	Induction of T-cell apoptosis and down-modulation of cell surface molecules (i.e. MHC-I and CD4); enhance HIV replication; production of pro-inflammatory cytokines; stimulate signaling in macrophages by TNFα release; Nef participate in suppressing of viral recognition by immune cells and death or senescence in CD4+ T lymphocytes.	[20,96,112,113,126,152–159]
Human papillomavirus	Viral DNA, mRNA, miRNA, cytokines, lncRNAs within HeLa-derived exosomes; circRNA; cellular molecules of the host like survivin and other members of the IAP family, oxidative stress-related proteins; viral molecules of L1, E6 and E7	Inhibition of apoptosis and necrosis, enhance tumor progression and pro-proliferative potential	[86,160–166]
Herpes simplex virus type 1	Viral RNA, viral miRNAs (miR-H28, miR-H29, miR-H3, miR-H5 and miR-H6), STING proteins and viral glycoprotein B	Increase infectivity, prevent the elimination by the host and establish persistent infection; immune evasion	[82,95,115,167]
Human T-lymphotropic virus	Viral proteins such as Tax and glycoprotein 46, viral mRNA transcripts (Tax, HBZ, and Env)	Proliferation and transformation of T cells; viral dissemination	[85,152,168]
JC polyomavirus	JC-miRNAs 5p and 3p	Increase viral autoregulation	[78,169]
Kaposi's sarcoma-associated herpesvirus (Human Herpes virus 8)	IFI16, Cleaved IL-1β, Hexokinase, Pyruvate kinase, Lactose dehydrogenase, viral miRNAs (miR-K12 − 1, 5,7, 9,10 y 11 y K12-3-5p), viral RNA, properdin, mitochondrial DNA	Inflammation, induction of glycolysis, downregulation of common mRNA targets, including those with related with cell growth regulation, tumor induction; exacerbate disease progression and pathogenesis, cell proliferation, immune evasion, regulation of the life cycle and latent-lytic switch, anti-apoptosis	[84,100,118,170–175]
Norovirus	Virions	Enhance viral propagation	[92]
Pegivirus	Viral RNA	Viral persistence and replication	[176]
Respiratory syncytial virus	Viral RNA and proteins like nucleocapsid protein N, attachment protein G and fusion protein F	Not clear the role of exosomes cargo in pathogenesis or protection against disease	[177]
Rift valley fever virus	v-protein (N- and NSs), viral RNA	Negatively impact the viability of recipient immune cells destroying T-cells and monocytes, immune evasion	[178]
Coronaviruses	Viral RNA, CD9, ACE2, Spike S protein	Viral dissemination, immunomodulation, inflammation, virus entry	[27,83,97,179–185]
Torquetenovirus	Viral DNA, viral miRNAs	Viral persistence	[186,187]

Viral components released in exosomes in different virus-related diseases. We describe the viral cargo of exosomes and their possible effects in the host. ACE2: Angiotensin-converting enzyme 2; Ago2: Argonaute 2 protein; APOBEC3G: Apolipoprotein B mRNA editing enzyme catalytic subunit 3G; BART miRNAs: BamHI fragment A rightward transcript miRNAs; circRNA: circular RNA; DC-SIGN: DC-specific intercellular adhesion molecule-3 grabbing nonintegrin; EBER: Epstein-Barr virus-encoded small RNAs; EGFR: Epidermal growth factor receptor; FasL: Fas ligand; Env: envelope protein; FGF-2: Basic fibroblast growth factor; HBeAg: Hepatitis B e antigen; HBsAg: Hepatitis B surface antigen; HBZ: Human T-lymphotropic virus bZIP factor; HIF-1α: Hypoxia-inducible factor 1-alpha; HSP: Heat shock protein; IAP family: inhibitors of apoptosis; ICP27: Infected-cell protein 27; IFI16: Interferon Gamma Inducible Protein 16; LMP1: Epstein–Barr virus latent membrane protein 1; LMP2A: Epstein–Barr virus latent membrane protein 2; lncRNAs: long non-coding RNAs; mRNA: messenger RNA; miRNA: micro RNA; RNAi: RNA interference; rRNA: ribosomal RNA; STING: Stimulator of interferon genes; Tax: nuclear transcriptional transactivator.

exosomes expressing the receptor angiotensin-converting enzyme 2 (ACE2) compete with cellular ACE2 for the neutralization of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) [103–105].

In Table 2 we summarized the viral components of exosomes released from virus-infected cells and their role in different biological processes. According to this information, viral dissemination is one of the main potential effects of the exosomes during viral infections, reaching distant tissues, and consequently, longer and persistent infections can be better established [80,83,106,107]. In this regard, other effects like viral persistence and a higher replication may also be related to viral dissemination. Exosome-viral cargo may also induce immune suppression and immune evasion, by decreasing the normal response of the immune cells (like NKs or DC) [77,108–113], and avoiding the immune cell recognition [82,110,114,115]. Tumor induction and tumor progression are common effects of the exosomes related to the oncogenic viruses [100,116–118]. Altogether these effects of the exosomes' viral cargo suggest that exosomes contribute mainly to viral replication, dissemination and persistence within the body, with likely an impact on disease progression.

Pathogenic and commensal bacteria-derived exosomes

The domains of life Archaea and Bacteria also secrete vesicles that resemble mammalian cell-derived exosomes and microvesicles [17]. While mammalian exosomes biogenesis involves the endosomal systems, the extracellular vesicles from bacteria are generated by membrane blebbing, cell lysis or by extrusion of the cell membrane and release through cell wall [311]. Similar to mammalian exosomes, bacterial extracellular vesicles consist in a lipid bilayer that encloses a variety of biomolecules allowing communication between cells [312]. Outer-membrane vesicles are heterogeneous size particles (10-300 nm) released by Gram-negative bacteria and are formed by the outer membrane filled with periplasmic content [7,313]. Their cargo is highly mutable depending on the physiological environment and the bacterial species, and their functions are equally diverse as we describe below.

Outer-membrane vesicles may play an important role in pathogen infection since they can pack multiple virulence factors and toxins that can be delivered into host cells. Some *Escherichia coli* strains have been shown to release vesicles containing toxins, such as the heat-labile enterotoxin derived from enterotoxigenic *E. coli* [227,228], and the Shiga toxin released from the Shiga toxin-producing *E. coli* [235,236]. The vacuolating cytotoxin VacA of *Helicobacter pylori* has also been detected in outer-membrane vesicles present in the human gastric epithelium [250]; whereas the vesicles from *Actinobacillus actinomycetemcomitans* are also cytotoxic [196,197,199]. In addition to toxins, they can contain other virulence factors including adhesins to allow interaction with host cells, proteases and signaling molecules (Table 3).

The implications of outer-membrane vesicles acting as delivery vehicles include the modulation of the host's innate and adaptive immune responses. For example, the outer-membrane vesicles generated from *Salmonella* stimulate the expression of the MHC-II and proinflammatory cytokines in macrophages and DC [314]; *H. pylori* and *Pseudomonas aeruginosa* vesicles induce a potent interleukin-8 (IL-8) response [246,283]; whereas the vesicles released from *Neisseria* activate DC inducing MHC-II expression, and release of the chemoattractants IL-8, RANTES and Interferon gamma-induced protein 10 (IP-10) [315]. This innate immune response may result from the identification of vesicle pathogen-associated molecular patterns (PAMPs) and lipopolysaccharide (LPS). It is well-characterized that LPS is sensed by the Toll-like receptor- (TLR-) 4 eliciting a pro-inflammatory response [316]. In addition to LPS, other PAMPs in the vesicles can activate the immune response. Vesicles from *P. aeruginosa* contain flagellin monomers and CpG DNA [283,317] which can be recognized by TLR-5 and TLR-9, respectively.

Outer-membrane vesicles can also aid in bacterial survival under stress conditions and nutrient acquisition. They can provide envelope stress relief through the disposal of misfolded proteins, peptidoglycan fragments, or lipopolysaccharide [318–320]. Moreover, vesiculation increases during oxidative stress [318–321]. Furthermore, these vesicles are also proposed to have a role in bacterial community formation and provide nutrients during colonization. For example, the outer-membrane vesicles from *Borrelia burgdorferi* contain enolase which is essential to bacterial glycolysis and may contribute to colonization [17,218]. Several bacterial species release outer-membrane vesicles containing iron acquisition proteins and receptors for haem groups, such as FetA and FetB47 (iron transporter components) present in the vesicles of *N. meningitidis* [272]; IhtB, HmuY and gingipains released by *Porphyromonas gingivalis* [278]; as well as CopB, the haem chaperone CcmE and the surface

Table 3. Bacterial-related cargo in outer-membrane vesicles and membrane vesicles, and possible function during bacterial-host interactions.

Bacteria	Cargo reported in outer-membrane vesicles or membrane vesicles	Potential effect	References
Acinetobacter baumannii	OmpA, proteases, phospholipases, SOD, catalase, Omp38, EpsA, Ptk, GroEL, hemagglutinin-like protein, FilF, β-lactamases (AmpC, TEM, OXA-23, NDM-1), CsuA/B, CsuC, CsuD, fimbrial protein, putative hemolysin	Cytotoxic, inflammatory response, dissemination, biofilm formation, attachment, and antibiotic resistance	[188–193]
Acinetobacter nosocomialis	147 proteins including OmpA, CsuA, CsuC, CsuD, PilW, hemolysin, and serine protease	Cytotoxic in HEp-2 cells, inflammatory response	[194]
Acinetobacter radioresistens	71 proteins including GroEL, MucD, OmpA-like protein, cytoplasmic elongation factor Tu, SOD and malate dehydrogenase	Biofilm formation, quorum sensing, oxidative stress tolerance, and cytotoxicity	[195]
Actinobacillus actinomycetemcomitans	Leukotoxin, GroEL, CDT, Pal, Omp100, RcpA, RcpB, NOD1- and NOD2-active peptidoglycan, msRNAs	Bone-resorbing activity, chicken embryo lethality, cytotoxicity, pro-inflammatory response, adhesion/invasion, immune evasion, scavenging of iron and nutrients	[196–203]
Bacillus anthracis	Anthrax toxin components and anthrolysin	Cytotoxicity	[204]
Bacteroides fragilis	Hemmagglutinin, alkaline phosphatase, esterase lipase, acid phosphate, phosphohydrolase, α- and β- galactosidases, α- glucosidase, glucosaminidase, β- glucuronidase, BFT, PSA	Hemagglutinating and enzymatic activities, tolerogenic DCs and regulatory T cell activation, and mucosal tolerance	[205–207]
Bacteroides succinogenes	Cellulase, xylanase	Aryl- β-glucosidase, aryl-β-xylosidase, endoglucanase, xylanase activities	[208]
Bacteroides thetaiotaomicron	β-Lactamases (BtCepA)	Antibiotic resistance	[209]
Bartonella henselae	HbpC	Resistance to heme toxicity	[210]
Bordetella parapertussis	Pertactin, GroEL, elongation factor Tu, porins	Inflammation	[211]
Bordetella pertussis	AC-Hly, FHA, pertussis toxin, pertactin, OmpC, GroEL like protein	Inflammation, Th1/Th17 response, cytotoxicity, iron acquisition	[212–215]
Borrelia burgdorferi	OM complexes including the proteins P13, Osp-A, -B, -C, -D, and Lp6.6, enolase, and around 1200 unique transcripts including 38 plasmid-encoded outer-membrane vesicles-enriched proteins	HUVEC adherence, external proteolysis, nutrition and dissemination, bacteria–bacteria or bacteria–host communications	[216–220]
Brucella melitensis	Omp25, Omp31	ND	[221]
Burkholderia cepacian	PLC-N, lipase, PSCP, 40-kDa protease	Enzyme activities	[222]
Campylobacter jejuni	The three subunits (CdtA, CdtB, and CdtC) of the CDT, 134 proteins including nitrate and nitrite reductases, flagellar proteins, adhesins, pore-forming proteins (PorA and Omp50), fibronectin-binding proteins, proteases (HtrA, Cj0511 and Cj1365c)	Cell distending effects on a human intestinal cell line, host colonization, bacterial-host interaction, secretion of non-functioning enzymes, bacterial adhesion and invasion	[223–225]
Enterohemorrhagic *Escherichia coli*	ClyA	Pore forming	[226]
Enterotoxigenic *E. coli*	LT, EtpA adhesin, CexE, flagellin. Differential under oxidative stress.	Enterotoxic and vacuolating activities, pathogenicity (colonization), stress relief	[227–232]
Extra-intestinal pathogenic *E. coli*	Alpha-hemolysin, CDT, iron and hemin binding OMPs	Hemolytic, causing detachment of cells from monolayer	[233,234]
Shiga-like toxin–producing *E. coli*	Shiga toxin 2	Cytotoxic	[235,236]
Uropathogenic *E. coli*	CNF1	Cytotoxic	[237]
Francisella tularensis	Proteins of the OmpA and OmpH family, components of Bam-complex, histidine acid phosphatase, quitinases, β-lactamases, peroxidase/catalase, SodC, FipB, FumA and TktA. Selectively packed into outer-membrane vesicles during stressful cultivations	Protection against bacteriophages, bacteriocins, environmental adaptation, biofilm formation, nutrients acquisition, oxidative stress resistance, delivery of effector molecules into host cells, protection against antimicrobial peptides	[238,239]
Fusobacterium nucleatum	98 proteins, of which 6 autotransporters represent 31-51% of the total protein	Adhesion, invasion, colonization	[240]
Kingella kingae	RtxA toxin and PilC2 pilus adhesin	Leukotoxic and hemolytic, pro-inflammatory (GM-CSF and IL-6)	[241]
Klebsiella pneumonia	69 proteins in the hypervirulent strain ATCC1706 including ribosomal proteins, outer membrane lipoproteins (RcsF), OmpA family lipoproteins and DNA coding for regulator of mucoid phenotype (*prmpA*) and siderophores (*iroB*)	Inflammation (IL-6 and IL-8 induction), transference of hypermucoviscosity phenotype	[242,243]
Haemophilus influenza	β-lactamases. 53 different proteins, including MglB, HtrA, Omp26 and Protein D present in 4 strains (encapsulated and nonencapsulated). Palmitic acid and PE	Antibiotic resistance, host-pathogen interaction	[244,245]
Helicobacter pylori	Depending on the growth stages and on outer-membrane vesicles size. VacA, Lewis antigen LPS, CagA, carbonic anhydrases belonging to the α-class, Lpp20, adhesins, NapA, BabA, OipA, Cag3, UreG, UreF, Cag8, ureB, ureA, β-lactamase, HtrA, catalase, SOD and thioredoxin, bacterial non-heme ferritin, GGT. 578,015 unique sncRNA sequences including sR-2509025 and sR-989262	Vacuolating activity, cytotoxic, stimulating proliferation, inflammation (IL-8 secretion), host-pathogen interaction, colonization, biofilm formation, chemotaxis, neutralization of the acidic environment, antibiotic resistance, disruption of cell-cell junction, protection from oxidative stress, iron acquisition	[246–256]
Legionella pneumophila	Mip (lpg0791), IcmK/IcmX, flagellin, phospholipase C, LaiE/LaiF, phospholipase, chitinase, acid phosphatases, proteases, diphosphohydrolase	Inhibition of phagolysosome fusion, proteolytic and lipase activity	[257,258]

(*continued*)

Table 3. Continued.

Bacteria	Cargo reported in outer-membrane vesicles or membrane vesicles	Potential effect	References
Leptospira interrogans	Outer membrane proteins OmpL1, Qlp42, LipL32, LipL41, LipL36, Loa22; and, flagella	ND	[259]
Listeria monocytogenes	LLO, PI-PLC, SecDF, PrsA2, and SipZ, enriched in PE, sphingolipids and triacylglycerols unsaturated fatty acids, ornithine and citrulline, myo-inositol, phenylalanine, citric acid, and pyruvic acid	Cytotoxicity	[260]
Moraxella catarrhalis	UspA1/UspA2, CopB, CcmE, MID and unmethylated CpG-DNA motifs, β-Lactamases	Binds C3 complement in serum; B cell activation, antibiotic resistance	[261–263]
Mycobacterium tuberculosis	Mycobactin, lipoglycans (LAM and LM), lipoproteins (LpqH and LprG), HbhA, TatA, FbpA, FbpB, and FbpC	Iron acquisition, transference of bacterial components, immune response regulation, inflammation, adhesion, antibiotic resistance	[22,264,265]
Neisseria gonorrhoeae	168 proteins common in 4 strains, including a homolog of LptD, PorB, catalase, PilQ, phospholipase A, adhesion MafA 1/4 and BamA (Omp85)	Bacterial survival	[266]
Neisseria meningitidis	PorA, N1pB, NarE (putative), Omp85, FetA, FetB47, PorB, RmpM, OpcA, NspA, PilQ 155 proteins identified in spontaneous outer-membrane vesicles, depleted of PorA, PorB and PilQ, and enriched with complement regulatory proteins and factors involved in iron/zinc acquisition	TNF-α, IL-6, activation of tissue factor (procoaggulant), profibrinolytic and antifibrinolytic factors, iron/zinc acquisition	[267–272]
Porphyromonas gingivalis	Arg- and Lys- gingipain cysteine proteinases, heme-binding lipoproteins HmuY and IhtB, fimbrial proteins (FimA, C, D, E and Mfa1), LptO, HagA, DNA fragments of genes encoding the major subunit of fimbriae, SOD, gingipains, msRNAs	Cleavage and loss of CD14 from macrophage, cleavage of IgG, C3, IgM, attachment and invasion, inhibition of the invasion of *Fusobacterium nucleatum* into oral epithelial cells, iron/heme acquisition, host adaptive immune response evasion	[203,273–282]
Pseudomonas aeruginosa	Phospholipase C, hemolysin, alkaline phosphatase, Cif, PQS, quinolines, proteases, β-lactamase, exoenzyme S, 481,480 unique sRNA sequences 120 proteins identified in 4 different strains of planktonic *P. aeruginosa* including AprA, efflux pumps (MexA and MexB), and PilQ; whereas 207 proteins were identified in the biofilms, including porins adhesion components, iron and Fe(III) dicitrate receptors, and enzymes (lipases, peptidases and ribonucleases)	Decrease of apical CFTR expression, *in vitro* enzyme activities, bactericidal quinolones, IL-8 stimulation, antibiotic resistance, dissemination. sRNA52320 attenuates IL-8 secretion by human airway epithelial cells, and reduce KC and neutrophil recruitment in lungs	[268,283–292]
Salmonella enterica serovar typhimurium	Protective antigens, virulence factors (PagK, PagJ, and STM2585A), flagellin, T3SS1 effector proteins. Several mRNAs and ncRNAs (differential upon culture conditions), present as full-length transcripts or in a processed or degraded form	Inflammasome response, modulation of host cellular functions Targeted transfer or undesirable RNAs disposal?	[293–297]
Shigella dysenteria serotype 1	Shiga toxin 1	Toxicity	[298]
Shigella flexneri	IpaB, IpaC, IpaD	Invasion	[299]
Staphylococcus aureus	β-lactamase, coagulase, hemolysin	Inflammation, antibiotic resistance	[300–303]
Treponema denticola	Dentilysin, adhesins, proteases, msRNAs	Chymotryptic activity, disruption of tight junctions, host adaptive immune response evasion	[203,304,305]
Vibrio cholerae	RTX toxin, OmpU and OmpT, protease PrtV, cholera toxin, RNA (abundant from intergenic regions)	Cell rounding depolymerizing actin, cellular uptake, resistance towards the antimicrobial peptide LL-37, cytotoxicity, bacteria-host and bacteria-bacteria interactions	[306–310]

AC-Hly: adenylate cyclase-hemolysin; AprA: alkaline protease; BabA: blood group antigen binding adhesin; BFT: *B. fragilis* toxin; C3: Complement component 3; Cag: Cag pathogenicity island protein; CcmE: Cytochrome c-type biogenesis protein; CDT: cytolethal distending toxin; CexE: cfaD-dependent expression extracytoplasmic protein; CFTR: cystic fibrosis transmembrane conductance regulator; Cif: CFTR inhibitory factor; ClyA: Cytolysin A; CNF1: cytotoxic necrotizing factor 1; Csu: chaperon-usher pilus; EspA: putative polysaccharide export outer membrane protein; Fbp: ferric binding protein; FHA: filamentous hemagglutinin; FilF: Putative pilus assembly protein; Fim: Major fimbrium subunit; FipB: Francisella infectivity potentiator B; FumA: Fumarate hydratase A; GGT: gamma-glutamyltransferase; GM-CSF: Granulocyte-macrophage colony-stimulating factor; HagA: hemagglutinin gene A; HbhA: heparin-binding hemagglutinin adhesin; HbpC: Hemin binding protein C; HmuY: heme-binding lipoprotein; HtrA: high temperature requirement protein A; Icm: intracellular multiplication protein; IhtB: Iron Heme Transport Protein; Ipa: invasion plasmid antigen; LAM: lipoarabinomannan; LLO: pore-forming toxin listeriolysin; LM: lipomannan; Lp6.6: lipoprotein 6.6; Lpp20: lipoprotein 20; Lpt: LPS-assembly protein; LPS: Lipopolysaccharide; LT: heat-labile enterotoxin; MafA: multiple adhesion family A; Mfa1: Minor fimbrium subunit; MglB: Galactose abc transporter, periplasmic-binding protein; MID: *Moraxella* immunoglobulin (Ig) D-binding superantigen; Mip: macrophage infectivity potentiator; msRNAs: microRNA (miRNA)-sized sRNAs; mRNAs: Messenger RNAs; NapA: Neutrophil-activating protein; ncRNAs: noncoding RNAs; ND: not determined; NDM-1: New Delhi metallo-β-lactamase; NOD: Nucleotide oligomerization domain; OipA: Outer inflammatory protein A; OM: outer membrane; Omp: outer membrane protein; Osp: Outer surface protein; Pal: peptidoglycan-associated lipoprotein; PE: phosphatidylethanolamine; PI-PLC: phosphatidylinositol- specific phospholipase C; Pil: pili associated protein; PLC-N: phospholipase nonhemolytic; Por: porin; PQS: quinolone-signaling molecule; PSA: capsular polysaccharide; PSCP: *Pseudomonas cepacia* protease; Ptk: putative protein tyrosine kinase; Qlp42: quasi-lipoprotein 42; Rcp: Rough colony protein; Rtx: Repeat in Toxin; sncRNAs: small noncoding RNAs; SipZ: similar to type-I signal peptidase; SOD: superoxide dismutase; T3SS1: Salmonella pathogenicity island 1-encoded type III secretion system; TatA: Sec-independent protein translocase protein; TktA: Transketolase 1; TNF-α: Tumor necrosis factor alpha; Ure: urease accessory protein; ureA: urease subunit alpha; ureB: urease subunit beta; Usp: ubiquitous surface protein; VacA: vacuolating cytotoxin autotransporter.

receptor transferrin-binding protein B from *Moraxella catarrhalis* [322–324]. In addition, the zinc acquisition proteins ZnuA and ZnuD47 have also been detected in the outer-membrane vesicles of *N. meningitidis* showing that metal acquisition through these vesicles is not only restricted to iron [272].

As expected, not only pathogenic but also microbiota bacteria release outer-membrane vesicles. It has been reported that microbiota-derived vesicles can either prevent or induce inflammation. For instance, *Bacteroides fragilis* release outer-membrane vesicles containing a capsular polysaccharide with immunomodulatory effects that prevent experimental colitis [206], but in contrast, the vesicles of *Bacteroides thetaiotaomicron* passing through the gut mucosal barrier activate macrophages and induce inflammation [325]. These differential effects of the outer-membrane vesicles released by commensal bacteria probably depend on vesicle content and host susceptibility [17]. Additionally, the genus *Bacteroides* generates vesicles that contain enzymes to metabolize polysaccharides, acting as public goods and aiding other bacteria with nutrient acquisition [326].

Some studies have addressed the capability of outer-membrane vesicles to protect against antibiotics, phages and toxins. It has been shown that effective antibiotic concentration can be reduced by vesicle-mediated absorption [327,328]; however, these vesicles can also transport enzymes such as ß-lactamases [262,284,329] that confer resistance to susceptible species, and, likely, the DNA encoding antibiotic resistance can be transferred in these vesicles [327–330]. Furthermore, outer-membrane vesicles can protect bacteria by binding and inactivating phages as found in *E. coli* cultured with the lytic T4 phage [327], whereas the hemin-binding protein C (HbpC) packed into the vesicles of *Bartonella henselae* protects the bacteria against toxic concentrations of hemin [210].

Due to the thick cell wall present in Gram-positive bacteria and mycobacteria, historically there was a lack of interest in the study of their extracellular vesicles since it was thought that their generation was not possible [331]. Recently, evidence of membrane vesicles generated by Gram-positive bacteria and mycobacteria emerged [22,264,265,302], although their biogenesis is still not well understood [331].

The most studied membrane vesicles of Gram-positive bacteria are from *Staphylococcus aureus*. They were characterized as spherical structures of 20-100 nm [302] and their proteomic analysis revealed virulence factors such as ß-lactamase, coagulase and hemolysin [302]. Moreover, they have been found to induce inflammation during atopic dermatitis [300] and in pulmonary inflammation [303], and transfer ß-lactamase to ampicillin-sensitive strains [329]. Some studies have shown that *Bacillus subtilis*, *Bacillus anthracis, Streptomyces coelicolor, Listeria monocytogenes, Clostridium perfringens, Streptococcus mutans* and *Streptococcus pneumoniae* also generate these vesicles [204,302,329,332–335].

In summary, the outer membrane vesicles released by Gram-negative bacteria are enriched in periplasmic proteins including efflux pumps and outer membrane proteins [283,290,312]. They commonly contain virulence factors that likely contribute to pathogenesis [204,227,231,237,243]. In contrast to Gram-positive bacteria, outer-membrane vesicles contain LPS which activate the immune response [312,316]. In addition, these extracellular vesicles protect bacteria against antibiotics [209, 245, 262, 284], phages [327] and toxins [223,228,235], allow the elimination of unwanted bacterial products [318–320], and help in the acquisition of nutrients that improve their survival [272,278,322]. They can also modulate the host's immune response [246,283,314,315] and, in the case of the microbiota, are often immunomodulatory [206]. The content of Gram-positive bacteria and mycobacteria membrane vesicles has been less described; however, they contain virulence factors that may contribute to pathogenesis [265,300,301,336]. Taken together, the load of bacterial extracellular vesicles suggests that they contribute primarily to bacterial survival, colonization and disease progression.

Exosomes generated during fungus infections

In fungi, extracellular vesicles were discovered more than a decade ago in the pathogen *Cryptococcus neoformans* [337]. In contrast to mammalian cells and similarly to Gram-positive bacteria, these fungal-vesicles have to traverse a cell wall to be released, however, until now, many steps of this process are still unknown [338]. It has been suggested that vesicles would pass through channels for their release, that cell wall is remodelled by enzymes facilitating areas for extracellular vesicles transit, or that they are forced to pass through cell wall pores by turgor pressure [338,339]. Moreover, secretion in the Fungi is particular, since the majority of proteins lack the signal peptide [340], and different secretory mechanisms may be involved including the conventional route (ER-Golgi pathway), the ESCRT-mediated pathway

and the one involving the Golgi reassembly stacking proteins (GRASP) [311].

Fungal extracellular vesicles consist of a collection of vesicular structures of 10 to 350 nm [87] combining multi-vesicular body-derived exosomes, plasma-membrane-derived microvesicles, and vesicle-like cytoplasmic bodies [339–341]. So far, extracellular vesicles have been characterized in different fungal species, where they participate in a wide array of diverse mechanisms of molecular export of lipids, polysaccharides, proteins and nucleic acids [340,342,343] which have been described as virulence factors. On this basis, these vesicles have been proposed as key regulators of host-pathogen mechanisms during fungal infections [343–346] and their complete role in the interaction of pathogen-host is still not fully understood.

In Table 4 we describe the cargo reported in the extracellular vesicles from fungal infections and their potential effect on the host. Their main effects are related to the host-pathogen interaction [339,342,344] and immune response modulation [347–350], which can be both consequences of virulence factors carried in these vesicles [87,345,346,351]. All these effects seem to be key players in the mechanism of infection and persistence in fungal diseases. These vesicles may also be advantageous to the pathogens by transporting molecules to adjust the physiology of the host and to increase their survival.

Exosome secretion by the parasitic protozoan

In contrast to the vast information available regarding other infections, studies about exosomes generated during parasitic protozoans' infections are limited. During host-pathogen interaction protozoans employ evasion mechanisms to subvert the immune response and establish the infection [365]. Transferring virulence factors, genes that mediate drug resistance, as well as molecules related to the host-pathogen interaction are likely mediated by exosomes [26,358,359]. Among the potential effects of exosomes derived from intracellular parasites, *Leishmania* exosomes acting on macrophages may dampen the innate immune response [360–364], *Trypanosoma cruzi* may mediate host-parasite interactions and immunomodulation [365,366], and transport of proteins involved in drug resistance and host-pathogen interaction during *Plasmodium falciparum* infections [88] may enhance parasite transmission [367] and dissemination of pathogenic material [368]. Among the group of extracellular parasitic protozoa, *Trichomonas vaginalis* exosomes have been involved with

Table 4. Fungal-related cargo in extracellular vesicles-like exosomes and their potential effect during fungal infections.

Fungus	Cargo reported	Potential effect	References
Candida albicans	GlcCer, sterols, RNA	ND	[344]
Cryptococcus neoformans	GlcCer, sterols; SOD, thioredoxin, thioredoxin reductase, thiol-specific antioxidant protein, catalase A, enzymes essential to glucuronic acid metabolism, urease, laccase and acid phosphatase; RNA	Adhesion to target cells, modulation of the host-pathogen interaction, host cell damage and/or modulation of immune response. Urease enhances the invasion of host central nervous system	[337,344–346,351]
Histoplasma capsulatum	Catalase B, SOD precursors and a thiol-specific antioxidant protein, proteins from the Rab family and HSP 6	Key molecules related to virulence, stress response, and proteins involved in vesicular transport and fusion	[87,352–355]
Malassezia sympodialis	Antigens (allergens)	Sensitization and maintenance of the inflammatory response. Allergens may induce inflammatory cytokine responses and participate in allergic immune response	[347]
Paracoccioides brasiliensis	GlcCer, brassica sterol, ergosterol, and lanosterol, galactopyranosyl epitopes, residues of mannose and N-acetylglucosamine, enzimes like glyceraldehyde-3-phosphate dehydrogenase and phosphatase and RNA	Mediation of host-cell adhesion, damage and/or modulation of immune response	[346,348,349,356]
Saccharomyces cerevisiae	RNA and proteins like glucanases, glucanosyl transferases, peptidases, vacuolar and secretory proteins; HSP and stress-related proteins.	Cell organization and biogenesis, transporters of macromolecules, carbohydrate metabolism, stress response, protein biosynthesis and degradation, sporulation. Modulation of the host-pathogen interaction	[341,346]
Sporothrix brasiliensis	Proteins related to metabolism and transport, serine/threonine protein kinases and glucanase.	Mediation of host-cell damage and/or modulation of immune response	[350,357]

For fungal extracellular vesicles-like exosomes, components including lipids such as sterols, polysaccharides like glucuronoxylomannan (GXM), proteins like urease, and nucleic acids have been described as virulence factors in different fungal species. HSP: Heat shock protein; GlcCer: Glucuronoxylomannan, glucosylceramide; Rab family: Ras-Related Proteins; ND: not determined; SOD: superoxide dismutase.

immunomodulation, adhesion improvement, and host-pathogen communication [369,370].

As shown in Table 5, the main effects observed for the exosome cargo from parasites are immune modulation [360–362,370–386], enhancement of parasite transmission [373,376,387,388], cell-to-cell communication [88,367,378,389], transport of virulence factors [374,375,382,383], effects on parasite survival or infectivity [365,390–392], host-parasite interactions [360,392–395] and less commonly evasion of the immune system [394,396]. Therefore, parasite exosomes seem to be more prone to modulate the immune system for their benefit instead of evading it, the last could be a consequence of the former.

Mammalian and microbial-derived exosomes: a brief insight

Until now, we described the content of the exosomes generated by different human pathogens, however, it is important to highlight how microbial-derived and human-derived exosomes are similar or differ. In this context, despite their origin, exosomes are composed of a lipid bilayer containing a variety of biomolecules that allow communication between cells. Canonical exosomes (human) are identified in a range of 30–100 nm, which is similar in size to the protozoan extracellular vesicles-like exosomes (50–100 nm) [369] and the membrane vesicles from Gram-positive bacteria (20–100 nm) [302]. However, other exosomes can be bigger such as

Table 5. Parasite cargo in exosomes and their potential effect during parasitic infections.

Parasite	Exosome cargo from parasites	Potential effects	References
Leishmania spp	Leishmanolysin (GP63) (*Leishmania spp*); SAcP, LmPRL-1 (*L. major),* HSP100 (*L. donovani*), HSP10; in *L. infantum* HSP70, HSP83/90 and acetylcholinesterase activity, rRNA, tRNA and tRNA-derived small RNAs (*L. braziliensis and L. donovani*); siRNA-coding regions in *L. braziliensis*, TRYP1, tryparedoxin peroxidase, 14-3-3 like proteins	Modulation of macrophage PTPs and transcription factors; inhibition of macrophage IL-1β production; intracellular survival of the parasites in macrophages; regulation of protein packaging into exosomes; augmented number and intracellular survival of the parasites in macrophages; RNAs could regulate and mediate parasite-host cell interactions; intracellular survival	[360–364,371–377,387,397]
Plasmodium falciparum	EBA175 and EBA181, PfPTP2, *P. falciparum* DNA, PfEMP1, rRNAs, snRNAs and tRNAs	Enhance parasite transmission; promote gametocytogenesis of a subset of parasites in vitro; dissemination of pathogenic material to enhance virulence via STING; cytoadherence of infected cells to host endothelial receptors; proteins involved in drug resistance and host-pathogen interaction.	[88,367,368,378,379,389,393]
Plasmodium yoeli	Proteins from the parasite like serine-repeat antigens, merozoite surface proteins 1 and 9, enzymes, proteases and HSPs	ND	[25]
Toxoplasma gondii	mRNAs from Rab-13, EEF1A1, thymosin and LLP protein homologue; miRNAs (miR-23b, miR-146a and miR-155). SAG, MIC, GRA, GPI, ubiquitin and cyclophilin, HSP70, CD63, and *T. gondii* surface marker P30.	Regulation of the host-parasite interaction; pathogenesis	[380,381,390,398]
Trichomonas vaginalis	Strain-specific factors and small RNA species	Responsible for the binding phenotype, parasite adhesion and modulation of cytokines IL-6 and IL-8 in ectocervical cells. RNA species of unknown function.	[369,370]
Trypanosoma brucei	Virulence factors like serum resistance-associated protein	Human infectivity	[382]
Trypanosoma cruzi	GP82, GP85/trans-sialidase family, TcSMP, α-galactosyl glycoconjugates, FCaBP, Cruzipain, TcPIWI-tryp, rRNA, mRNAs, and small RNAs, phosphatase	Invasion to mammalian cells; cell adhesion, ERK1/2 activation; parasite adhesion to host cells; immune evasion and digestion of 'hinges' off all humans IgG subclasses; increasing metacyclogenesis and susceptibility to infection; survival, and establishment of infection in Chagas disease	[365,366,383–386,388,391,392,394–396,399–408]

Specific parasitic components carried in exosomes and released into the host as well as their possible effect. EBA175: Erythrocyte binding antigen 175; EBA181: Erythrocyte binding antigen 181; EEF1A1: eukaryotic translation elongation factor 1 alpha 1; FCaBP: Flagellar calcium-binding protein; GPI: glycosyl-phosphatidylinositol; GRA: dense granule proteins; GP63: Glycoprotein 63; GP82: Glycoprotein 82; GP85: Glycoprotein 85; HSP: Heat shock protein; LLP homolog: long-term synaptic facilitation factor; LmPRL-1: *L. major* tyrosine phosphatase; MIC: Microneme proteins; mRNA: messenger RNA; ND: not determined; PfPTP2: *Plasmodium falciparum* protein; PfEMP1: *Plasmodium falciparum* erythrocyte membrane protein 1; PTPs: protein tyrosine phosphatases; miRNA: microRNA; Rab-13: Ras-Related Protein Rab-13; rRNA: ribosomal RNA; SAcP: membrane-bound secreted acid phosphatase; SAG: Surface antigen 1; siRNA: small interference RNA; snRNAs: small nuclear RNA; TcSMP: *Trypanosoma cruzi* surface membrane proteins; TcPIWI-tryp: *Trypanosoma cruzi* AGO/PIWI protein; tRNA: transfer RNA; TRYP1: Tyrosinase-related protein 1.

the outer-membrane vesicles (10–300 nm) [17,313], and the fungus-derived exosomes (10–350 nm) [87]. Differences are also evident in the exosomes' biogenesis. Mammalian exosomes of infected and non-infected cells are generated from the endosomal compartment by ESCRT-dependent and independent mechanisms [53,54]. In contrast, outer-membrane vesicles are generated by membrane blebbing [311], whereas the biogenesis of the Gram-positive bacteria, mycobacteria and fungal cells depend on the pass through a thick cell wall by mechanisms that are not well understood [331,338,339].

As we described, exosome composition varies depending on the cell type of origin. Therefore, the types of exosomes which can exist are enormous for superior organisms in comparison with unicellular organisms. Moreover, exosomes' content also depends on the physiological or metabolic state of the cells, and their microenvironment [18,30,106]. This is important because according to the cell type, the exosome content could be more 'helpful' to a particular infectious agent to establish infection. For example, Hepatitis A virions released from infected hepatocytes in form of exosomes are protected from antibody-mediated neutralization by the host-membranes [89].

Despite their origin, some molecules are common among exosomes from different sources, and between infected and uninfected cells, such as proteins involved in exosome biogenesis and release [35,312]. Moreover, exosomes derived from different pathogens contain a particular cargo including virulence factors that may have an impact on infectious diseases. As we present in Figure 1, exosomes contain components that vary randomly depending on the cell in which they were formed. Modulation of the immune system, replication, dissemination, antibiotics resistance, manipulation of the microenvironment and modulation of the host-pathogen interactions, are some of the effects induced by the exosome cargo from different microorganisms that may contribute to pathogenesis.

Potential of exosomes as biomarkers for infectious diseases

Exosomes are now intensively studied as possible biomarkers in diagnosis, disease progression, prognosis and therapy monitoring during infectious diseases [23,75,78,409,410]. The cargo composition of exosomes derived from healthy controls and individuals undergoing an infection has been proven to be different, and in some instances track with pathology or disease progression (as reviewed in [36,409]). For instance, exosomal protein CD81 was found elevated in the serum of hepatitis C patients when compared to healthy controls [24], and the thimet oligopeptidase A could be a potential diagnostic marker for *T. brucei* [411]; additionally, urinary exosomes can help to detect kidney diseases during viral and bacterial infections [75,76,412]. Moreover, studies with oncogenic viruses suggest that cancer-secreted exosomes can change the tumor microenvironment enhancing metastasis, inflammation, and angiogenesis [101,172].

More recently, quantitative analysis of serum by omics has allowed a deep characterization of exosome content. For example, proteomic analysis of exosomes in cerebrospinal fluid of HIV patients suggests an exosome-based protein signature in individuals with cognitive impairment [23]; on the other hand, lipidome analysis in COVID-19 patients and healthy controls indicate that monosialodihexosyl gangliosides-enriched exosomes positively correlated with disease severity [413], and selective RNA cargoes are present under different stages of *M. tuberculosis* infection [410].

Potential exosome-based immunotherapies for infectious diseases

Due to their capacity as biological messengers, exosome potential in therapeutics and vaccinology is enormous. Their physical and chemical properties allow them to transport a wide variety of cargo in a stable and targeted manner, allowing intercellular communication [2,35]. Therefore, the possibility of customizing its content by incorporating drugs, genetic modifiers or antigens, among others, is of considerable scientific interest. On top of that, they are biocompatible and safe [35].

A wide variety of research has been focused on the design of exosome-based cancer therapeutic strategies; however, fewer studies have focused on its possible application in the area of infectious diseases. Among them, DNA vectors expressing viral proteins fused at the C-terminus of an exosome-anchoring protein have been shown to induce cytotoxic T lymphocytes immunity against antigens derived from Human Papillomavirus, HIV-1, Hepatitis B Virus, Ebola, Influenza virus, West Nile virus, Crimean-Congo Hemorrhagic Fever and Hepatitis C Virus NS3 [414–416]. In other studies, based on the principle of trogocytosis, exosomes from DC expressing the HIV-1 antigen Gp120, a major target for HIV-1 vaccines, were used to stimulate CD8+ T cells inducing *in vivo* and *in vitro* functional T cell responses [417,418].

Moreover, this strategy allowed CD8+ T cells activation independently of CD4+ T cells and DC, thus, offering promising immunotherapy for AIDS patients with deficiency of these cell populations [417–419]. Exosomes containing miRNAs to block HSV-1 infection [420], as well as exosomes containing a Y-class small RNA with antiviral effects against influenza [421], have also been developed. Moreover, an exosomal vaccine was achieved through the replacement of the cytoplasmic and transmembrane domains of the S protein of the Severe Acute Respiratory Syndrome Coronavirus 1 (SARS-CoV-1) with those of the G protein of Vesicular stomatitis virus inducing neutralizing antibodies in immunized mice [27]. More recently, some clinical trials investigate the safety and potential efficacy of exosome-based therapies for COVID-19 patients and long haulers (ClinicalTrials.gov).

Although extracellular vesicles derived from bacteria have been associated with immune modulation [422], several studies have demonstrated their potential use for vaccination [62,211,244,423,424]. One of the most outstanding applications is to control outbreaks caused by *N. meningitidis*. There are vaccines based on capsular proteins for most serogroups, except for the most prevalent (serogroup B) due to the risk of autoimmunity. Then, the vaccine approach for serogroup B was based on proteins from the outer membrane, mainly the porin protein PorA, maintaining their stability in a membranous environment such as the vesicles [62]. Due to the high variation in PorA among B serogroup strains, there is no universal vaccine to cover all *N. meningitidis* infections, however, outer-membrane vesicles-based vaccines have been proven to be safe and effective to control epidemics caused by this pathogen [62].

Advances in exosome research may also help to prevent whooping cough caused by *Bordetella pertussis*. Recently, an outer-membrane vesicles-based vaccine showed to be more effective than the available commercial pertussis vaccines in a mouse model [423]. Other mouse immunization studies using this type of vesicles have also been effective in conferring protection against *E. coli* [230,424,425], *N. meningitidis* [426], *Burkholderia pseudomallei* [427], *Brucella melitensis* [428], *Shigella flexneri* [429], *Haemophilus influenzae* [244] and *Vibrio cholerae* [430]. A bivalent vaccine candidate against enteric fever was recently generated through engineering outer-membrane vesicles containing the Vi polysaccharide from *Salmonella typhi* and the somatic O-antigen from *Salmonella paratyphi* A [431]. Using a different approach, protection against *M. tuberculosis* and diphtheria toxoid was achieved in mice by immunization with exosomes derived from macrophages or DC treated with bacterial antigens [432,433]. Moreover, macrophage-derived exosomes containing the antibiotic linezolid have also been effective against intracellular methicillin-resistant *S. aureus* infections *in vitro* and *in vivo* [336].

Since the bacterial outer membrane contains multiple virulence factors including LPS and outer membrane proteins, an alternative to reduce the potential toxicity of outer-membrane vesicles is the generation of protoplast-derived nanovesicles. They lack outer membrane components, can be produced at significantly higher yields than outer-membrane vesicles, and are safer [434]. Furthermore, they can be loaded with different antigens, emerging as an alternative for an adjuvant-free vaccine delivery system [434]. On the other hand, bacterial-derived exosomes have also been studied as adjuvants. Outer-membrane vesicles derived from a nonpathogenic mutant strain of *E. coli* containing penta-acylated LPS have been shown to retain their T-cell adjuvant activity with attenuated endotoxicity compared to hexa-acylated LPS from the wild-type strain [424].

The potential use of exosomes to protect against protozoan parasitic diseases has also been assessed. DC-derived exosomes containing antigens from *Toxoplasma gondii* are protective against this obligate intracellular parasite in both syngeneic and allogeneic mouse models [435]. They are also effective in the prevention of congenital and ocular infections [436,437]. Antigen-loaded DC exosomes may be also able to serve as effective vaccines against *Leishmania major* as they produce protective immunity in mice [438]. Lastly, immunization of mice with reticulocyte-derived exosomes obtained from mice infected with a non-lethal strain of *Plasmodium yoelii* attenuates parasitemia and increases the survival time when challenged with a lethal *P. yoelii* strain [25].

To this date, on ClinicalTrials.gov using as search terms ‘Exosomes’ and ‘infection’ there are 16 studies evaluating exosomes as a treatment for infectious diseases (exosomes as intervention). Among these studies, 15 are related to COVID-19, and one is for the treatment of pulmonary infection with carbapenem-resistant Gram-negative bacilli. Whereas searching for ‘outer membrane vesicles’ and ‘infection’, 12 studies are evaluating vaccines for meningococcal disease and for *N. gonorrhoeae* infections. However, except for MeNZB and BEXSERO (outer-membrane vesicles-based meningococcal group B vaccines) [62], no other exosome product or outer-membrane vesicles vaccine has been approved for human

use by the USA Food and Drug Administration (https://www.fda.gov/).

Concluding remarks and future directions

Exosomes are a kind of extracellular vesicles released from practically all cell types [9,10]. They are crucial channels of communication since they can envelop a wide range of contents, including all kinds of biomolecules such as nucleic acids, proteins, and lipids to target specific recipient cells [16,30,35,41]. Therefore, these vesicles play an essential role in homeostasis and participate in pathogenesis processes [30,41,111].

Exosome secretion is an evolutionarily conserved mechanism among species, not only mammalian cells but also microorganisms can transfer components via exosomes [1,10,17]. Thus, during an infection, host- and pathogen-derived exosomes can be found in the extracellular milieu [18]. Numerous studies have shown that exosomal composition changes during infection, some of these exosomes can transfer host or pathogen components between infected to uninfected cells or tissues and contribute to the spread of the infection [87,245,345,382]. Release of virions via exosomes as well as immune evasion have also been reported [80,94]. However, exosomes can also help to limit infection progression and enhance the immune response [18]. Thus, exosomes have an enormous importance due to their implications in the host-pathogen interaction dynamic. Further studies are needed to clarify the mechanisms that determine host protection or infection/disease dissemination via exosomes.

Recent advances in the extracellular vesicles field have shown the promising potential of exosomes as biomarkers [14,30,48]. Since they can be released in almost all biological fluids, detection of host-derived or pathogen components can be identified in liquid biopsies (urine, saliva, serum) avoiding the use of invasive approaches for diagnostic and prognostic purposes [165]. The properties of exosomes also make them attractive for therapeutics. Some studies have addressed their possible application for immunization against viral, bacterial and protozoan infectious diseases [25,27–29]. Moreover, some exosomal preparations are currently being used and others are being evaluated in clinical trials [29,62,439]. Of note, in several experimental approaches, exosomes are obtained from antigen-presenting cells such as DC and macrophages [418,432,433,435]. These cells carry MHC-I and MHC-II molecules on their surface, as well as other costimulatory molecules such as CD86 that may promote the activation of T cells [74], although, pathogen-associated molecular patterns present in exosomes may also play a role in the activation of the immune system [440].

Furthermore, the versatility of exosomes for packing different cargo, specific targeting, and low immunogenicity, make them ideal candidates for drug-delivery systems [2,35]. However, some issues such as exosome composition, preparation homogeneity, target specificity, dosages and route of administration are critical to achieving the desired effect and must be addressed [2,61,409]. In this context, to deal with the poor targeting ability of natural exosomes, bioengineered exosomes modified by physical, biological or chemical methods are in development [312]. These kinds of preparations derived from bacteria are of special interest to the industry for their low-cost, the possibility of gene-editing techniques and scalability [312]. This exemplifies the promise that exosomes hold for translation to the clinic.

Future research in the exosomes field should be focused on the development of new methodologies that can distinguish between different subpopulations of exosomes (host vs pathogen, cellular/tissue source, function and cargo), and ensure that sample processing (isolation and purification) is standardized for its possible translation to clinics [37,52,61]. Finding specific markers for microbial-derived exosomes is still a challenge [312]. Moreover, to contribute to the development of novel therapeutic strategies, an exhaustive investigation of exosome biogenesis, sorting of cargo, and biological functions in physiological and pathological conditions are needed. Many steps of pathogen-derived extracellular vesicles biogenesis, in particular of the exosomes derived from protozoan parasites, fungus and Gram-positive bacteria, still have conceptual gaps. Lastly, although important progress in the characterization of exosomes during infectious diseases has been made, the role and composition of many other pathogen-derived exosomes remain to be uncovered.

Acknowledgments

To the International Centre for Genetic Engineering and Biotechnology (CRP/MEX20-04_EC) (HMG-S). We wish to acknowledge Alondra Yareli Martínez Mora for assisting with the preparation of the tables.

Author contributions

VVR-R and HMG-S conceived the study and drafted the manuscript, CL-G modified and polished the manuscript. All authors contributed to literature analysis and interpretation, commented

on the drafts of the manuscript, and approved the final draft of the paper.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This work was supported by International Center for Genetic Engineering and Biotechnology (CRP/MEX20-04_EC).

References

[1] Rilla K, Mustonen A-M, Arasu UT, et al. Extracellular vesicles are integral and functional components of the extracellular matrix. Matrix Biol. 2019;75–76:201–219.
[2] Jones L, Bell C, Bibb K, et al. Pathogens and their effect on exosome biogenesis and composition. Biomedicines. 2018;6:79.
[3] Li X, Corbett AL, Taatizadeh E, et al. Challenges and opportunities in exosome research-Perspectives from biology, engineering, and cancer therapy. APL Bioeng. 2019 3(1):011503.
[4] Johnstone RM, Adam M, Hammond JR, et al. Vesicle formation during reticulocyte maturation. Association of plasma membrane activities with released vesicles (exosomes). J Biol Chem. 1987;262:9412–9420.
[5] Hosseini HM, Fooladi AAI, Nourani MR, et al. The role of exosomes in infectious diseases. Inflamm Allergy Drug Targets. 2013;12:29–37.
[6] Harding C v., Heuser JE, Stahl PD. Exosomes: looking back three decades and into the future. J Cell Biol. 2013;200: 367–371.
[7] Schorey JS, Bhatnagar S. Exosome function: from tumor immunology to pathogen biology. Traffic. 2008;9:871–881.
[8] Andre F, Schartz NEC, Movassagh M, et al. Malignant effusions and immunogenic tumour-derived exosomes. Lancet. 2002;360:295–305.
[9] Corrado C, Raimondo S, Chiesi A, et al. Exosomes as intercellular signaling organelles involved in health and disease: basic science and clinical applications. Int J Mol Sci. 2013;14:5338–5366.
[10] Raposo G, Stoorvogel W. Extracellular vesicles: exosomes, microvesicles, and friends. J Cell Biol. 2013;200:373–383.
[11] Wiley RD, Gummuluru S. Immature dendritic cell-derived exosomes can mediate HIV-1 trans infection. Proc Natl Acad Sci USA. 2006;103:738–743.
[12] Street JM, Barran PE, Mackay CL, et al. Identification and proteomic profiling of exosomes in human cerebrospinal fluid. J Transl Med. 2012;10:5.
[13] Admyre C, Johansson SM, Qazi KR, et al. Exosomes with immune modulatory features are present in human breast milk. J Immunol. 2007;179:1969–1978.
[14] Masyuk AI, Masyuk T v, Larusso NF. Exosomes in the pathogenesis, diagnostics and therapeutics of liver diseases. J Hepatol. 2013;59:621–625.
[15] Vella LJ, Sharples RA, Nisbet RM, et al. The role of exosomes in the processing of proteins associated with neurodegenerative diseases. European Bio J. 2008;37:323–332.
[16] Bobrie A, Colombo M, Raposo G, et al. Exosome secretion: molecular mechanisms and roles in immune responses. Traffic. 2011;12:1659–1668.
[17] Schwechheimer C, Kuehn MJ. Outer-membrane vesicles from gram-negative bacteria: biogenesis and functions. Nat Rev Microbiol. 2015;13:605–619.
[18] Schorey JS, Harding C v. Extracellular vesicles and infectious diseases: new complexity to an old story. J Clin Invest. 2016;126:1181–1189.
[19] Cheng Y, Schorey JS. Exosomes carrying mycobacterial antigens can protect mice against mycobacterium tuberculosis infection. Eur J Immunol. 2013;43:3279–3290.
[20] Fang Y, Wu N, Gan X, et al. Higher-order oligomerization targets plasma membrane proteins and HIV gag to exosomes. PLoS Biol. 2007;5:e158.
[21] Pleet ML, Erickson J, DeMarino C, et al. Ebola virus VP40 modulates cell cycle and biogenesis of extracellular vesicles. J Infect Dis. 2018;218:S365–S387.
[22] Prados-Rosales R, Weinrick BC, Piqué DG, et al. Role for mycobacterium tuberculosis membrane vesicles in iron acquisition. J Bacteriol. 2014;196:1250–1256.
[23] Guha D, Lorenz DR, Misra V, et al. Proteomic analysis of cerebrospinal fluid extracellular vesicles reveals synaptic injury, inflammation, and stress response markers in HIV patients with cognitive impairment. J Neuroinflammation. 2019;16:1–19.
[24] Welker M-W, Reichert D, Susser S, et al. Soluble serum CD81 is elevated in patients with chronic hepatitis C and correlates with alanine aminotransferase serum activity. PLoS One. 2012;7:e30796.
[25] Martin-Jaular L, Nakayasu ES, Ferrer M, et al. Exosomes from Plasmodium yoelii-infected reticulocytes protect mice from lethal infections. PLoS One. 2011;6:e26588.
[26] Coakley G, McCaskill JL, Borger JG, et al. Extracellular vesicles from a helminth parasite suppress macrophage activation and constitute an effective vaccine for protective immunity. Cell Rep. 2017;19:1545–1557.
[27] Kuate S, Cinatl J, Doerr HW, et al. Exosomal vaccines containing the S protein of the SARS coronavirus induce high levels of neutralizing antibodies. Virology. 2007;362:26–37.
[28] Colino J, Snapper CM. Dendritic cell-derived exosomes express a streptococcus pneumoniae capsular polysaccharide type 14 cross-reactive antigen that induces protective immunoglobulin responses against pneumococcal infection in mice. Infect Immun. [Internet] 2007;75: 220–230.
[29] Chaput N, Théry C. Exosomes: immune properties and potential clinical implementations. Semin Immunopathol. 2011;33:419–440.
[30] D'Souza-Schorey C, Clancy JW. Tumor-derived microvesicles: shedding light on novel microenvironment modulators and prospective cancer biomarkers. Genes Dev. 2012; 26:1287–1299.
[31] Théry C, Amigorena S, Raposo G, et al. Isolation and characterization of exosomes from cell culture supernatants

and biological fluids. Curr Protoc Cell Biol. 2006;30: 3.22.1–3.22.29.
[32] Robbins PD, Morelli AE. Regulation of immune responses by extracellular vesicles. Nat Rev Immunol. 2014;14: 195–208.
[33] Conde-Vancells J, Rodriguez-Suarez E, Embade N, et al. Characterization and comprehensive proteome profiling of exosomes secreted by hepatocytes. J Proteome Res. 2008;7:5157–5166.
[34] Théry C, Ostrowski M, Segura E. Membrane vesicles as conveyors of immune responses. Nat Rev Immunol. 2009; 9:581–593.
[35] Arenaccio C, Federico M. The multifaceted functions of exosomes in health and disease: an overview. Exosomes in Cardiovascular Diseases. 2017;3–19.
[36] Chahar HS, Bao X, Casola A. Exosomes and their role in the life cycle and pathogenesis of RNA viruses. Viruses. 2015;7:3204–3225.
[37] Colombo M, Raposo G, Théry CJAROC, et al. Biogenesis, secretion, and intercellular interactions of exosomes and other extracellular vesicles. Annu Rev Cell Dev Biol. 2014; 30:255–289.
[38] van Niel G, Porto-Carreiro I, Simoes S, et al. Exosomes: a common pathway for a specialized function. J Biochem. 2006;140:13–21.
[39] Logozzi M, Milito A, de Lugini L, et al. High levels of exosomes expressing CD63 and caveolin-1 in plasma of melanoma patients. PLoS One. 2009;4:e5219.
[40] Kowal J, Tkach M, Théry C. Biogenesis and secretion of exosomes. Curr Opin Cell Biol. 2014;29:116–125.
[41] Thakur BK, Zhang H, Becker A, et al. Double-stranded DNA in exosomes: a novel biomarker in cancer detection. Cell Res. 2014;24:766–769.
[42] Minciacchi VR, You S, Spinelli C, et al. Large oncosomes contain distinct protein cargo and represent a separate functional class of tumor-derived extracellular vesicles. Oncotarget. 2015;6:11327.
[43] Guescini M, Genedani S, Stocchi V, et al. Astrocytes and Glioblastoma cells release exosomes carrying mtDNA. J Neural Transm. 2010;117:1–4.
[44] Miranda KC, Bond DT, McKee M, et al. Nucleic acids within urinary exosomes/microvesicles are potential biomarkers for renal disease. Kidney Int. 2010;78:191–199.
[45] Zou G, Benktander JD, Gizaw ST, et al. Comprehensive analytical approach toward glycomic characterization and profiling in urinary exosomes. Anal Chem. 2017;89: 5364–5372.
[46] Saraswat M, Joenväära S, Musante L, et al. N-linked (N-) glycoproteomics of urinary exosomes. Mol Cell Proteomics. 2015;14:2298.
[47] Staubach S, Schadewaldt P, Wendel U, et al. Differential glycomics of epithelial membrane glycoproteins from urinary exovesicles reveals shifts toward complex-type N-glycosylation in classical galactosemia. J Proteome Res. 2012;11:906–916.
[48] Zhang W, Jiang X, Bao J, et al. Exosomes in pathogen infections: a bridge to deliver molecules and link functions. Front Immunol. 2018;9:90.
[49] Simpson RJ, Kalra H, Mathivanan S. ExoCarta as a resource for exosomal research. J Extracell Vesicles. 2012;1:18374.
[50] Kalra H, Simpson RJ, Ji H, et al. Vesiclepedia: a compendium for extracellular vesicles with continuous community annotation. PLoS Biol. 2012;10:e1001450.
[51] Dae-Kyum K, Byeongsoo K, Youn KO, et al. EVpedia: an integrated database of high-throughput data for systemic analyses of extracellular vesicles. J Extracell Vesicles. 2013; 2:20384.
[52] Zhang Y, Liu Y, Liu H, et al. Exosomes: biogenesis, biologic function and clinical potential. Cell Biosci. 2019;9:19.
[53] Record M, Subra C, Silvente-Poirot S, et al. Exosomes as intercellular signalosomes and pharmacological effectors. Biochem Pharmacol. 2011;81:1171–1182.
[54] Record M, Carayon K, Poirot M, et al. Exosomes as new vesicular lipid transporters involved in cell-cell communication and various pathophysiologies. Biochim Biophys Acta. 2014;1841:108–120.
[55] Henne WM, Stenmark H, Emr SD. Molecular mechanisms of the membrane sculpting ESCRT pathway. Cold Spring Harb Perspect Biol. 2013;5:a016766.
[56] Hanson PI, Cashikar A. Multivesicular body morphogenesis. Annu Rev Cell Dev Biol 2012;28:337–362.
[57] Colombo M, Moita C, van Niel G, et al. Analysis of ESCRT functions in exosome biogenesis, composition and secretion highlights the heterogeneity of extracellular vesicles. J Cell Sci. 2013;126:5553–5565.
[58] Hurley JH, Hanson PI. Membrane budding and scission by the ESCRT machinery: it's all in the neck. Nat Rev Mol Cell Biol. 2010;11:556–566.
[59] Poteryaev D, Datta S, Ackema K, et al. Identification of the switch in early-to-late endosome transition. Cell. 2010;141: 497–508.
[60] Perez-Hernandez D, Gutiérrez-Vázquez C, Jorge I, et al. The intracellular interactome of tetraspanin-enriched microdomains reveals their function as sorting machineries toward exosomes. J Biolog Chem. 2013;288: 11649–11661.
[61] Gurunathan S, Kang M-H, Jeyaraj M, et al. Review of the isolation, characterization, biological function, and multifarious therapeutic approaches of exosomes. Cells. 2019;8: 307.
[62] Balhuizen MD, Veldhuizen EJA, Haagsman HP. Outer membrane vesicle induction and isolation for vaccine development. Front Microbiol. 2021;12:629090.
[63] Prunotto M, Farina A, Lane L, et al. Proteomic analysis of podocyte exosome-enriched fraction from normal human urine. J Proteomics. 2013;82:193–229.
[64] Shao H, Im H, Castro CM, et al. New technologies for analysis of extracellular vesicles. Chem Rev. 2018;118: 1917–1950.
[65] Peterson MF, Otoc N, Sethi JK, et al. Integrated systems for exosome investigation. Methods. 2015;87:31–45.
[66] Gerlach JQ, Krüger A, Gallogly S, et al. Surface glycosylation profiles of urine extracellular vesicles. PLoS One. 2013;8:e74801.

[67] Llorente A, Skotland T, Sylvänne T, et al. Molecular lipidomics of exosomes released by PC-3 prostate cancer cells. Biochim Biophys Acta. 2013;1831:1302–1309.

[68] Yang JS, Kim JY, Lee JC, et al. Investigation of lipidomic perturbations in oxidatively stressed subcellular organelles and exosomes by asymmetrical flow field–flow fractionation and nanoflow ultrahigh performance liquid chromatography–tandem mass spectrometry. Anal Chim Acta. 2019;1073:79–89.

[69] Gould SJ, Raposo G. As we wait: coping with an imperfect nomenclature for extracellular vesicles. J Extracell Vesicles. 2013;1:20389.

[70] Lötvall J, Hill AF, Hochberg F, et al. Minimal experimental requirements for definition of extracellular vesicles and their functions: a position statement from the International Society for Extracellular Vesicles. J Extracell Vesicles. 2014;3:26913.

[71] Théry C, Witwer KW, Aikawa E, et al. Minimal information for studies of extracellular vesicles 2018 (MISEV2018): a position statement of the International Society for Extracellular Vesicles and update of the MISEV2014 guidelines. J Extracell Vesicles. 2018;7:1535750.

[72] Witwer KW, Goberdhan DCI, O'Driscoll L, et al. Updating MISEV: evolving the minimal requirements for studies of extracellular vesicles. J Extracell Vesicles. 2021;10:e12182.

[73] el Andaloussi S, Mäger I, Breakefield XO, et al. Extracellular vesicles: biology and emerging therapeutic opportunities. Nat Rev Drug Discov. 2013;12:347–357.

[74] Tran T-H, Mattheolabakis G, Aldawsari H, et al. Exosomes as nanocarriers for immunotherapy of cancer and inflammatory diseases. Clinical Immunol. 2015;160:46–58.

[75] Li JYZ, McNicholas K, Yong TY, et al. BK virus encoded microRNAs are present in blood of renal transplant recipients with BK viral nephropathy. American J Transplantation 2014;14:1183–1190.

[76] Kim MH, Lee YH, Seo J-W, et al. Urinary exosomal viral microRNA as a marker of BK virus nephropathy in kidney transplant recipients. PLoS One. 2017;12:e0190068.

[77] Higuchi H, Yamakawa N, Imadome K-I, et al. Role of exosomes as a proinflammatory mediator in the development of EBV-associated lymphoma. Blood. 2018;131:2552–2567.

[78] Rocca A, Martelli F, Delbue S, et al. The JCPYV DNA load inversely correlates with the viral microrna expression in blood and cerebrospinal fluid of patients at risk of PML. J Clin Virol. 2015;70:1–6.

[79] Anderson MR, Kashanchi F, Jacobson S. Exosomes in viral disease. Neurotherapeutics. 2016;13:535–546.

[80] Chapuy-Regaud S, Dubois M, Plisson-Chastang C, et al. Characterization of the lipid envelope of exosome encapsulated HEV particles protected from the immune response. Biochimie. 2017;141:70–79.

[81] Pleet ML, DeMarino C, Stonier SW, et al. Extracellular vesicles and ebola virus: A new mechanism of immune evasion. Viruses. 2019;11:410.

[82] Bello-Morales R, Praena B, de la Nuez C, et al. Role of microvesicles in the spread of herpes simplex virus 1 in oligodendrocytic cells. J Virol. 2018;92:e00088-18.

[83] Barberis E, Vanella V v, Falasca M, et al. Circulating exosomes are strongly involved in SARS-CoV-2 infection. Front Mol Biosci. 2021;8:632290.

[84] Chugh PE, Sin S-H, Ozgur S, et al. Systemically circulating viral and tumor-derived microRNAs in KSHV-associated malignancies. PLoS Pathog. 2013;9:e1003484.

[85] Jaworski E, Narayanan A, van Duyne R, et al. Human T-lymphotropic virus type 1-infected cells secrete exosomes that contain Tax protein. J Biological Chemistry. 2014;289:22284–2305.

[86] Harden ME, Munger K. Human papillomavirus 16 E6 and E7 oncoprotein expression alters microRNA expression in extracellular vesicles. Virology. 2017;508:63–69.

[87] Albuquerque PC, Nakayasu ES, Rodrigues ML, et al. Vesicular transport in Histoplasma capsulatum: an effective mechanism for trans-cell wall transfer of proteins and lipids in ascomycetes. Cell Microbiol. 2008;10:1695–1710.

[88] Babatunde KA, Mbagwu S, Hernández-Castañeda MA, et al. Malaria infected red blood cells release small regulatory RNAs through extracellular vesicles. Sci Rep. 2018;8:1–15.

[89] Feng Z, Hensley L, McKnight KL, et al. A pathogenic picornavirus acquires an envelope by hijacking cellular membranes. Nature. 2013;496:367–371.

[90] Vora A, Zhou W, Londono-Renteria B, et al. Arthropod EVs mediate dengue virus transmission through interaction with a tetraspanin domain containing glycoprotein Tsp29Fb. Proc Nal Acad Sci 2018;115:E6604–13.

[91] Mao L, Wu J, Shen L, et al. Enterovirus 71 transmission by exosomes establishes a productive infection in human neuroblastoma cells. Virus Genes. 2016;52:189–194.

[92] Santiana M, Ghosh S, Ho BA, et al. Vesicle-cloaked virus clusters are optimal units for inter-organismal viral transmission. Cell Host Microbe. 2018;24:208–220.

[93] Altan-Bonnet N. Extracellular vesicles are the Trojan horses of viral infection. Curr Opin Microbiol. 2016;32:77–81.

[94] Masciopinto F, Giovani C, Campagnoli S, et al. Association of hepatitis C virus envelope proteins with exosomes. Eur J Immunol. 2004;34:2834–2842.

[95] Han Z, Liu X, Chen X, et al. miR-H28 and miR-H29 expressed late in productive infection are exported and restrict HSV-1 replication and spread in recipient cells. Proc Natl Acad Sci 2016;113:E894–E901.

[96] Bernard MA, Zhao H, Yue SC, et al. Novel HIV-1 miRNAs stimulate TNFα release in human macrophages via TLR8 signaling pathway. PLoS One. 2014;9:e106006.

[97] Sur S, Khatun M, Steele R, et al. Exosomes from COVID-19 patients carry tenascin-C and fibrinogen-β in triggering inflammatory signals in cells of distant organ. Int J Mol Sci. 2021;22(6):3184.

[98] Plummer M, Peto J, Franceschi S, et al. Time since first sexual intercourse and the risk of cervical cancer. Int J Cancer. 2012;130:2638–2644.

[99] Ahmed W, Philip PS, Tariq S, et al. Epstein-Barr virus-encoded small RNAs (EBERs) are present in fractions related to exosomes released by EBV-transformed cells. PLoS One. 2014;9:e99163.

[100] Gottwein E, Mukherjee N, Sachse C, et al. A viral microRNA functions as an orthologue of cellular miR-155. Nature. 2007;450:1096–1099.
[101] Wu J, Yang J, Ding J, et al. Exosomes in virus-associated cancer. Cancer Lett. 2018;438:44–51.
[102] Huang R, Wu J, Zhou X, et al. Herpes simplex virus 1 microRNA miR-H28 exported to uninfected cells in exosomes restricts cell-to-cell virus spread by inducing gamma interferon mRNA. J Virol. 2019;93:e01005-19.
[103] El-Shennawy L, Hoffmann AD, Dashzeveg NK, et al. Circulating ACE2-expressing extracellular vesicles block broad strains of SARS-CoV-2. Nat Commun. 2022;13(1):405.
[104] Cocozza F, Névo N, Piovesana E, et al. Extracellular vesicles containing ACE2 efficiently prevent infection by SARS-CoV-2 Spike protein-containing virus. J Extracell Vesicles. 2020;10:e12050.
[105] Inal JM. Decoy ACE2-expressing extracellular vesicles that competitively bind SARS-CoV-2 as a possible COVID-19 therapy. Clin Sci. 2020;134:1301–1304.
[106] Kapoor NR, Chadha R, Kumar S, et al. The HBx gene of hepatitis B virus can influence hepatic microenvironment via exosomes by transferring its mRNA and protein. Virus Res. 2017;240:166–174.
[107] Mori Y, Koike M, Moriishi E, et al. Human herpesvirus-6 induces MVB formation, and virus egress occurs by an exosomal release pathway. Traffic. 2008;9:1728–1742.
[108] Ahmed W, Philip PS, Attoub S, et al. Epstein–Barr virus-infected cells release Fas ligand in exosomal fractions and induce apoptosis in recipient cells via the extrinsic pathway. J General Virol. 2015;96:3646–3659.
[109] Klibi J, Niki T, Riedel A. Blood diffusion and Th1-suppressive effects of galectin-9-containing exosomes released by Epstein-Barr virus-infected nasopharyngeal carcinoma cells. Blood. 2009;113:1957–1966.
[110] Wang J, Cao D, Yang J. Exosomes in Hepatitis B virus transmission and related immune response. Tohoku J Exp Med. 2020;252:309–320.
[111] Yang Y, Han Q, Hou Z, et al. Exosomes mediate hepatitis B virus (HBV) transmission and NK-cell dysfunction. Cell Mol Immunol. 2017;14:465–475.
[112] Gray LR, Gabuzda D, Cowley D, et al. CD4 and MHC class 1 down-modulation activities of nef alleles from brain-and lymphoid tissue-derived primary HIV-1 isolates. J Neurovirol. 2011;17:82–91.
[113] Lenassi M, Cagney G, Liao M, et al. HIV Nef is secreted in exosomes and triggers apoptosis in bystander CD4+ T cells. Traffic. 2010;11:110–122.
[114] Longatti A. The dual role of exosomes in hepatitis A and C virus transmission and viral immune activation. Viruses. 2015;7:6707–115.
[115] Temme S, Eis-Hübinger AM, McLellan AD, et al. The herpes simplex virus-1 encoded glycoprotein B diverts HLA-DR into the exosome pathway. J Immunol. 2010;184:236–243.
[116] Meckes DGJ, Shair KHY, Marquitz AR, et al. Human tumor virus utilizes exosomes for intercellular communication. Proc Natl Acad Sci USA. 2010;107:20370–20375.
[117] Aga M, Bentz GL, Raffa S, et al. Exosomal HIF1α supports invasive potential of nasopharyngeal carcinoma-associated LMP1-positive exosomes. Oncogene. 2014;33:4613–46122.
[118] Skalsky RL, Samols MA, Plaisance KB, et al. Kaposi's sarcoma-associated herpesvirus encodes an ortholog of miR-155. J Virol. 2007;81:12836–12845.
[119] Plazolles N, Humbert J, Vachot L, et al. Pivotal Advance: The promotion of soluble DC-SIGN release by inflammatory signals and its enhancement of cytomegalovirus-mediated cis-infection of myeloid dendritic cells. J Leukoc Biol. 2011;89:329–342.
[120] Walker JD, Maier CL, Pober JS. Cytomegalovirus-infected human endothelial cells can stimulate allogeneic CD4+ memory T cells by releasing antigenic exosomes. J Immunol. 2009;182:1548–1559.
[121] Casseb SM, Simith DB, Melo KF, et al. Drosha, DGCR8, and Dicer mRNAs are down-regulated in human cells infected with dengue virus 4, and play a role in viral pathogenesis. Genet Mol Res. 2016;15(2). DOI:10.4238/gmr.15027891.
[122] Pleet ML, Mathiesen A, DeMarino C, et al. Ebola VP40 in exosomes can cause immune cell dysfunction. Front Microbiol. 2016;7:1765.
[123] Pleet ML, DeMarino C, Lepene B, et al. The role of exosomal VP40 in Ebola virus disease. DNA Cell Biol. 2017;36:243–248.
[124] Ariza ME, Rivailler P, Glaser R, et al. Epstein-Barr virus encoded dUTPase containing exosomes modulate innate and adaptive immune responses in human dendritic cells and peripheral blood mononuclear cells. PLoS One 2013;8:e69827.
[125] Keryer-Bibens C, Pioche-Durieu C, Villemant C, et al. Exosomes released by EBV-infected nasopharyngeal carcinoma cells convey the viral latent membrane protein 1 and the immunomodulatory protein galectin 9. BMC Cancer. 2006;6:283.
[126] Pegtel DM, Cosmopoulos K, Thorley-Lawson DA, et al. Functional delivery of viral miRNAs via exosomes. Proc Natl Acad Sci USA. 2010;107:6328–6333.
[127] Raposo G, Nijman HW, Stoorvogel W, et al. B lymphocytes secrete antigen-presenting vesicles. J Exp Med. 1996;183:1161–1172.
[128] Vazirabadi G, Geiger TR, III WFC, Martin JM. Epstein–Barr virus latent membrane protein-1 (LMP-1) and lytic LMP-1 localization in plasma membrane-derived extracellular vesicles and intracellular virions. J General Virol. 2003;84:1997–2008.
[129] Pang M-F, Lin K-W, Peh S-C. The signaling pathways of Epstein-Barr virus-encoded latent membrane protein 2A (LMP2A) in latency and cancer. Cell Mol Biol Lett. 2009;14:222–247.
[130] Ceccarelli S, Visco V, Raffa S, et al. Epstein-Barr virus latent membrane protein 1 promotes concentration in multivesicular bodies of fibroblast growth factor 2 and its release through exosomes. Int J Cancer. 2007;121:1494–1506.
[131] Ansari MA, Singh VV, Dutta S, et al. Constitutive interferon-inducible protein 16-inflammasome activation during Epstein-Barr virus latency I, II, and III in B and epithelial cells. J Virol. 2013;87:8606–8623.

[132] Sato Y, Ochiai S, Murata T, et al. Elimination of LMP1-expressing cells from a monolayer of gastric cancer AGS cells. Oncotarget. 2017;8:39345–3955.

[133] Wiklander OPB, Nordin JZ, O'Loughlin A, et al. Extracellular vesicle in vivo biodistribution is determined by cell source, route of administration and targeting. J Extracell Vesicles. 2015;4:26316.

[134] Wang Y, Zhang S, Song W, et al. Exosomes from EV71-infected oral epithelial cells can transfer miR-30a to promote EV71 infection. Oral Dis. 2020;26:778–788.

[135] Gu J, Wu J, Fang D, et al. Exosomes cloak the virion to transmit Enterovirus 71 non-lytically. Virulence. 2020;11: 32–38.

[136] Fu Y, Zhang L, Zhang F, et al. Exosome-mediated miR-146a transfer suppresses type I interferon response and facilitates EV71 infection. PLoS Pathog. 2017;13:e1006611.

[137] McKnight KL, Xie L, González-López O, et al. Protein composition of the hepatitis A virus quasi-envelope. Proc Natl Acad Sci USA. 2017;114:6587–6592.

[138] Jiang B, Himmelsbach K, Ren H, et al. Subviral hepatitis B virus filaments, like infectious viral particles, are released via multivesicular bodies. J Virol. 2016;90:3330–3341.

[139] Jia X, Chen J, Megger DA, et al. Label-free proteomic analysis of exosomes derived from inducible Hepatitis B virus-replicating HepAD38 cell line. Mol Cell Proteomics. 2017; 16:S144–S160.

[140] Bukong TN, Momen-Heravi F, Kodys K, et al. Exosomes from hepatitis C infected patients transmit HCV infection and contain replication competent viral RNA in complex with Ago2-miR122-HSP90. PLoS Pathog. 2014;10: e1004424.

[141] Dreux M, Garaigorta U, Boyd B, et al. Short-range exosomal transfer of viral RNA from infected cells to plasmacytoid dendritic cells triggers innate immunity. Cell Host Microbe. 2012;12:558–570.

[142] Xiao F, Fofana I, Heydmann L, et al. Hepatitis C virus cell-cell transmission and resistance to direct-acting antiviral agents. PLoS Pathog. 2014;10:e1004128.

[143] Ramakrishnaiah V, Thumann C, Fofana I, et al. Exosome-mediated transmission of hepatitis C virus between human hepatoma Huh7. 5 cells. Proc Natl Acad Sci USA2013;110:13109–13113.

[144] Devhare PB, Sasaki R, Shrivastava S, et al. Exosome-mediated intercellular communication between hepatitis C virus-infected hepatocytes and hepatic stellate cells. J Virol 2017;91:e02225–16.

[145] Henke JI, Goergen D, Zheng J, et al. microRNA-122 stimulates translation of hepatitis C virus RNA. EMBO J. 2008; 27:3300–3310.

[146] Jangra RK, Yi M, Lemon SM. Regulation of hepatitis C virus translation and infectious virus production by the microRNA miR-122. J Virol. 2010;84:6615–6625.

[147] Jopling CL. Regulation of hepatitis C virus by microRNA-122. Biochem Soc Trans. 2008;36:1220–1223.

[148] Khatun M, Ray RB. Mechanisms underlying hepatitis C virus-associated hepatic fibrosis. Cells. 2019;8.1249

[149] Shimakami T, Yamane D, Jangra RK, et al. Stabilization of hepatitis C virus RNA by an Ago2-miR-122 complex. Proc Natl Acad Sci USA. 2012;109:941–946.

[150] Okamoto T, Nishimura Y, Ichimura T, et al. Hepatitis C virus RNA replication is regulated by FKBP8 and Hsp90. EMBO J. 2006;25:5015–5025.

[151] Nagashima S, Takahashi M, Jirintai S, et al. The membrane on the surface of hepatitis E virus particles is derived from the intracellular membrane and contains trans-Golgi network protein 2. Arch Virol. 2014;159:979–991.

[152] Narayanan A, Iordanskiy S, Das R, et al. Exosomes derived from HIV-1-infected cells contain trans-activation response element RNA. J Biol Chem. 2013;288:20014–20033.

[153] Arenaccio C, Chiozzini C, Columba-Cabezas S, et al. Cell activation and HIV-1 replication in unstimulated CD4+ T lymphocytes ingesting exosomes from cells expressing defective HIV-1. Retrovirology. 2014;11:46.

[154] Bridgeman A, Maelfait J, Davenne T, et al. Viruses transfer the antiviral second messenger cGAMP between cells. Science. 2015;349:1228–1232.

[155] Columba Cabezas S, Federico M. Sequences within RNA coding for HIV-1 Gag p17 are efficiently targeted to exosomes. Cell Microbiol. 2013;15:412–429.

[156] Rezaie J, Aslan C, Ahmadi M, et al. The versatile role of exosomes in human retroviral infections: from immunopathogenesis to clinical application. Cell Biosci. 2021;11:19.

[157] Rozmyslowicz T, Majka M, Kijowski J, et al. Platelet- and megakaryocyte-derived microparticles transfer CXCR4 receptor to CXCR4-null cells and make them susceptible to infection by X4-HIV. AIDS. 2003;17:33–42.

[158] Gentili M, Kowal J, Tkach M, et al. Transmission of innate immune signaling by packaging of cGAMP in viral particles. Science. 2015;349:1232–1236.

[159] Mack M, Kleinschmidt A, Brühl H, et al. Transfer of the chemokine receptor CCR5 between cells by membrane-derived microparticles: a mechanism for cellular human immunodeficiency virus 1 infection. Nat Med. 2000;6: 769–775.

[160] Chiantore MV, Mangino G, Iuliano M, et al. Human papillomavirus E6 and E7 oncoproteins affect the expression of cancer-related microRNAs: additional evidence in HPV-induced tumorigenesis. J Cancer Res Clin Oncol. 2016;142: 1751–1763.

[161] Honegger A, Schilling D, Bastian S, et al. Dependence of intracellular and exosomal microRNAs on viral E6/E7 oncogene expression in HPV-positive tumor cells. PLoS Pathog. 2015;11:e1004712.

[162] Tong F, Andress A, Tang G, et al. Comprehensive profiling of extracellular RNA in HPV-induced cancers using an improved pipeline for small RNA-seq analysis. Sci Rep. 2020;10:19450.

[163] Sadri Nahand J, Moghoofei M, Salmaninejad A, et al. Pathogenic role of exosomes and microRNAs in HPV-mediated inflammation and cervical cancer: A review. Int J Cancer. 2020;146:305–320.

[164] Mata-Rocha M, Rodríguez-Hernández RM, Chávez-Olmos P, et al. Presence of HPV DNA in extracellular vesicles

from HeLa cells and cervical samples. Enfermedades Infecciosas Y Microbiologia Clinica. 2020;38:159–165.
[165] Guenat D, Hermetet F, Prétet J-L, et al. Exosomes and other extracellular vesicles in HPV transmission and carcinogenesis. Viruses. 2017;9.211
[166] Acevedo-Sánchez V, Rodríguez-Hernández RM, Aguilar-Ruíz SR, et al. Extracellular vesicles in cervical cancer and HPV infection. Membranes. 2021;11:453.
[167] Kalamvoki M, Deschamps T. Extracellular vesicles during Herpes Simplex virus type 1 infection: an inquire. Virol J. 2016;13:1–12.
[168] Alefantis T, Jain P, Ahuja J, et al. HTLV-1 tax nucleocytoplasmic shuttling, interaction with the secretory pathway, extracellular signaling, and implications for neurologic disease. J Biomed Sci. 2005;12:961–974.
[169] Martelli F, Mencarini J, Rocca A, et al. Polyomavirus microRNA in saliva reveals persistent infectious status in the oral cavity. Virus Res. 2018;249:1–7.
[170] Hoshina S, Sekizuka T, Kataoka M, et al. Profile of exosomal and intracellular microRNA in gamma-herpesvirus-infected lymphoma cell lines. PloS One. 2016;11:e0162574.
[171] Meckes DGJ, Gunawardena HP, Dekroon RM, et al. Modulation of B-cell exosome proteins by gamma herpesvirus infection. Proc Natl Acad Sci USA. 2013;110:E2925–33.
[172] Zheng J, Shi Y, Feng Z, et al. Oncogenic effects of exosomes in γ-herpesvirus-associated neoplasms. J Cell Physiol. 2019;234:19167–1979.
[173] Jeon H, Lee J, Lee S, et al. Extracellular vesicles from KSHV-infected cells stimulate antiviral immune response through mitochondrial DNA. Front Immunol. 2019;10:876.
[174] Jeon H, Yoo S-M, Choi HS, et al. Extracellular vesicles from KSHV-infected endothelial cells activate the complement system. Oncotarget. 2017;8:99841–99860.
[175] Singh VV, Kerur N, Bottero V, et al. Kaposi's sarcoma-associated herpesvirus latency in endothelial and B cells activates gamma interferon-inducible protein 16-mediated inflammasomes. J Virol. 2013;87:4417–4431.
[176] Chivero ET, Bhattarai N, Rydze RT, et al. Human pegivirus RNA is found in multiple blood mononuclear cells in vivo and serum-derived viral RNA-containing particles are infectious in vitro. J Gen Virol. 2014;95:1307.
[177] Chahar HS, Corsello T, Kudlicki AS, et al. Respiratory syncytial virus infection changes cargo composition of exosome released from airway epithelial cells. Sci Rep. 2018;8:1–18.
[178] Ahsan NA, Sampey GC, Lepene B, et al. Presence of viral RNA and proteins in exosomes from cellular clones resistant to rift valley fever virus infection. Front Microbiol. 2016;7:139.
[179] Kwon PS, Oh H, Kwon S-J, et al. Sulfated polysaccharides effectively inhibit SARS-CoV-2 in vitro. Cell Discov. 2020;6:1–4.
[180] Wan Y, Shang J, Graham R, et al. Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus. J Virol. 2020;94:e00127–20.
[181] Teng Y, Xu F, Zhang X, et al. Plant-derived exosomal microRNAs inhibit lung inflammation induced by exosomes SARS-CoV-2 Nsp12. Mol Ther. 2021;29:2424–2440.
[182] Owczarek K, Szczepanski A, Milewska A, et al. Early events during human coronavirus OC43 entry to the cell. Sci Rep. 2018;8:7124.
[183] Earnest JT, Hantak MP, Li K, et al. The tetraspanin CD9 facilitates MERS-coronavirus entry by scaffolding host cell receptors and proteases. PLoS Pathog. 2017;13:e1006546.
[184] Hassanpour M, Rezaie J, Nouri M, et al. The role of extracellular vesicles in COVID-19 virus infection. Infect Genet Evol. 2020;85:104422.
[185] Jabbari N, Karimipour M, Khaksar M, et al. Tumor-derived extracellular vesicles: insights into bystander effects of exosomes after irradiation. Lasers Med Sci. 2020;35:531–545.
[186] Vignolini T, Macera L, Antonelli G, et al. Investigation on torquetenovirus (TTV) microRNA transcriptome in vivo. Virus Res. 2016;217:18–22.
[187] Martelli F, Macera L, Spezia PG, et al. Torquetenovirus detection in exosomes enriched vesicles circulating in human plasma samples. Virol J. 2018;15:1–10.
[188] Tiku V, Kofoed EM, Yan D, et al. Outer membrane vesicles containing OmpA induce mitochondrial fragmentation to promote pathogenesis of Acinetobacter baumannii. Sci Rep. 2021;11:618.
[189] Skerniškytė J, Karazijaitė E, Lučiūnaitė A, et al. OmpA protein-deficient acinetobacter baumannii outer membrane vesicles trigger reduced inflammatory response. Pathogens. 2021;10.407
[190] Jin JS, Kwon S-O, Moon DC, et al. Acinetobacter baumannii secretes cytotoxic outer membrane protein A via outer membrane vesicles. PLoS One. 2011;6:e17027.
[191] Kwon S-O, Gho YS, Lee JC, et al. Proteome analysis of outer membrane vesicles from a clinical Acinetobacter baumannii isolate. FEMS Microbiol Lett. 2009;297:150–156.
[192] Li Z-T, Zhang R-L, Bi X-G, et al. Outer membrane vesicles isolated from two clinical Acinetobacter baumannii strains exhibit different toxicity and proteome characteristics. Microb Pathog. 2015;81:46–52.
[193] Chatterjee S, Mondal A, Mitra S, et al. Acinetobacter baumannii transfers the blaNDM-1 gene via outer membrane vesicles. J Antimicrob Chemother. 2017;72:2201–2207.
[194] Nho JS, Jun SH, Oh MH, et al. Acinetobacter nosocomialis secretes outer membrane vesicles that induce epithelial cell death and host inflammatory responses. Microb Pathog. 2015;81:39–45.
[195] Fulsundar S, Kulkarni HM, Jagannadham MV, et al. Molecular characterization of outer membrane vesicles released from acinetobacter radioresistens and their potential roles in pathogenesis. Microb Pathog. 2015;83–84:12–22.
[196] Demuth DR, James D, Kowashi Y, et al. Interaction of actinobacillus actinomycetemcomitans outer membrane vesicles with HL60 cells does not require leukotoxin. Cell Microbiol. 2003;5:111–121.
[197] Kato S, Kowashi Y, Demuth DR. Outer membrane-like vesicles secreted by Actinobacillus

actinomycetemcomitans are enriched in leukotoxin. Microb Pathog. 2002;32:1–13.

[198] Goulhen F, Hafezi A, Uitto VJ, et al. Subcellular localization and cytotoxic activity of the GroEL-like protein isolated from Actinobacillus actinomycetemcomitans. Infect Immun. 1998;66:5307–5313.

[199] Nowotny A, Behling UH, Hammond B, et al. Release of toxic microvesicles by Actinobacillus actinomycetemcomitans. Infect Immun. 1982;37:151–154.

[200] Rompikuntal PK, Thay B, Khan MK, et al. Perinuclear localization of internalized outer membrane vesicles carrying active cytolethal distending toxin from Aggregatibacter actinomycetemcomitans. Infect Immun. 2012;80:31–42.

[201] Thay B, Damm A, Kufer TA, et al. Aggregatibacter actinomycetemcomitans outer membrane vesicles are internalized in human host cells and trigger NOD1- and NOD2-dependent NF-κB activation. Infect Immun. 2014;82:4034–4046.

[202] Kieselbach T, Zijnge V, Granström E, et al. Proteomics of Aggregatibacter actinomycetemcomitans outer membrane vesicles. PLoS One. 2015;10:e0138591.

[203] Choi J-W, Kim S-C, Hong S-H, et al. Secretable small RNAs via outer membrane vesicles in periodontal pathogens. J Dent Res. 2017;96:458–466.

[204] Rivera J, Cordero RJB, Nakouzi AS, et al. Bacillus anthracis produces membrane-derived vesicles containing biologically active toxins. Proc Natl Acad Sci USA. 2010;107:19002–19007.

[205] Patrick S, McKenna JP, O'Hagan S, et al. A comparison of the haemagglutinating and enzymic activities of bacteroides fragilis whole cells and outer membrane vesicles. Microb Pathog. 1996;20:191–202.

[206] Shen Y, Torchia MLG, Lawson GW, et al. Outer membrane vesicles of a human commensal mediate immune regulation and disease protection. Cell Host Microbe. 2012;12:509–520.

[207] Zakharzhevskaya NB, Tsvetkov VB, Vanyushkina AA, et al. Interaction of bacteroides fragilis toxin with outer membrane vesicles reveals new mechanism of its secretion and delivery. Front Cell Infect Microbiol. 2017;7:2.

[208] Forsberg CW, Beveridge TJ, Hellstrom A. Cellulase and xylanase release from bacteroides succinogenes and its importance in the rumen environment. Appl Environ Microbiol. 1981;42:886–896.

[209] Stentz R, Horn N, Cross K, et al. Cephalosporinases associated with outer membrane vesicles released by Bacteroides spp. protect gut pathogens and commensals against β-lactam antibiotics. J Antimicrob Chemother. 2015;70:701–709.

[210] Roden JA, Wells DH, Chomel BB, et al. Hemin binding protein C is found in outer membrane vesicles and protects Bartonella henselae against toxic concentrations of hemin. Infect Immun. 2012;80:929–942.

[211] Bottero D, Gaillard ME, Errea A, et al. Outer membrane vesicles derived from Bordetella parapertussis as an acellular vaccine against Bordetella parapertussis and Bordetella pertussis infection. Vaccine. 2013;31:5262–5268.

[212] Hozbor D, Rodriguez ME, Fernández J, et al. Release of outer membrane vesicles from Bordetella pertussis. Curr Microbiol. 1999;38:273–278.

[213] Nasso M, Fedele G, Spensieri F, et al. Genetically detoxified pertussis toxin induces Th1/Th17 immune response through MAPKs and IL-10-dependent mechanisms. J Immunol. 2009;183:1892–1899.

[214] Ormazábal M, Bartel E, Gaillard ME, et al. Characterization of the key antigenic components of pertussis vaccine based on outer membrane vesicles. Vaccine. 2014;32:6084–6090.

[215] Gasperini G, Arato V, Pizza M, et al. Physiopathological roles of spontaneously released outer membrane vesicles of Bordetella pertussis. Future Microbiol. 2017;12:1247–1259.

[216] Dorward DW, Schwan TG, Garon CF. Immune capture and detection of Borrelia burgdorferi antigens in urine, blood, or tissues from infected ticks, mice, dogs, and humans. J Clin Microbiol. 1991;29:1162–1170.

[217] Shoberg RJ, Thomas DD. Specific adherence of Borrelia burgdorferi extracellular vesicles to human endothelial cells in culture. Infect Immun. 1993;61:3892–3900.

[218] Toledo A, Coleman JL, Kuhlow CJ, et al. The enolase of Borrelia burgdorferi is a plasminogen receptor released in outer membrane vesicles. Infect Immun. 2012;80:359–368.

[219] Yang X, Promnares K, Qin J, et al. Characterization of multiprotein complexes of the Borrelia burgdorferi outer membrane vesicles. J Proteome Res. 2011;10:4556–4566.

[220] Malge A, Ghai V, Reddy PJ, et al. mRNA transcript distribution bias between Borrelia burgdorferi bacteria and their outer membrane vesicles. FEMS Microbiol Lett. 2018;365:fny135.

[221] Gamazo C, Moriyón I. Release of outer membrane fragments by exponentially growing Brucella melitensis cells. Infect Immun. 1987;55:609–615.

[222] Allan ND, Kooi C, Sokol PA, et al. Putative virulence factors are released in association with membrane vesicles from Burkholderia cepacia. Can J Microbiol. 2003;49:613–624.

[223] Lindmark B, Rompikuntal PK, Vaitkevicius K, et al. Outer membrane vesicle-mediated release of cytolethal distending toxin (CDT) from Campylobacter jejuni. BMC Microbiol. 2009;9:220.

[224] Jang K-S, Sweredoski MJ, Graham RLJ, et al. Comprehensive proteomic profiling of outer membrane vesicles from Campylobacter jejuni. J Proteomics. 2014;98:90–98.

[225] Elmi A, Nasher F, Jagatia H, et al. Campylobacter jejuni outer membrane vesicle-associated proteolytic activity promotes bacterial invasion by mediating cleavage of intestinal epithelial cell E-cadherin and occludin. Cell Microbiol. 2016;18:561–572.

[226] Wai SN, Lindmark B, Söderblom T, et al. Vesicle-mediated export and assembly of pore-forming oligomers of the enterobacterial ClyA cytotoxin. Cell. 2003;115:25–35.

[227] Horstman AL, Kuehn MJ. Enterotoxigenic Escherichia coli secretes active heat-labile enterotoxin via outer membrane vesicles. J Biol Chem. 2000;275:12489–12496.

[228] Kesty NC, Mason KM, Reedy M, et al. Enterotoxigenic Escherichia coli vesicles target toxin delivery into mammalian cells. EMBO J. 2004;23:4538–4549.
[229] Wai SN, Takade A, Amako K. The release of outer membrane vesicles from the strains of enterotoxigenic Escherichia coli. Microbiol Immunol. 1995;39:451–456.
[230] Roy K, Hamilton DJ, Munson GP, et al. Outer membrane vesicles induce immune responses to virulence proteins and protect against colonization by enterotoxigenic Escherichia coli. Clin Vaccine Immunol. 2011;18: 1803–1808.
[231] Rivas ZP, Talbot KM, Merselis LC, et al. CexE is a coat protein and virulence factor of diarrheagenic pathogens. Front Microbiol 2020;11:1374.
[232] Orench-Rivera N, Kuehn MJ. Differential packaging into outer membrane vesicles upon oxidative stress reveals a general mechanism for cargo selectivity. Front Microbiol. 2021;12:561863.
[233] Balsalobre C, Silván JM, Berglund S, et al. Release of the type I secreted alpha-haemolysin via outer membrane vesicles from Escherichia coli. Mol Microbiol. 2006;59: 99–112.
[234] Scorza FB, Doro F, Rodríguez-Ortega MJ, et al. Proteomics characterization of outer membrane vesicles from the extraintestinal pathogenic Escherichia coli ΔtolR IHE3034 mutant. Mol Cell Proteom. 2008;7:473–85.
[235] Yokoyama K, Horii T, Yamashino T, et al. Production of shiga toxin by Escherichia coli measured with reference to the membrane vesicle-associated toxins. FEMS Microbiol Lett. 2000;192:139–44.
[236] Kolling GL, Matthews KR. Export of virulence genes and Shiga toxin by membrane vesicles of Escherichia coli O157:H7. Appl Environ Microbiol. 1999;65:1843–8.
[237] Kouokam JC, Wai SN, Fällman M, et al. Active cytotoxic necrotizing factor 1 associated with outer membrane vesicles from uropathogenic Escherichia coli. Infect Immun. 2006;74:2022–30.
[238] Sampath V, McCaig WD, Thanassi DG. Amino acid deprivation and central carbon metabolism regulate the production of outer membrane vesicles and tubes by Francisella. Mol Microbiol. 2018;107:523–41.
[239] Klimentova J, Pavkova I, Horcickova L, et al. Francisella tularensis subsp. holarctica releases differentially loaded outer membrane vesicles under various stress conditions. Front Microbiol 2019;10:2304.
[240] Liu J, Hsieh C-L, Gelincik O, et al. Proteomic characterization of outer membrane vesicles from gut mucosa-derived fusobacterium nucleatum. J Proteomics. 2019;195:125–37.
[241] Maldonado R, Wei R, Kachlany SC, et al. Cytotoxic effects of Kingella kingae outer membrane vesicles on human cells. Microb Pathog. 2011;51:22–30.
[242] Zhang J, Zhao J, Li J, et al. Outer membrane vesicles derived from hypervirulent Klebsiella pneumoniae stimulate the inflammatory response. Microb Pathog. 2021;154: 104841.
[243] Hua Y, Wang J, Huang M, et al. Outer membrane vesicles-transmitted virulence genes mediate the emergence of new antimicrobial-resistant hypervirulent Klebsiella pneumoniae. Emerg Microbes Infect. 2022;11:1281–92.
[244] Roier S, Blume T, Klug L, et al. A basis for vaccine development: Comparative characterization of Haemophilus influenzae outer membrane vesicles. Int J Med Microbiol. 2015;305:298–309.
[245] Schaar V, Uddbäck I, Nordström T, et al. Group A streptococci are protected from amoxicillin-mediated killing by vesicles containing β-lactamase derived from Haemophilus influenzae. J Antimicrob Chemother. 2014; 69:117–20.
[246] Ismail S, Hampton MB, Keenan JI. Helicobacter pylori outer membrane vesicles modulate proliferation and interleukin-8 production by gastric epithelial cells. Infect Immun. 2003;71:5670–5.
[247] Keenan JI, Allardyce RA. Iron influences the expression of Helicobacter pylori outer membrane vesicle-associated virulence factors. Eur J Gastroenterol Hepatol. 2000;12: 1267–73.
[248] Keenan J, Day T, Neal S, et al. A role for the bacterial outer membrane in the pathogenesis of Helicobacter pylori infection. FEMS Microbiol Lett. 2000;182:259–64.
[249] Hynes SO, Keenan JI, Ferris JA, et al. Lewis epitopes on outer membrane vesicles of relevance to Helicobacter pylori pathogenesis. Helicobacter. 2005;10:146–156.
[250] Fiocca R, Necchi V, Sommi P, et al. Release of Helicobacter pylori vacuolating cytotoxin by both a specific secretion pathway and budding of outer membrane vesicles. Uptake of released toxin and vesicles by gastric epithelium. J Pathol. 1999;188:220–226.
[251] Mullaney E, Brown PA, Smith SM, et al. Proteomic and functional characterization of the outer membrane vesicles from the gastric pathogen Helicobacter pylori. Proteomics Clin Appl. 2009;3:785–796.
[252] Olofsson A, Vallström A, Petzold K, et al. Biochemical and functional characterization of Helicobacter pylori vesicles. Mol Microbiol. 2010;77:1539–1555.
[253] Zhang H, Zhang Y, Song Z, et al. sncRNAs packaged by Helicobacter pylori outer membrane vesicles attenuate IL-8 secretion in human cells. Int J Med Microbiol. 2020;310: 151356.
[254] Zavan L, Bitto NJ, Johnston EL, et al. Helicobacter pylori growth stage determines the size, protein composition, and preferential cargo packaging of outer membrane vesicles. Proteomics. 2019;19:e1800209.
[255] Ronci M, del Prete S, Puca V, et al. Identification and characterization of the α-CA in the outer membrane vesicles produced by helicobacter pylori. J Enzyme Inhib Med Chem. 2019;34:189–95.
[256] Melo J, Pinto V, Fernandes T, et al. Isolation method and characterization of outer membranes vesicles of helicobacter pylori grown in a chemically defined medium. Front Microbiol. 2021;12:654193.
[257] Fernandez-Moreira E, Helbig JH, Swanson MS. Membrane vesicles shed by Legionella pneumophila inhibit fusion of phagosomes with lysosomes. Infect Immun. 2006;74: 3285–95.

[258] Galka F, Wai SN, Kusch H, et al. Proteomic characterization of the whole secretome of Legionella pneumophila and functional analysis of outer membrane vesicles. Infect Immun. 2008;76:1825–1836.

[259] Nally JE, Whitelegge JP, Aguilera R, et al. Purification and proteomic analysis of outer membrane vesicles from a clinical isolate of Leptospira interrogans serovar Copenhageni. Proteomics. 2005;5:144–152.

[260] Coelho C, Brown L, Maryam M, et al. Listeria monocytogenes virulence factors, including listeriolysin O, are secreted in biologically active extracellular vesicles. J Biol Chem. 2019;294:1202–1217.

[261] Tan TT, Morgelin M, Forsgren A, et al. Haemophilus influenzae survival during complement-mediated attacks is promoted by Moraxella catarrhalis outer membrane vesicles. J Infect Dis. 2007;195:1661–1670.

[262] Schaar V, Nordström T, Mörgelin M, et al. Moraxella catarrhalis outer membrane vesicles carry β-lactamase and promote survival of Streptococcus pneumoniae and Haemophilus influenzae by inactivating amoxicillin. Antimicrob Agents Chemother. 2011;55:3845–3853.

[263] Vidakovics MLAP, Jendholm J, Mörgelin M, et al. B cell activation by outer membrane vesicles–a novel virulence mechanism. PLoS Pathog. 2010;6:e1000724.

[264] Lee J, Kim S-H, Choi D-S, et al. Proteomic analysis of extracellular vesicles derived from Mycobacterium tuberculosis. Proteomics. 2015;15:3331–7.

[265] Athman JJ, Wang Y, McDonald DJ, et al. Bacterial membrane vesicles mediate the release of mycobacterium tuberculosis lipoglycans and lipoproteins from infected macrophages. J Immunol. 2015;195:1044–1053.

[266] Zielke RA, Wierzbicki IH, Weber J v, et al. Quantitative proteomics of the Neisseria gonorrhoeae cell envelope and membrane vesicles for the discovery of potential therapeutic targets. Mol Cell Proteomics. 2014;13:1299–1317.

[267] Bjerre A, Brusletto B, Rosenqvist E, et al. Cellular activating properties and morphology of membrane-bound and purified meningococcal lipopolysaccharide. J Endotoxin Res. 2000;6:437–445.

[268] Schlichting E, Lyberg T, Solberg O, et al. Endotoxin liberation from Neisseria meningitidis correlates to their ability to induce procoagulant and fibrinolytic factors in human monocytes. Scand J Infect Dis. 1993;25:585–594.

[269] Masignani V, Balducci E, di Marcello F, et al. NarE: a novel ADP-ribosyltransferase from Neisseria meningitidis. Mol Microbiol. 2003;50:1055–1067.

[270] Vipond C, Suker J, Jones C, et al. Proteomic analysis of a meningococcal outer membrane vesicle vaccine prepared from the group B strain NZ98/254. Proteomics. 2006;6:3400–3413.

[271] Williams JN, Skipp PJ, Humphries HE, et al. Proteomic analysis of outer membranes and vesicles from wild-type serogroup B Neisseria meningitidis and a lipopolysaccharide-deficient mutant. Infect Immun. 2007;75:1364–1372.

[272] Lappann M, Otto A, Becher D, et al. Comparative proteome analysis of spontaneous outer membrane vesicles and purified outer membranes of Neisseria meningitidis. J Bacteriol. 2013;195:4425–4435.

[273] Grenier D. Inactivation of human serum bactericidal activity by a trypsinlike protease isolated from Porphyromonas gingivalis. Infect Immun. 1992;60:1854–1857.

[274] Duncan L, Yoshioka M, Chandad F, et al. Loss of lipopolysaccharide receptor CD14 from the surface of human macrophage-like cells mediated by Porphyromonas gingivalis outer membrane vesicles. Microb Pathog. 2004;36:319–325.

[275] Grenier D, Mayrand D. Functional characterization of extracellular vesicles produced by Bacteroides gingivalis. Infect Immun. 1987;55:111–117.

[276] Kamaguchi A, Ohyama T, Sakai E, et al. Adhesins encoded by the gingipain genes of Porphyromonas gingivalis are responsible for co-aggregation with Prevotella intermedia. Microbiology. 2003;149:1257–64.

[277] Mantri CK, Chen C-H, Dong X, et al. Fimbriae-mediated outer membrane vesicle production and invasion of Porphyromonas gingivalis. Microbiologyopen. 2015;4:53–65.

[278] Veith PD, Chen Y-Y, Gorasia DG, et al. Porphyromonas gingivalis outer membrane vesicles exclusively contain outer membrane and periplasmic proteins and carry a cargo enriched with virulence factors. J Proteome Res. 2014;13:2420–2432.

[279] Haurat MF, Aduse-Opoku J, Rangarajan M, et al. Selective sorting of cargo proteins into bacterial membrane vesicles. J Biol Chem. 2011;286:1269–1276.

[280] Nakao R, Takashiba S, Kosono S, et al. Effect of Porphyromonas gingivalis outer membrane vesicles on gingipain-mediated detachment of cultured oral epithelial cells and immune responses. Microbes Infect. 2014;16:6–16.

[281] Ho M-H, Chen C-H, Goodwin JS, et al. Functional advantages of porphyromonas gingivalis vesicles. PLoS One. 2015;10:e0123448.

[282] Zhang Z, Liu S, Zhang S, et al. Porphyromonas gingivalis outer membrane vesicles inhibit the invasion of Fusobacterium nucleatum into oral epithelial cells by downregulating FadA and FomA. J Periodontol. 2022;93:515–525.

[283] Bauman SJ, Kuehn MJ. Purification of outer membrane vesicles from Pseudomonas aeruginosa and their activation of an IL-8 response. Microbes Infect. 2006;8:2400–2408.

[284] Ciofu O, Beveridge TJ, Kadurugamuwa J, et al. Chromosomal beta-lactamase is packaged into membrane vesicles and secreted from Pseudomonas aeruginosa. J Antimicrob Chemother. 2000;45:9–13.

[285] Cota-Gomez A, Vasil AI, Kadurugamuwa J, et al. PlcR1 and PlcR2 are putative calcium-binding proteins required for secretion of the hemolytic phospholipase C of Pseudomonas aeruginosa. Infect Immun. 1997;65:2904–2913.

[286] Kadurugamuwa JL, Beveridge TJ. Virulence factors are released from Pseudomonas aeruginosa in association with membrane vesicles during normal growth and exposure to gentamicin: a novel mechanism of enzyme secretion. J Bacteriol. 1995;177:3998–4008.

[287] MacEachran DP, Ye S, Bomberger JM, et al. The Pseudomonas aeruginosa secreted protein PA2934 decreases apical membrane expression of the cystic fibrosis transmembrane conductance regulator. Infect Immun. 2007;75:3902–3912.

[288] Mashburn LM, Whiteley M. Membrane vesicles traffic signals and facilitate group activities in a prokaryote. Nature. 2005;437:422–425.

[289] Li Z, Clarke AJ, Beveridge TJ. Gram-negative bacteria produce membrane vesicles which are capable of killing other bacteria. J Bacteriol. 1998;180:5478–5483.

[290] Koeppen K, Barnaby R, Jackson AA, et al. Tobramycin reduces key virulence determinants in the proteome of Pseudomonas aeruginosa outer membrane vesicles. PLoS One. 2019;14:e0211290.

[291] Koeppen K, Hampton TH, Jarek M, et al. A novel mechanism of host-pathogen interaction through sRNA in bacterial outer membrane vesicles. PLoS Pathog. 2016;12: e1005672.

[292] Bette-Bobillo P, Giro P, Sainte-Marie J, et al. Exoenzyme S from P. aeruginosa ADP ribosylates rab4 and inhibits transferrin recycling in SLO-permeabilized reticulocytes. Biochem Biophys Res Commun. 1998;244:336–341.

[293] Bergman MA, Cummings LA, Barrett SLR, et al. CD4+ T cells and toll-like receptors recognize Salmonella antigens expressed in bacterial surface organelles. Infect Immun. 2005;73:1350–1356.

[294] Malabirade A, Habier J, Heintz-Buschart A, et al. The RNA complement of outer membrane vesicles from Salmonella enterica serovar typhimurium under distinct culture conditions. Front Microbiol. 2018;9:2015.

[295] Yoon H, Ansong C, Adkins JN, et al. Discovery of Salmonella virulence factors translocated via outer membrane vesicles to murine macrophages. Infect Immun. 2011;79:2182–2192.

[296] Yang J, Hwang I, Lee E, et al. Bacterial outer membrane vesicle-mediated cytosolic delivery of flagellin triggers host NLRC4 canonical inflammasome ignaling. Front Immunol. 2020;11:581165.

[297] Kim SI, Kim S, Kim E, et al. Secretion of Salmonella pathogenicity island 1-encoded type III secretion system effectors by outer membrane vesicles in Salmonella enterica serovar typhimurium. Front Microbiol. 2018;9:2810.

[298] Dutta S, Iida K, Takade A, et al. Release of Shiga toxin by membrane vesicles in Shigella dysenteriae serotype 1 strains and in vitro effects of antimicrobials on toxin production and release. Microbiol Immunol. 2004;48:965.

[299] Kadurugamuwa JL, Beveridge TJ. Delivery of the non-membrane-permeative antibiotic gentamicin into mammalian cells by using Shigella flexneri membrane vesicles. Antimicrob Agents Chemother. 1998;42:1476–83.

[300] Hong S-W, Kim M-R, Lee E-Y, et al. Extracellular vesicles derived from Staphylococcus aureus induce atopic dermatitis-like skin inflammation. Allergy. 2011;66:351–359.

[301] Lee J, Lee E-Y, Kim S-H, et al. Staphylococcus aureus extracellular vesicles carry biologically active β-lactamase. Antimicrob Agents Chemother. 2013;57:2589–2595.

[302] Lee E-Y, Choi D-Y, Kim D-K, et al. Gram-positive bacteria produce membrane vesicles: proteomics-based characterization of Staphylococcus aureus-derived membrane vesicles. Proteomics. 2009;9:5425–5436.

[303] Kim M, Hong S, Choi E, et al. S taphylococcus aureus-derived extracellular vesicles induce neutrophilic pulmonary inflammation via both T h1 and T h17 cell responses. Allergy. 2012;67:1271–1281.

[304] Chi B, Qi M, Kuramitsu HK. Role of dentilisin in Treponema denticola epithelial cell layer penetration. Res Microbiol. 2003;154:637–643.

[305] Rosen G, Naor R, Rahamim E, et al. Proteases of Treponema denticola outer sheath and extracellular vesicles. Infect Immun. 1995;63:3973–3979.

[306] Boardman BK, Meehan BM, Fullner Satchell KJ. Growth phase regulation of Vibrio cholerae RTX toxin export. J Bacteriol. 2007;189:1827–1835.

[307] Zingl FG, Thapa HB, Scharf M, et al. Outer membrane vesicles of vibrio cholerae protect and deliver active cholera toxin to host cells via porin-dependent uptake. mBio. 2021;12:e0053421.

[308] Rompikuntal PK, Vdovikova S, Duperthuy M, et al. Outer membrane vesicle-mediated export of processed PrtV protease from vibrio cholerae. PLoS One. 2015;10:e0134098.

[309] Rasti ES, Brown AC. Cholera toxin encapsulated within several vibrio cholerae O1 serotype inaba outer membrane vesicles lacks a functional B-subunit. Toxins. (Basel) 2019;11:207.

[310] Sjöström AE, Sandblad L, Uhlin BE, et al. Membrane vesicle-mediated release of bacterial RNA. Sci Rep. 2015;5: 15329.

[311] Fang Y, Wang Z, Liu X, et al. Biogenesis and biological functions of extracellular vesicles in cellular and organismal communication with microbes. Front Microbiol. 2022; 18:414.

[312] Liu H, Geng Z, Su J. Engineered mammalian and bacterial extracellular vesicles as promising nanocarriers for targeted therapy. Extracell Vesicles Circ Nucl Acids. 2022;3: 63–86.

[313] Ellis TN, Kuehn MJ. Virulence and immunomodulatory roles of bacterial outer membrane vesicles. Microbiol Mol Biol Rev. 2010;74:81–94.

[314] Alaniz RC, Deatherage BL, Lara JC, et al. Membrane vesicles are immunogenic facsimiles of Salmonella typhimurium that potently activate dendritic cells, prime B and T cell responses, and stimulate protective immunity in vivo. J Immunol 2007;179:7692–701.

[315] Durand V, MacKenzie J, Leon J, et al. Role of lipopolysaccharide in the induction of type I interferon-dependent cross-priming and IL-10 production in mice by meningococcal outer membrane vesicles. Vaccine 2009;27:1912–22.

[316] Opal SM. The host response to endotoxin, antilipopolysaccharide strategies, and the management of severe sepsis. Inter J Medical Microbiol. 2007;297:365–377.

[317] Renelli M, Matias V, Lo RY, et al. DNA-containing membrane vesicles of Pseudomonas aeruginosa PAO1 and their genetic transformation potential. Microbiology. 2004; 150 (Pt. 7): 2161–2169.

[318] MacDonald IA, Kuehn MJ. Stress-induced outer membrane vesicle production by Pseudomonas aeruginosa. J Bacteriol. 2013;195:2971.

[319] Uehara T, Park JT. An anhydro-N-acetylmuramyl-L-alanine amidase with broad specificity tethered to the outer membrane of Escherichia coli. J Bacteriol. 2007;189: 5634–5641.

[320] Klein G, Kobylak N, Lindner B, et al. Assembly of lipopolysaccharide in Escherichia coli requires the essential LapB heat shock protein. J Biol Chem. 2014;289:14829–14853.

[321] Maredia R, Devineni N, Lentz P, et al. Vesiculation from Pseudomonas aeruginosa under SOS. Scientific World J. 2012;2012:402919.

[322] Aebi C, Stone B, Beucher M, et al. Expression of the CopB outer membrane protein by Moraxella catarrhalis is regulated by iron and affects iron acquisition from transferrin and lactoferrin. Infect Immun. 1996;64:2024–2030.

[323] Myers LE, Yang Y, Du R, et al. The transferrin binding protein B of Moraxella catarrhalis elicits bactericidal antibodies and is a potential vaccine antigen. Infect Immun. 1998; 66:4183–4192.

[324] Schaar V, Vries SPW de, Vidakovics MLAP, et al. Multicomponent Moraxella catarrhalis outer membrane vesicles induce an inflammatory response and are internalized by human epithelial cells. Cell Microbiol. 2011;13: 432–449.

[325] Hickey CA, Kuhn KA, Donermeyer DL, et al. Colitogenic Bacteroides thetaiotaomicron antigens access host immune cells in a sulfatase-dependent manner via outer membrane vesicles. Cell Host Microbe. 2015;17:672–680.

[326] Rakoff-Nahoum S, Coyne M, Comstock L. An ecological network of polysaccharide utilization among human intestinal symbionts. Current Biology. 2014;24:40–49.

[327] Manning AJ, Kuehn MJ. Contribution of bacterial outer membrane vesicles to innate bacterial defense. BMC Microbiol. 2011;11:1–15.

[328] Kulkarni HM, Swamy CVB, Jagannadham M v. Molecular characterization and functional analysis of outer membrane vesicles from the antarctic bacterium Pseudomonas syringae suggest a possible response to environmental conditions. J Proteome Res. 2014;13:1345–1358.

[329] Lee JH, Choi C-W, Lee T, et al. Transcription factor σB plays an important role in the production of extracellular membrane-derived vesicles in Listeria monocytogenes. PLoS One. 2013;8:e73196.

[330] Fulsundar S, Harms K, Flaten GE, et al. Gene transfer potential of outer membrane vesicles of Acinetobacter baylyi and effects of stress on vesiculation. Appl Environ Microbiol. 2014;80:3469–3483.

[331] Briaud P, Carroll RK. Extracellular vesicle biogenesis and functions in gram-positive bacteria. Infect Immun. 2020; 88:e00433-20.

[332] Schrempf H, Koebsch I, Walter S, et al. Extracellular Streptomyces vesicles: amphorae for survival and defence. Microb Biotechnol. 2011;4:286–299.

[333] Jiang Y, Kong Q, Roland KL, III Membrane vesicles of Clostridium perfringens type A strains induce innate and adaptive immunity. Inter J Medical Microbiol. 2014;304: 431–443.

[334] Liao S, Klein MI, Heim KP, et al. Streptococcus mutans extracellular DNA is upregulated during growth in biofilms, actively released via membrane vesicles, and influenced by components of the protein secretion machinery. J Bacteriol. 2014;196:2355–2366.

[335] Olaya-Abril A, Prados-Rosales R, McConnell MJ, et al. Characterization of protective extracellular membrane-derived vesicles produced by Streptococcus pneumoniae. J Proteomics. 2014;106:46–60.

[336] Yang X, Shi G, Guo J, et al. Exosome-encapsulated antibiotic against intracellular infections of methicillin-resistant Staphylococcus aureus. Int J Nanomedicine. 2018;13: 8095.

[337] Rodrigues ML, Nimrichter L, Oliveira DL, et al. Vesicular polysaccharide export in Cryptococcus neoformans is a eukaryotic solution to the problem of fungal trans-cell wall transport. Eukaryot Cell. 2007;6:48–59.

[338] Rizzo J, Rodrigues ML, Janbon G. Extracellular vesicles in fungi: past, present, and future perspectives. Front Cell Infect Microbiol. 2020;15:346.

[339] Wolf JM, Casadevall A. Challenges posed by extracellular vesicles from eukaryotic microbes. Curr Opin Microbiol. 2014;22:73–78.

[340] Rodrigues ML, Franzen AJ, Nimrichter L, et al. Vesicular mechanisms of traffic of fungal molecules to the extracellular space. Curr Opin Microbiol. 2013;16:414–420.

[341] Oliveira DL, Nakayasu ES, Joffe LS, et al. Characterization of yeast extracellular vesicles: evidence for the participation of different pathways of cellular traffic in vesicle biogenesis. PLoS One. 2010;5:e11113.

[342] Zamith-Miranda D, Nimrichter L, Rodrigues ML, et al. Fungal extracellular vesicles: modulating host-pathogen interactions by both the fungus and the host. Microbes Infect. 2018;20:501–504.

[343] Matos Baltazar L, Nakayasu ES, Sobreira TJP, et al. Antibody binding alters the characteristics and contents of extracellular vesicles released by histoplasma capsulatum. mSphere. 2016;1(2):e00085–15.

[344] Vargas G, Rocha JDB, Oliveira DL, et al. Compositional and immunobiological analyses of extracellular vesicles released by C andida albicans. Cell Microbiol. 2015;17: 389–407.

[345] Rodrigues ML, Nakayasu ES, Oliveira DL, et al. Extracellular vesicles produced by Cryptococcus neoformans contain protein components associated with virulence. Eukaryot Cell. 2008;7:58–67.

[346] da Silva RP, Puccia R, Rodrigues ML, et al. Extracellular vesicle-mediated export of fungal RNA. Sci Rep. 2015;5: 1–12.

[347] Gehrmann U, Qazi KR, Johansson C, et al. Nanovesicles from Malassezia sympodialis and host exosomes induce cytokine responses–novel mechanisms for host-microbe interactions in atopic eczema. PLoS One. 2011;6:e21480.

[348] Barbosa MS, Báo SN, Andreotti PF, et al. Glyceraldehyde-3-phosphate dehydrogenase of Paracoccidioides brasiliensis is a cell surface protein involved in fungal adhesion to

extracellular matrix proteins and interaction with cells. Infect Immun. 2006;74:382–389.
[349] Vallejo MC, Nakayasu ES, Matsuo AL, et al. Vesicle and vesicle-free extracellular proteome of Paracoccidioides brasiliensis: comparative analysis with other pathogenic fungi. J Proteome Res. 2012;11:1676–1685.
[350] Nimrichter L, Souza MM, de Poeta M, et al. Extracellular vesicle-associated transitory cell wall components and their impact on the interaction of fungi with host cells. Front Microbiol. 2016;7:1034.
[351] Cox GM, Mukherjee J, Cole GT, et al. Urease as a virulence factor in experimental cryptococcosis. Infect Immun. 2000; 68:443–448.
[352] Demasi APD, Pereira GAG, Netto LES. Yeast oxidative stress response: influences of cytosolic thioredoxin peroxidase I and of the mitochondrial functional state. FEBS J. 2006;273:805–816.
[353] Scheckelhoff M, Deepe GS. The protective immune response to heat shock protein 60 of Histoplasma capsulatum is mediated by a subset of Vβ8. 1/8.2+ T cells. J Immunol. 2002;169:5818–58126.
[354] Zancopé-Oliveira RM, Reiss E, Lott TJ, et al. Molecular cloning, characterization, and expression of the M antigen of Histoplasma capsulatum. Infect Immun. 1999;67: 1947–1953.
[355] Deepe GSJ, Gibbons R. Protective efficacy of H antigen from Histoplasma capsulatum in a murine model of pulmonary histoplasmosis. Infect Immun. 2001;69:3128–3134.
[356] Vallejo MC, Nakayasu ES, Longo LVG, et al. Lipidomic analysis of extracellular vesicles from the pathogenic phase of Paracoccidioides brasiliensis. PLoS One. 2012;7:e39463.
[357] Ikeda MAK, Almeida JRF de, Jannuzzi GP, et al. Extracellular vesicles from Sporothrix brasiliensis are an important virulence factor that induce an increase in fungal burden in experimental sporotrichosis. Front Microbiol. 2018;9:2286.
[358] Evans-Osses I, Reichembach LH, Ramirez MI. Exosomes or microvesicles? Two kinds of extracellular vesicles with different routes to modify protozoan-host cell interaction. Parasitol Res. 2015;114:3567–3575.
[359] Nievas YR, Lizarraga A, Salas N, et al. Extracellular vesicles released by anaerobic protozoan parasites: Current situation. Cell Microbiol. 2020;22:e13257.
[360] Hassani K, Shio MT, Martel C, et al. Absence of metalloprotease GP63 alters the protein content of Leishmania exosomes. PLoS One. 2014;9:e95007.
[361] Silverman JM, Clos J, de'Oliveira CC, et al. An exosome-based secretion pathway is responsible for protein export from Leishmania and communication with macrophages. J Cell Sci. 2010;123:842–852.
[362] Shio MT, Christian JG, Jung JY, et al. PKC/ROS-mediated NLRP3 inflammasome activation is attenuated by Leishmania zinc-metalloprotease during infection. PLoS Negl Trop Dis. 2015;9:e0003868.
[363] Lambertz U, Ovando MEO, Vasconcelos EJR, et al. Small RNAs derived from tRNAs and rRNAs are highly enriched in exosomes from both old and new world Leishmania providing evidence for conserved exosomal RNA Packaging. BMC Genomics. 2015;16:1–26.
[364] Leitherer S, Clos J, Liebler-Tenorio EM, et al. Characterization of the protein tyrosine phosphatase LmPRL-1 secreted by Leishmania major via the exosome pathway. Infect Immun. 2017;85:e00084-17.
[365] Torrecilhas ACT, Tonelli RR, Pavanelli WR, et al. Trypanosoma cruzi: parasite shed vesicles increase heart parasitism and generate an intense inflammatory response. Microbes Infect. 2009;11:29–39.
[366] Bayer-Santos E, Cunha-e-Silva NL, Yoshida N, et al. Expression and cellular trafficking of GP82 and GP90 glycoproteins during Trypanosoma cruzi metacyclogenesis. Parasit Vectors. 2013;6:1–10.
[367] Mantel P-Y, Hoang AN, Goldowitz I, et al. Malaria-infected erythrocyte-derived microvesicles mediate cellular communication within the parasite population and with the host immune system. Cell Host Microbe. 2013;13:521–534.
[368] Sisquella X, Ofir-Birin Y, Pimentel MA, et al. Malaria parasite DNA-harbouring vesicles activate cytosolic immune sensors. Nat Commun. 2017;8:1–15.
[369] Twu O, de Miguel N, Lustig G, et al. Trichomonas vaginalis exosomes deliver cargo to host cells and mediate host : parasite interactions. PLoS Pathog. 2013;9:e1003482.
[370] Olmos-Ortiz LM, Barajas-Mendiola MA, Barrios-Rodiles M, et al. Trichomonas vaginalis exosome-like vesicles modify the cytokine profile and reduce inflammation in parasite-infected mice. Parasite Immunol. 2017;39:e12426.
[371] Castelli G, Bruno F, Saieva L, et al. Exosome secretion by Leishmania infantum modulate the chemotactic behavior and cytokinic expression creating an environment permissive for early infection. Exp Parasitol. 2019;198:39–45.
[372] Gomez MA, Contreras I, Hallé M, et al. Leishmania GP63 alters host signaling through cleavage-activated protein tyrosine phosphatases. Sci Signal. 2009;2:ra58–ra58.
[373] Hallé M, Gomez MA, Stuible M, et al. The Leishmania surface protease GP63 cleaves multiple intracellular proteins and actively participates in p38 mitogen-activated protein kinase inactivation. J Biol Chem. 2009;284:6893–6908.
[374] Joshi PB, Kelly BL, Kamhawi S, et al. Targeted gene deletion in Leishmania major identifies leishmanolysin (GP63) as a virulence factor. Mol Biochem Parasitol. 2002;120: 33–40.
[375] Marshall S, Kelly PH, Singh BK, et al. Extracellular release of virulence factor major surface protease via exosomes in Leishmania infantum promastigotes. Parasit Vectors. 2018; 11:1–10.
[376] Silverman JM, Reiner NE. Exosomes and other microvesicles in infection biology: organelles with unanticipated phenotypes. Cell Microbiol. 2011;13:1–9.
[377] Yao C, Donelson JE, Wilson ME. The major surface protease (MSP or GP63) of Leishmania sp. Biosynthesis, regulation of expression, and function. Mol Biochem Parasitol. 2003;132:1–16.
[378] Mantel P, Marti M. The role of extracellular vesicles in P lasmodium and other protozoan parasites. Cell Microbiol. 2014;16:344–354.

[379] Sampaio NG, Emery SJ, Garnham AL, et al. Extracellular vesicles from early stage Plasmodium falciparum-infected red blood cells contain PfEMP1 and induce transcriptional changes in human monocytes. Cell Microbiol. 2018;20: e12822.

[380] Li Y, Liu Y, Xiu F, et al. Characterization of exosomes derived from Toxoplasma gondii and their functions in modulating immune responses. Int J Nanomedicine. 2018;13:467.

[381] Silva VO, Maia MM, Torrecilhas AC, et al. Extracellular vesicles isolated from Toxoplasma gondii induce host immune response. Parasite Immunol. 2018;40:e12571.

[382] Szempruch AJ, Sykes SE, Kieft R, et al. Extracellular vesicles from Trypanosoma brucei mediate virulence factor transfer and cause host anemia. Cell. 2016;164:246–257.

[383] Alvarez VE, Niemirowicz GT, Cazzulo JJ. The peptidases of Trypanosoma cruzi: digestive enzymes, virulence factors, and mediators of autophagy and programmed cell death. Biochim Biophys Acta. 2012;1824:195–206.

[384] Nery E, del Juliano MA, Lima APCA, et al. Kininogenase activity by the major cysteinyl proteinase (cruzipain) from Trypanosoma cruzi. J Biol Chem. 1997;272:25713–25718.

[385] Ferrão PM, d'Avila-Levy CM, Araujo-Jorge TC, et al. Cruzipain activates latent TGF-β from host cells during T. cruzi invasion. PLoS One. 2015;10:e0124832.

[386] Nogueira PM, Ribeiro K, Silveira ACO, et al. Vesicles from different Trypanosoma cruzi strains trigger differential innate and chronic immune responses. J Extracell Vesicles. 2015;4:28734.

[387] Silverman JM, Reiner NE. Leishmania exosomes deliver preemptive strikes to create an environment permissive for early infection. Front Cell Infect Microbiol. 2012;1:26.

[388] Magdesian MH, Tonelli RR, Fessel MR, et al. A conserved domain of the gp85/trans-sialidase family activates host cell extracellular signal-regulated kinase and facilitates Trypanosoma cruzi infection. Exp Cell Res. 2007;313:210–218.

[389] Regev-Rudzki N, Wilson DW, Carvalho TG, et al. Cell-cell communication between malaria-infected red blood cells via exosome-like vesicles. Cell. 2013;153:1120–1133.

[390] Cannella D, Brenier-Pinchart M-P, Braun L, et al. miR-146a and miR-155 delineate a MicroRNA fingerprint associated with Toxoplasma persistence in the host brain. Cell Rep. 2014;6:928–937.

[391] Aparicio IM, Scharfstein J, Lima APCA. A new cruzipain-mediated pathway of human cell invasion by Trypanosoma cruzi requires trypomastigote membranes. Infect Immun. 2004;72:5892–5902.

[392] Neves RFC, Fernandes ACS, Meyer-Fernandes JR, et al. Trypanosoma cruzi-secreted vesicles have acid and alkaline phosphatase activities capable of increasing parasite adhesion and infection. Parasitol Res. 2014;113:2961–2972.

[393] Rug M, Cyrklaff M, Mikkonen A, et al. Export of virulence proteins by malaria-infected erythrocytes involves remodeling of host actin cytoskeleton. Blood, J Am Society Hematol. 2014;124:3459–3468.

[394] Borges BC, Uehara IA, Dias LOS, et al. Mechanisms of infectivity and evasion derived from microvesicles cargo produced by Trypanosoma cruzi. Front Cell Infect Microbiol. 2016;6:161.

[395] Martins NO, de Souza RT, Cordero EM, et al. Molecular characterization of a novel family of Trypanosoma cruzi surface membrane proteins (TcSMP) involved in mammalian host cell invasion. PLoS Negl Trop Dis. 2015;9: e0004216.

[396] Burleigh BA, Andrews NW. Signaling and host cell invasion by Trypanosoma cruzi. Curr Opin Microbiol. 1998;1: 461–465.

[397] Reiner NE, Malemud CJ. Arachidonic acid metabolism by murine peritoneal macrophages infected with Leishmania donovani: in vitro evidence for parasite-induced alterations in cyclooxygenase and lipoxygenase pathways. J Immunol. 1985;134:556–563.

[398] Pope SM, Lässer C. Toxoplasma gondii infection of fibroblasts causes the production of exosome-like vesicles containing a unique array of mRNA and miRNA transcripts compared to serum starvation. J Extracell Vesicles. 2013;2: 22484.

[399] Zanforlin T, Bayer-Santos E, Cortez C, et al. Molecular characterization of Trypanosoma cruzi SAP proteins with host-cell lysosome exocytosis-inducing activity required for parasite invasion. PLoS One. 2013;8:e83864.

[400] Souza W de, Barrias E. Exosomes in the pathogenic protozoan Trypanosoma cruzi. Inter J Pathol Clin Res. 2017;3: 1–9.

[401] Fernandez-Calero T, Garcia-Silva R, Pena A, et al. Profiling of small RNA cargo of extracellular vesicles shed by Trypanosoma cruzi reveals a specific extracellular signature. Mol Biochem Parasitol. 2015;199:19–28.

[402] Garcia-Silva MR, Cabrera-Cabrera F, das Neves RFC, et al. Gene expression changes induced by Trypanosoma cruzi shed microvesicles in mammalian host cells: relevance of tRNA-derived halves. Biomed Res Int. 2014;2014.

[403] Tonelli RR, Giordano RJ, Barbu EM, et al. Role of the gp85/trans-sialidases in Trypanosoma cruzi tissue tropism: preferential binding of a conserved peptide motif to the vasculature in vivo. PLoS Negl Trop Dis. 2010;4:e864.

[404] Rodriguez A, Samoff E, Rioult MG, et al. Host cell invasion by trypanosomes requires lysosomes and microtubule/kinesin-mediated transport. J Cell Biol. 1996;134:349–362.

[405] Ruiz CR, Favoreto S Jr, Dorta LM, et al. Infectivity of Trypanosoma cruzi strains is associated with differential expression of surface glycoproteins with differential Ca2+ signalling activity. Biochemical J. 1998;330:505–511.

[406] Scharfstein J, Schmitz V, Morandi V, et al. Host cell invasion by Trypanosoma cruzi is potentiated by activation of bradykinin B2 receptors. J Exp Med. 2000;192:1289–1300.

[407] Yoshida N, Jr, Ferreira AT, Manque PM. Signal transduction induced in Trypanosoma cruzi metacyclic trypomastigotes during the invasion of mammalian cells. Brazilian J Medical Biol Res. 2000;33:269–278.

[408] Yoshida N, Cortez M. Trypanosoma cruzi: parasite and host cell signaling during the invasion process. Mol Mechan Parasite Invasion. 2008;47:82–91.

[409] de Toro J, Herschlik L, Waldner C, et al. Emerging roles of exosomes in normal and pathological conditions: new insights for diagnosis and therapeutic applications. Front Immunol. 2015;6:203.

[410] Lv L, Li C, Zhang X, et al. RNA profiling analysis of the serum exosomes derived from patients with active and latent Mycobacterium tuberculosis infection. Front Microbiol. 2017;8:1051.
[411] Geiger A, Hirtz C, Bécue T, et al. Exocytosis and protein secretion in Trypanosoma. BMC Microbiol. 2010;10:1–17.
[412] RamachandraRao SP, Matthias MA, Kokoy-Mondragon C, et al. Proteomic analysis of urine exosomes reveals renal tubule response to leptospiral colonization in experimentally infected rats. PLoS Negl Trop Dis. 2015;9:e0003640.
[413] Song J-W, Lam SM, Fan X, et al. Omics-driven systems interrogation of metabolic dysregulation in COVID-19 pathogenesis. Cell Metab. 2020;32:188–202.e5.
[414] di Bonito P, Ridolfi B, Columba-Cabezas S, et al. HPV-E7 delivered by engineered exosomes elicits a protective $CD8^+$ T cell-mediated immune response. Viruses. 2015;7:1079–1099.
[415] Anticoli S, Manfredi F, Chiozzini C, et al. An exosome-based vaccine platform imparts cytotoxic T lymphocyte immunity against viral antigens. Biotechnol J. 2018;13:e1700443.
[416] Ferrantelli F, Manfredi F, Chiozzini C, et al. DNA vectors generating engineered exosomes potential CTL vaccine candidates against AIDS, hepatitis B, and tumors. Mol Biotechnol. 2018;60:773–782.
[417] Nanjundappa RH, Wang R, Xie Y, et al. Novel CD8+ T cell-based vaccine stimulates Gp120-specific CTL responses leading to therapeutic and long-term immunity in transgenic HLA-A2 mice. Vaccine. 2012;30:3519–3525.
[418] Nanjundappa RH, Wang R, Xie Y, et al. GP120-specific exosome-targeted T cell-based vaccine capable of stimulating DC-and CD4+ T-independent CTL responses. Vaccine. 2011;29:3538–3547.
[419] Wang R, Xie Y, Zhao T, et al. HIV-1 gag-specific exosome-targeted T cell-based vaccine stimulates effector CTL responses leading to therapeutic and long-term immunity against Gag/HLA-A2-expressing B16 melanoma in transgenic HLA-A2 mice. Trials Vaccinol. 2014;3:19–25.
[420] Wang L, Chen X, Zhou X, et al. miRNAs targeting ICP4 and delivered to susceptible cells in exosomes block HSV-1 replication in a dose-dependent manner. Mol Ther. 2018;26:1032–1039.
[421] Liu Y-M, Tseng C-H, Chen Y-C, et al. Exosome-delivered and Y RNA-derived small RNA suppresses influenza virus replication. J Biomed Sci. 2019;26:58.
[422] Dagnelie M, Corvec S, Khammari A, et al. Bacterial extracellular vesicles: A new way to decipher host-microbiota communications in inflammatory dermatoses. Exp Dermatol. 2020;29:22–28.
[423] Zurita ME, Wilk MM, Carriquiriborde F, et al. A pertussis outer membrane vesicle-based vaccine induces lung-resident memory CD4 T cells and protection against Bordetella pertussis, including pertactin deficient strains. Front Cell Infect Microbiol. 2019;9:125.
[424] Lee DH, Kim S-H, Kang W, et al. Adjuvant effect of bacterial outer membrane vesicles with penta-acylated lipopolysaccharide on antigen-specific T cell priming. Vaccine. 2011;29:8293–8301.
[425] Kim OY, Hong BS, Park K-S, et al. Immunization with Escherichia coli outer membrane vesicles protects bacteria-induced lethality via Th1 and Th17 cell responses. J Immunol. 2013;190:4092–4102.
[426] Pinto VB, Moran EE, Cruz F, et al. An experimental outer membrane vesicle vaccine from N. meningitidis serogroup B strains that induces serum bactericidal activity to multiple serogroups. Vaccine. 2011;29:7752–7758.
[427] Nieves W, Asakrah S, Qazi O, et al. Anaturally derived outer-membrane vesicle vaccine protects against lethal pulmonary Burkholderia pseudomallei infection. Vaccine 2011;29:8381–8389.
[428] Jain-Gupta N, Contreras-Rodriguez A, Vemulapalli R, et al. Pluronic P85 enhances the efficacy of outer membrane vesicles as a subunit vaccine against Brucella melitensis challenge in mice. FEMS Immunol Med Microbiol. 2012;66:436–444.
[429] Camacho AI, de Souza J, Sánchez-Gómez S, et al. Mucosal immunization with Shigella flexneri outer membrane vesicles induced protection in mice. Vaccine. 2011;29:8222–8229.
[430] Bishop AL, Tarique AA, Patimalla B, et al. Immunization of mice with vibrio cholerae outer-membrane vesicles protects against hyperinfectious challenge and blocks transmission. J Infect Dis. 2012;205:412–421.
[431] Gasperini G, Alfini R, Arato V, et al. Salmonella paratyphi a outer membrane vesicles displaying Vi polysaccharide as a multivalent vaccine against enteric fever. Infect Immun. 2021;89(4):e00699–20.
[432] Giri PK, Schorey JS. Exosomes derived from M. Bovis BCG infected macrophages activate antigen-specific CD4+ and CD8+ T cells in vitro and in vivo. PLoS One. 2008;3:e2461.
[433] Colino J, Snapper CM. Exosomes from bone marrow dendritic cells pulsed with diphtheria toxoid preferentially induce type 1 antigen-specific IgG responses in naive recipients in the absence of free antigen. J Immunol. 2006;177:3757–3762.
[434] Kim OY, Choi SJ, Jang SC, et al. Bacterial protoplast-derived nanovesicles as vaccine delivery system against bacterial infection. Nano Lett. 2015;15:266–274.
[435] Beauvillain C, Ruiz S, Guiton R, et al. A vaccine based on exosomes secreted by a dendritic cell line confers protection against T. gondii infection in syngeneic and allogeneic mice. Microbes Infect. 2007;9:1614–1622.
[436] Beauvillain C, Juste MO, Dion S, et al. Exosomes are an effective vaccine against congenital toxoplasmosis in mice. Vaccine. 2009;27:1750–1757.
[437] Jung B-K, Kim E-D, Song H, et al. Immunogenicity of exosomes from dendritic cells stimulated with toxoplasma gondii lysates in ocularly immunized mice. Korean J Parasitol. 2020;58:185–189.
[438] Schnitzer JK, Berzel S, Fajardo-Moser M, et al. Fragments of antigen-loaded dendritic cells (DC) and DC-derived exosomes induce protective immunity against Leishmania major. Vaccine. 2010;28:5785–5793.
[439] Santos P, Almeida F. Exosome-based vaccines: history, current state, and clinical trials. Front Immunol. 2021;14:12.
[440] Anand PK. Exosomal membrane molecules are potent immune response modulators. Commun Integr Biol. 2010;3:405–408.