REVIEW ARTICLE

Exosomes on the border of species and kingdom intercommunication

CHRISTINA M.A.P. SCHUH, JIMENA CUENCA, FRANCISCA ALCAYAGA-MIRANDA, and MAROUN KHOURY

SANTIAGO, CHILE

Over the last decades exosomes have become increasingly popular in the field of medicine. While until recently they were believed to be involved in the removal of obsolete particles from the cell, it is now known that exosomes are key players in cellular communication, carrying source-specific molecules such as proteins, growth factors, miRNA/mRNA, among others. The discovery that exosomes are not bound to intraspecies interactions, but are also capable of interkingdom communication, has once again revolutionized the field of exosomes research. A rapidly growing body of literature is shedding light at novel sources and participation of exosomes in physiological or regenerative processes, infection and disease. For the purpose of this review we have categorized 6 sources of interest (animal products, body fluids, plants, bacteria, fungus and parasites) and linked their innate roles to the clinics and potential medical applications, such as cell-based therapy, diagnostics or drug delivery. (Translational Research 2019; 210:80–98)

Abbreviations: BTG 1 = B-cell translocation gene; CAR-T = chimeric antigen receptor T-cells; CRISP = cysteine-rich secretory proteins; CRNN = cornulin; DC = dendritic cell; DSS colitis = dextran sulfate sodium induced colitis; EPDEN = edible plant derived exosome-like nanoparticles; ERM = Ezrin Radixin Moesin family; ESC = embyonic stem cell; GELN = grape exosome-like nanoparticles; GPC 1 = Glypican-1; GTSP1 = Glutathione S-transferase P; GXM = glucuronoxylomannan; HUVEC = Human umbilical vein endothelial cells; IL-1 = Interleukin 1; iPSC = induced pluripotent stem cell; IQGAP = Ras GTPase-activating-like protein; lcnARSR = long non coding RNA Activated in renal cell carcinoma with Sunitinib Resistance; LGTV = Langat virus; MCP1 = Monocyte chemoattractant protein 1; MHC = major histocompatibility complex; miRNA = micro RNA; mRNA = messenger RNA; MSC = mesenchymal stem cell; mTOR = mechanistic Target of Rapamycin; Muc5b = Mucin 5b; nm = nanometer; OMV = outer membrane vesicle; PEDF = Pigment epithelium-derived factor; PME = pectin methylesterase; SNX 25 = Sorting Nexin 25; TACSTD2 = Tumor-associated calcium signal transducer 2; TLR4 = Toll-like receptor 4; TNBS = Trinitrobenzenesulfonic acid; TNF-α = Tumor necrosis factor α

INTRODUCTION

Exosomes were first described in mammalian cell culture by Trams et al in 1981 as the cargo of shed microvesicles,[1] believed to be mainly involved in the removal of obsolete molecules from the cell and cell wall.[2] After key findings such as their role in

From the Consorcio Regenero, Chilean Consortium for Regenerative Medicine, Santiago, Chile; Cells for Cells, Santiago, Chile; Laboratory of Nano-Regenerative Medicine, Faculty of Medicine, Universidad de los Andes, Santiago, Chile; Centro de Medicina Regenerativa, Facultad de Medicina Clínica Alemana-Universidad del Desarrollo, Santiago, Chile.

Submitted for Publication January 2, 2019; received submitted March 25, 2019; accepted for publication March 26, 2019.

Reprint requests: Christina M.A.P. Schuh, Universidad del Desarrollo, Avenida Las Condes 12587, Santiago, Chile.
Reprint requests: Maroun Khoury, Universidad de los Andes, Monseñor Álvaro del Portillo 12455, Santiago, Chile. e-mail: cschuh@udd.cl Mkhoury@uandes.cl.

1931-5244/$ - see front matter

https://doi.org/10.1016/j.trsl.2019.03.008

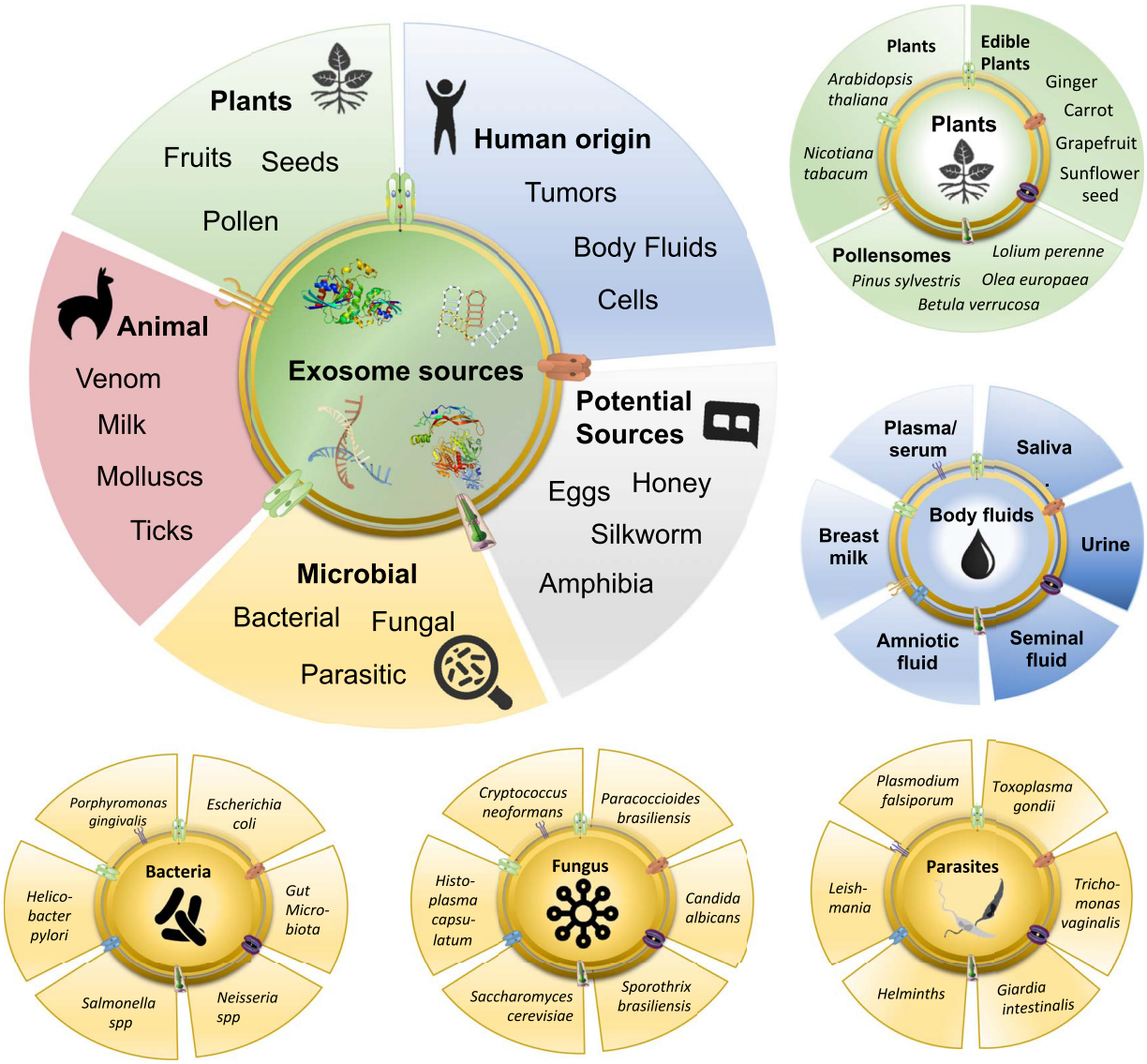

Fig 1. Illustration of the different sources for the production of exosomes, covering human, plants, animal and microbial origins. Human tissues include: tumors, cells and body fluids. Non-exhaustive examples of plants, body fluids, parasites, fungus and bacteria are depicted in the diagrams. Novel potential sources of interest for the identifications of exosomes are also highlighted in the chart, including honey, silkworm, eggs and amphibia.

expression of antigens[3] and ability to transfer mRNA/miRNA,[4] they are now established as one of the main factors in intercellular communication. By definition, exosomes are between 30 and 150 nm in size, and in an attempt to differentiate exosomes from other vesicles, the International Society for Extracellular Vesicles defined a number of criteria in their 2014 and 2018 position papers. This included isolation from extracellular fluid as well as analysis of markers that are expected to be present such as transmembrane, lipid bound extracellular proteins (CD9, CD63, CD81, integrins) or cytosolic proteins (endosome, membrane binding proteins, synthenins), but also markers that are expected to not be present, such as intracellular proteins (calnexin, histones, cytochrome C).[5,6] Aside from markers defining exosomes, it has been shown that exosome cargo can be associated with the phenotype, metabolic status, and biological role of their cell of origin.[4,7,8] Many articles and reviews have focused on the use of mammalian cells and body fluids as a source for the production and isolation of exosomes. These "conventional" sources display an important basis in understanding roles of exosomes in physiological processes, as well as for their use in the clinics as biomarkers and therapy, as reviewed by Jing et al.[9] Over the last decades, a growing body of literature has

shown that a number of other sources display interesting characteristics, shedding light into biological processes and furthermore could potentially be beneficial alternatives for medical applications. For the purposes of this review, we have categorized exosomes into human and nonhuman sources, with the latter divided into (a) animal product-derived exosomes, (b) bacterial/fungal/parasitic exosomes, and (c) plant-derived exosomes (Fig 1).

HUMAN SOURCES OF EXOSOMES

It is well known that mesenchymal stem cell (MSCs) partly exert their regenerative and therapeutic effect through the release of soluble factors, which have been mechanistically linked to exosomes in a number of preclinical studies[10-15] and clinical settings. Interestingly, exosomes secreted by MSCs of different sources (eg, bone marrow, umbilical cord[11,16]) display different physiological, pathologic, or regenerative function as mediators of cell-cell communication. For example, while exosomes derived from bone-marrow MSCs promote tumor induced angiogenesis in prostate and breast cancer, exosomes derived from menstrual fluid MSCs act as blockers.[12]

Embryonic stem cells (ESCs) were hypothesized to increase pluripotency of hematopoietic progenitor cells after horizontal transfer of ESC mRNA.[7] Therapeutically, it has been reported that after myocardial infarction ESC-exosomes may promote endogenous repair mechanisms and enhance cardiac function.[17] Induced pluripotent stem cell demonstrated in preclinical models a protective effect on limbs from ischemic injury by promoting angiogenesis through the activation of angiogenesis-related gene expression[18] as well as a hepatoprotective effect in ischemia-reperfusion injury by suppression of inflammatory responses and inhibition of apoptosis.[19]

Dendritic cells (DCs), macrophages, and lymphocytes secrete immunologically active exosomes that could modulate physiological and pathologic processes, as well as innate and adaptive immunity.[20] Since 1998, DC-derived exosomes have demonstrated a high potential as immunotherapy to treat cancer, when Zitvogel et al showed that they carry functional MHC I and II molecules, and are able to induce an antitumor immune responses in vivo.[21] Since then, several phase I or II clinical trials of DC-exosomes to treat different tumors have been reported, with increased survival and mild vaccination-related side effects.[22-24] Exosomes of chimeric antigen receptor T cells (CAR-T) display a promising alternative for anti−cancer-immunotherapy Tang et al proposed the use of CAR-T exosomes as a safer alternative to CAR-T cell therapy, in order to avoid some adverse effects (eg, cytokine release syndrome) observed in clinical trials utilizing cells.[25]

Tumors in various tissues have been shown to be secretory active, and with the advancement of exosome research have also been demonstrated to secrete exosomes (eg, breast, colorectum, kidney, brain, and pancreas).[26-29] Exosomes derived from metastasis were shown to contain cargo promoting migration, proliferation, invasion, and angiogenesis while non−metastatic-exosomes contained mostly proteins involved in cell-cell/cell-matrix adhesion and polarity maintenance.[30] Interestingly, several studies have shown that tumor-derived exosomes play a role in drug resistance. Safaei et al demonstrated in an in vitro model that cells resistant to the chemotherapeutic agent cisplatin produce higher numbers of exosomes, and that those exosomes containing cisplatin effectively decrease the intracellular concentration of the agent.[31] It also has been hypothesized that the property of breast cancer cells to transmit chemoresistance is probably mediated by their release of exosomes, which may alter the chemosusceptibility of recipient cells by a horizontal transfer of miRNAs modulating cell cycle distribution and drug-induced apoptosis.[32]

To target the issue drug delivery across the blood brain barrier, Yang et al used exosomes from mammalian culture to test their properties to deliver drugs (eg, Paclitaxel) in a zebrafish model, demonstrating the ability of fish cells to take up mammalian/human cell-derived exosomes.[33]

Human body fluid-derived exosomes. As most cells and tissues produce exosomes, it is not surprising that they utilize body fluids as transportation vehicles in physiological processes such as cell-to-cell signaling,[34] immune responses,[35] and in certain pathologic processes. Since exosomes secreted into biological fluids carry a cell-distinctive cargo signature, they have potential to serve as biomarkers in diagnostics, as well as for prognosis and tracking treatment response in pathologies such as vascular and autoimmune disorders and cancer[36] (Table 1).

Regarding saliva, relatively few studies have investigated the presence, composition, and function of exosomes. Ogawa et al discovered in an initial study that dipeptidyl peptidase IV, actin, polymeric immunoglobulin receptor, immunoglobulin A, and galectin-3 were associated to saliva-derived exosomes.[37] In a follow-up study the presence of 2 different types of exosomes in saliva was discussed: one of the groups contained proteins involved in migration, coagulation, and inflammation (proteins of ERM family: ezrin, radixin, and moesin; annexins), and gelforming proteins (mucin 5B), while the other group expressed metabolically active dipeptidyl peptidase IV, cleaving CXCL11 and

Table 1. Exosomes derived from body fluids, their role in physiologic processes and medicine, as well as cargo molecules studied

Body fluid	Proposed function	Analysed cargo molecule	Reference
Amniotic fluid	Sex determination	CD24	178
Aqueous humor	Role in intra-ocular pressure	glaucoma-causing protein, myocilin	179
	Pathogenesis of glaucoma	miR-486-5p, miR-204, miR-184	180
Ascites (peritoneal lavage fluid)	Biomarker gastric cancer	miR-21, miR-1225-5p, miR-320c, miR-1202, miR-1207-5p, miR-4270	181
	Biomarker ovarian cancer	CD24, EpCAM	182
Blood (plasma, serum)	Biomarker hematological tumors	CD9, CD13, CD19, CD30, CD38, CD63	183
	Biomarker prostate cancer	CD9, CD63; N-linked glycans	184,185
	Biomarker lung cancer		186, 187,188
	Biomarker ovarian cancer	Claudin-4; miR-21, miR-141, miR-200a, miR-200c, miR-200b, miR-203, miR-205 and miR-214	
	Biomarker brain cancer	Heatshock proteins; miR-21, miR-222, miR-124-3p; Endothelia Growth Factor Receptor variant 3;	189–191
	Prediction drug resistance renal cell carcinoma	lncARSR	192
	Biomarker breast cancer	survivin-2B	193
	Prediction drug resistance breast cancer	GSTP1	194
	Biomarker colorectal cancer	GPC1	195,196
	Biomarker pancreas cancer	GPC1	197
	Biomarker pre-eclampsia	placental alkaline phosphatase, has-miR-486-1-5p, has-miR-486-2-5p	44,45
	Biomarker rheumatoid arthritis	lncRNA, HOTAIR	198
	Biomarker acute coronary syndrome	miR-208a	199
Breast milk	Promote intestinal epithelial cell growth and epithelial–mesenchymal transition		200,201
	Influence immune responses		47–49
Bronchoalveolar lavage fluid	Presence of histocompatibility complex class II and co-stimulatory molecules in exosomes	MHC class I and II, CD54, CD63, CD86	47
Cerebrospinal fluid	Influence neuron cell proliferation *in vitro*		202
	Biomarker for glioblastoma	miR-21	203
Follicular fluid	Biomarkers (oocyte quality)	miRNA expression patterns	50
	Age associated differential miRNA	miRNA expression patterns	204
Malignant pleural effusions	Proteomic characterization	SNX25, BTG1, PEDF, thrombospondin 2	205
Saliva	Biomarker (microarray analyses of mRNA)		206
	Biomarker Sjorens syndrome	miRNA expression patterns	207
	Catabolism of bioactive peptides; regulatory role in local immune defense in the oral cavity	CD26, immunoglobulin A, polymeric immunoglobulin receptor	37
	Biomarker lung cancer	PIFA1, CRNN, MUC5B, IQGAP	208
Seminal fluid	Delivery of regulatory signals to the recipient mucosa	Non-coding RNAs	54
	Sperm maturation and function		51–53
Synovial fluid	Association with citrullinated proteins (rheumatoid arthritis)	Fibrin alpha-chain fragment, fibrin beta-chain, fibrinogen beta-chain precursor, fibrinogen D fragment, Sp alpha (CD5 antigen-like protein) receptor	209
	Gender specific changes in osteoarthritis	miRNA expression patterns	210
	Role in disease progression of osteoarthritis		211

(*continued*)

Table 1. (*Continued*)

Body fluid	Proposed function	Analysed cargo molecule	Reference
Tears	Characterization in healthy individuals		212
Urine	Reflect defects in distal renal tubular acidosis		213
	Biomarker bladder cancer	lncRNA HOTAIR, tetraspanins, TACSTD2	214–216
	Biomarker renal cell carcinoma	miRNA and protein expression patterns	217,218
	Biomarker prostate cancer		219
	Paracrine modulation of tubular transporters in kidney		220
	Biomarker early IgA nephropathy;	Aminopeptidase N, vasorin precursor, α-1-antitrypsin, and ceruloplasmin	221
	Biomarker polycystic kidney disease;	Polycystin-1 and polycystin-2 expression	162
	Biomarker diabetic nephropathy	Wilm's tumor-1 protein	163
	Role at the fetal-maternal interphase (in kidney)	CD24	222
	Biomarker kidney transplantation	Neutrophil gelatinase-associated lipocalin	223
	Express prostatic secretions		224
	Biomarker active lupus nephritis	miR29c	225,226

CXCL12.[38] Berckmann et al investigated the phenomenon of regenerative wound licking and discovered that saliva-derived exosomes contain tissue factor, with the ability of triggering coagulation of fresh wounds.[39]

In urine, exosomes are produced throughout the entire length of the nephron and have been found to fulfill a variety of interesting and specific functions. They appear to play a role in host defense of the urinary tract by inhibiting bacterial growth via induction of bacterial lysis,[40] but have also been associated to intercellular signaling by transferring Aquaporin 2 (a vasopressin-regulated water-channel protein involved in urine concentration).[41,42]

During pregnancy, placental and amniotic fluid exosomes have been hypothesized to be involved in a number of processes related to fetal development. A study by Salomon et al analyzed the concentration and bioactivity of exosomes in normal pregnancies over time. They found that both indicators increase significantly during early pregnancy and subsequently decline, and that early pregnancy exosomes promote endothelial cell migration.[43] An increase of placental exosomes is suspected to be of interest for detection of pre-eclampsia—an obstetrical disorder associated to severe complications during pregnancy[44-46]—and micro-RNAs has-miR-486-1-5p and has-miR-486-2-5p have been found to be potential markers for the disorder.[45] Another interesting fluid containing exosomes is human breast milk. Admyre et al demonstrated the presence of exosomes in breast milk, with the capacity to influence immune response.[47] However, recent studies determined differences in the exosomal content and phenotype between early and mature breast milk, probably originated from immune cells present in breast milk or from breast epithelial cells.[48,49] A study using follicular fluid—important for the oocyte and the fertilization process—and plasma of female patients undergoing intracytoplasmic sperm injection, identified a series of exosomal microRNAs that are highly represented in follicular fluid compared to plasma. These upregulated miRNAs are involved in crucial pathways for follicle growth and oocyte maturation.[50]

In males, the seminal fluid has also been shown to be a source of exosomes, facilitating sperm maturation, and function.[51-53] Cargo of seminal exosomes could potentially exert regulatory functions to the recipient mucosa.[54,55] Numerous studies also related these exosomes with immunologic and antimicrobial activity, spermatozoa motility and as potential biomarkers for several diseases, as reviewed by Ronquist et al, Arienti et al, and Aalberts et al.[56-58]

ALTERNATIVE SOURCES OF EXOSOMES

Animal–fluid-derived exosomes. Structurally, animal-derived exosomes do not differ from human body fluid-derived exosomes. However, a number of interesting, animal-specific biological functions and mechanisms have been observed in the past years.

Cow milk, one of the most abundant components of the western diet, contains 2 different membrane-

originating vesicles. The majority of vesicles are milk fat globule membranes, however a small part of vesicles has been found to be exosomes, which are distinctly different in proteome and function. Reinhardt et al assessed the proteome of milk-derived exosomes and in KEGG pathway analysis found the majority to be involved in endocytosis, regulation of the actin cytoskeleton, and chemokine signaling. Interestingly, 23 proteins associated to cancer pathways have also been identified.[59] Several studies were performed assessing differences between early and late stage milk production, but also between healthy and pathologic milk. When looking at colostrum (early stage milk) in comparison mature milk using functional enrichment analysis, Samuel et al found an enrichment in acute phase response proteins, which are associated to inhibition of bacterial growth, but also in proteins associated to platelet activation and inflammatory responses. This suggests an involvement of colostrum exosomes in infant immune response and growth.[60] Exosomal changes have also been observed in Staphylococcus aureus mastitis, where exosome proteome shifts toward host defense proteins compared to healthy cows.[61]

Furthermore, in the context of nutraceuticals, Mobley et al discovered in an in vitro study that hydrolyzed whey protein exosomes increased skeletal muscle protein synthesis and anabolism. They hypothesised this effect is more likely to be due to a novel mechanism that increases translation initiation factors, as opposed to enhancing mTOR signaling or bovine-specific microRNA.[62]

Besides milk, other interesting animal sources for exosomes have been described. In oysters, exosomes have been found to be involved in reparative mechanisms. When the outer shell is damaged, a thin layer of extracellular matrix is formed into which exosomes containing crystalline shell components are deposited, initiating the process of forming the structured folia mineral.[63] Interestingly, Zhou et al discovered that tick-derived exosomes might be involved in transmission of viruses. They cultivated Ixodes Scapularis cells infected with Langat virus (LGTV) and detected replicative LGTV RNA as well as E- and NS-1 proteins in the exosomes. In functional studies, they demonstrated that viral RNA can be transmitted via exosomes into human cells in a clathrin dependent manner, and furthermore are able to cross the blood brain barrier. Once neurons become infected, they are also able to spread the virus via their own exosomes and further disseminate the infection.[64]

Carneiro et al were the first to report the presence of exosomes in snake venom, finding similar vesicles of 40-80 nm in size in the venom glands as well as in collected venom of Crotalus durissus terrificus, but leaving the mechanism of action of these exosomes unexplained.[65] A subsequent study by Ogawa et al investigated cargo and composition of vesicles derived from Gloydius blomhoffii blomhoffii venom and found dipeptidyl peptidase IV, aminopeptidase A, ecto-5′-nucleotidase, as well as actin and in truncated form angiotensin II, substance P, cholecystokinin-octapeptide, glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1. Testing bioactivity in vitro, they found that exosome-like vesicles were able to cleave these regulatory peptides and concluded that the vesicles following envenomation may play a role in altering blood pressure due to the presence of substance P and neuropeptide Y, as well as glucose homeostasis, with dipeptidyl peptidase IV found to inactivate hormones such as the insulin-release stimulators glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1.[66] Corassolla Carregali et al described similar findings for the species *Agkistrodon contortrix contortrix, Crotalus atrox, Crotalus viridis*, and *Crotalus cerberus oreganus*, finding proteins in the vesicles associated to the following subgroups: snake venom metalloprotease, serine protease, phospholipase A2, CRISP and disintegrin, among others. In functional assays they were able to demonstrate metalloproteinase and fibrinogenolytic activity as well as cytotoxicity in HUVEC cells.[67]

Microbial exosomes

Bacterial exosomes. Bacterial exosomes—or outer membrane vesicles (OMVs)—have shown to be released by all studied Gram-negative bacteria independent of their pathogenicity. Kuehn et al listed in their 2005 review species such as *Escherichia coli, Shigella* spp., *Neisseria* spp., *Bacteroides* (including *Porphyromonas*) spp., *Pseudomonas aeruginosa, Helicobacter pylori, Vibrio* spp., *Salmonella* spp., *Brucella melitensis, Campylobacter jejuni, Actinobacillus actinomycetemcomitans, Xenorhabdus nematophilus,* and *Borrelia burgdorferi*,[68] but to date many more have been investigated. Sizes of OMVs range from 50 to 250-300 nm (diameter) and shedding occurs constitutively, but appears to be increased under stress.[69,70] Interestingly, OMVs can carry cargo such as DNA, RNA, proteins, or LPS in the intravesicular lumen but also in the outer shell, having the membrane as an active component. OMVs have shown to be internalized by mammalian cells and their uptake has been associated to four main mechanisms summarized by O'Donoghue et al: (1) macropinocytosis,[71] the process of membrane ruffling, and subsequent vesiculation and unspecific uptake of extracellular components[72,73]; (2) clathrin-dependent endocytosis[74], where clathrin-coated pits are formed to capture and internalize cargo[75]; (3) non-clathrin mediated endocytosis through lipid rafts, either via caveolins[76] or small GTPases[77]; and (4) direct membrane fusion.[77]

Bacteria-derived OMVs have shown to play a role in several important bacteria-bacteria and bacteria-host

interactions. Derived from commensal bacteria, OMVs participate in intestinal homeostasis, which has been studied by Shen et al in a TNBS induced mouse model. Treated with *Bacteroides fragilis PSA* containing OMVs, an immune-modulatory effect was triggered, reflected in enhanced regulatory T cell as well as anti-inflammatory cytokine production that prevented colitis in mice.[78] Kang et al analyzed feces-derived bacteria and OMVs in a DSS colitis mouse model, to assess changes in the gut microbiota, finding a decrease in the commensal strains *Akkermansia muciniphila* and *Bacteroides acidifaciens*. Oral application of *A. muciniphila* OMVs ameliorated symptoms associated to DSS colitis, suggesting that not only live bacteria, but also their OMVs could be used for potential therapies.[79]

Furthermore, pathogenic bacteria utilize OMV shedding to distribute virulence factors, such as adenylate cyclase toxin by *Bordetella pertussis*,[80] phospholipase C by *Acenitobacter baumannii*[81] and *P. aeruginosa*,[82] shiga toxin by *Shigella dysenteriae*[83] and *Escherichia coli O157:H7*,[84] as well as VacA by *Helicobacter pylori*[85] or alkaline phosphatase by *Vibrio shilonii*[86] and *Myxococcus xanthus*.[87] Furthemore, antibiotic resistance can be increased due to OMVs, as strains such as *P. aeruginosa,*[88] *Stenotrophomonas maltophilia*,[89] and *Staphylococcus aureus*[90] have shown to shed OMVs containing b-lactamase; and *A. baumannii* is capable of transferring OXA-24 carpapenemase via OMVs, demonstrating a new route of disseminating antibiotical resitance via horizontal gene transfer.[91]

Aside from distribution of specific virulence factors, OMVs have demonstrated to modulate immune reactions. Effects on the immune response include stimulation of chemokine release, such as IL-1b, IL-6, IL-8, or MCP1, but also direct interaction with immune cells such as neutrophils, macrophages or DCs.[92-94] One interesting example for the significance and versatility of OMVs is *Porphyromoras gingivalis*, which is a keystone pathogen in oral biofilm formation and periodontal disease. Grenier et al showed in an early study that *P. gingivalis* OMVs are decreasing responsiveness to Chlorhexidin, one of the most frequently used oral antibacterial washes.[95] Continuous exposure to *P. Gingivalis* OMVs also decreased responsiveness of monocytes, which has been speculated to be related to induction of tumor necrosis factor tolerance in a TLR4- and mTOR-mediated way.[96] One of *P. gingivalis* virulence factors is gingipain, a endopeptidase involved in nutrient collection, which is also found on OMVs and has been shown to be involved in altering host cell functions and decreasing viability.[97] Gingipain is capable of modulating the host immune response by degration of immunoglobulin, inactivation of cytokines, increasing vascular permeability, among others.[98] One mechanism of gingipain immune modulation is worth highlighting: the biphasic effect on the complement system. In early stages of *P. gingivalis* infection gingipain activates the C1 complex, creating a local inflammatory response which is believed to increase nutrient supply and improve colonisation, while in later stages it can inactivate complement factors (C3, C4, C5) leading to resistance to the complement system.[99] Failing to elicit a sufficient immune response as well as altering host cell viability does not only lead to the local issue of chronic peridontitis, but also should be seen as part of the bigger picture: *P. gingivalis* has been described as an important pathogen in a number of systemic diseases including arteriosclerosis, cardiovascular disease, Buerger disease, diabetes mellitus, and Alzheimer's disease. For most of these diseases the role of OMVs has not been elucidated yet, however, Yang et al discovered that these OMVs promote calcification of vascular smooth muscle cells through RunX2—a transcription factor involved in osteogenic differentiation—in a ERK1/2 dependent manner,[100] linking arteriosclerosis to *P. gingivalis* OMVs.[101]

While OMVs of Gram-negative bacteria are well studied, OMVs of Gram-positive bacteria are acknowledged as such, but mechanisms behind their secretion and function are fairly unknown. One of the first Gram-positive bacterial OMVs to be studied more extensively was derived from *S. aureus*. As mentioned above, these OMV's have shown to contain b-lactamase as cargo, decreasing antibiotic treatment efficacy. Kim et al found the presence of *S. aureus* OMVs in house dust[90] and furthermore revealed their involvement in pulmonary inflammatory disease as well as atopic dermatitis.[102]

Interestingly, pathogenicity and immune modulation of OMVs is not limited to mammals, but also appears in plants. One of the factors in pathogenicity of bacteria in plants is degradation of the cell wall, usually by secretion of enzymes into the extracellular space (type II secretion). Solé et al analyzed Xanthomonas campestris pv. vesicatoria secretome as well as its OMVs, and found that degradative enzymes (xylanase) can be found both secreted as well as in vesicles, suggesting an alternative sustained route of virulence factor delivery.[103] Bahar et al demonstrated in an in vitro Arabidopsis thaliana model that OMVs trigger a reactive oxygen species release, change in pH, as well as overexpression of flg22-induced receptor-like kinase 1 and At5g57220 which are associated to defense mechanisms.[104]

Fungal exosomes. The presence of fungal exosomes has first been described a decade ago and until now has been reported for a number of fungal strains, such as *Crytococcus neoformans, Saccharomyces cerevisiae, Histoplasma capsulatum, Paracoccioides brasiliensis, Pichia fermentans, Candida albicans*, and *Sporothrix brasiliensis*.[105-111] Until today, the structure of the

fungal cell wall, consisting of a lipid bilayer as well as chitin, glucans, and glycoproteins[112] raises questions on the mechanism of vesicle release as well as uptake. Wolf et al visualized *Cryptococcus neoformans* vesicles traversing the cell wall[105] and Joffe et al hypothesized in their review on potential roles of fungal exosomes, that one of the potential mechanisms for entering cells could involve cell-wall degrading enzymes in fungal exosomes, naming *Saccharomyces cerevisiae* or *Histoplasma capsulatum* as examples, among others.[106,107,113]

Functionally, fungal exosomes appear to be involved in cell-cell communication as well as fungal virulence. It has been shown for *Cryptococcus neoformans*—a major pathogen especially for immune-compromised humans and causative agent of cryptococcosis that vesicles contain GXM and glucosylceramide, as well as other virulence factors such as urease, laccase, acid phosphatase, and several antioxidant proteins such as superoxide dismutase, thioredoxin, thioredoxin reductase, thiol-specific antioxidant protein, and catalase A.[114] Kazuo Ikeda et al demonstrated that *Sporothrix brasiliensis* extracellular vesicles lead to higher expression of IL-12p40 and TNF-α by DCs in vitro, and an increased virulence in a skin lesion mouse model.[111] An interesting example for the interplay of fungal cells and exosome-related virulence is *Cryptococcus gattii*. Bielska et al showed an increased in virulence of this strain can be related to their extracellular vesicles by the following mechanism: macrophages in the infected host internalize *C. gattii* extracellular vesicles, which are trafficked to Cryptococci residing within the phagosome, causing an increase in proliferation and therefore driving pathogenesis.[115]

Parasite-derived exosomes. Within the last decades, studies enlightening the role of parasitic EVs in parasite-parasite communication as well as in parasite-host interaction have become increasingly popular. As in the case of bacteria and fungal vesicles, exosomes of parasites carry virulence factors that are taken up by host cells and participate in pathogen dissemination. Li et al observed that *Toxoplasma gondii*, an obligate intracellular apicomplexan parasite, has the ability to modulate macrophage activation in vitro and trigger humoral and cellular immune responses, suggesting a potential strategy for vaccine development.[116] In Malaria infection caused by *Plasmodium falsiporum*, increased levels of vesicles were detected in the patients serum,[117] containing small regulatory RNAs, that have been found to code for exported proteins as well as proteins involved in drug resistance.[118] Furthermore, Regev-Rutzki et al revealed that *P. falsiporum* utilize exosomes to transfer drug resistance.[119]

Silverman et al speculated in their 2012 review that *Leishmania* exosomes play a key role in the initial phases of infection. They propose that GP63 and EF-1a are delivered to the host cells, activating host protein-tyrosine phosphatases and preventing IFN-γ-induced signaling, and as a consequence weaken the proinflammatory cytokine response.[120-123] A similar finding was reported for *Trichomonas vaginalis*, the causative parasite of trichomoniasis. *Trichomonas* exosomes were found to modulate the macrophage response and change the cytokine profile, inducing IL-10 production and decreasing IL-6, IL-13, and IL-17, which suggests an overall decrease in inflammatory processes during infection.[124] The intestinal parasite *Giardia intestinalis* has been found to respond to environmental changes (eg, decrease of pH) with increased secretion of exosomes, which is utilized to increase its attachment to the host cells. Furthermore, *Giardia* exosomes are taken up by immature DCs, increasing their activation.[125]

Besides these negative effects, some parasitic exosomes may have beneficial effects for humans. Harnett et al discussed in their review how parasitic helminths are able to suppress host immune responses,[126] which raises interest in their use as therapeutics for autoimmune conditions such as inflammatory bowel disease or rheumatoid arthritis.[127,128] Several groups demonstrated that helminth exosomes are taken up by mammalian cells such as small intestinal epithelial cells and macrophages, and downregulate expression of IL-5, IL-6, IL-13, and TNF, which are associated to immune responses.[129,130] However, the question remains whether treatment with exosomes collected from helminths would be sufficient to elicit a therapeutic effect.

Plant exosomes. Plant cells differ structurally from animal cells, especially in one of the key structures for exosome release: the outer membrane. While animal cells possess a phospholipid bilayer enabling exosome release into the extracellular space, plant cells are additionally encased within a cell wall consisting of polysaccharides, in between which paramural bodies—exosome-like vesicles—are released from the cell membrane. In the model organism Arabidopsis thaliana it has been discovered that plant exosomes are carrying miRNAs, sRNAs (small RNAs, 18-24 nt) as well as tyRNA (tiny RNAs, 10-17 nt), in addition to proteins, lipids, and metabolites. Comparing the cargo to the presence of the mi/s/tyRNAs in the apoplast, different appearance patterns could be found, suggesting a specific loading pattern and a use for long-distance delivery.[131] Furthermore, plant cell exosomes are believed to be involved in host-defense mechanisms, such as defense against parasites, for example, *Arabidopsis thaliana* against *Pseudomonas syringae*[132] or barley (*Hordeum vulgare*) against mildew fungus (*Blumeria graminis*).[133]

As a first group to identify exosome-like nanoparticles in edible plants, Regente et al revealed the

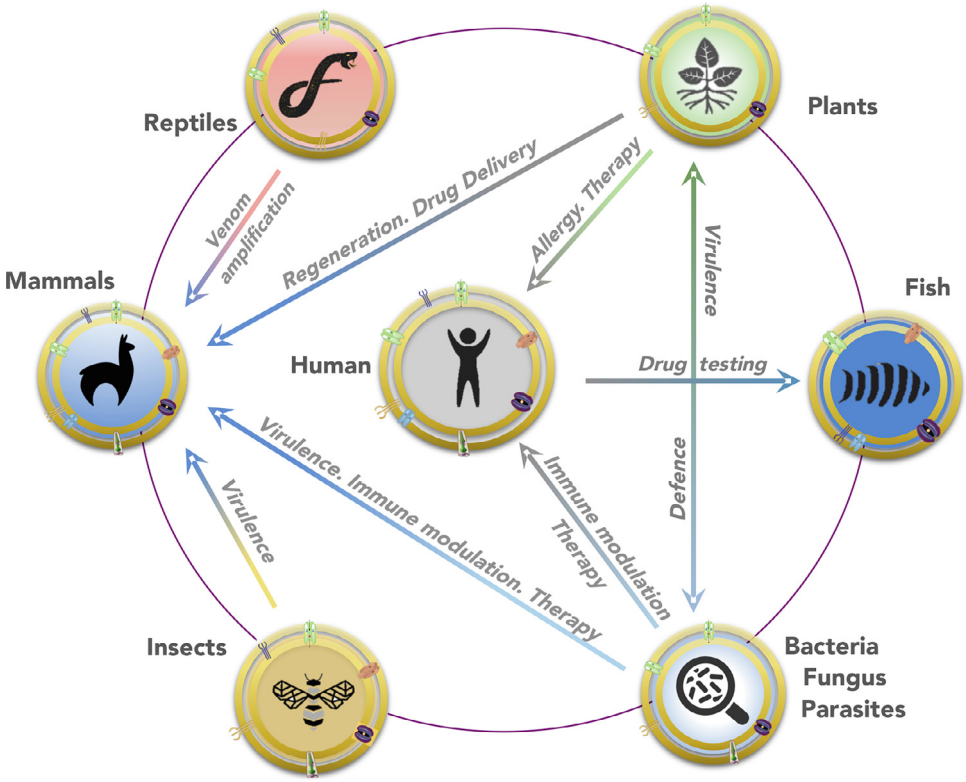

Fig 2. Overview of exosome interkingdom communication, including microbes (bacteria, fungus, parasites), plants, insects, reptiles and fish. Mammals and humans are depicted separately, to depict differences between model organism and clinical trials. Arrow origin indicates species donating exosomes, while arrow tip indicates at exosome receiving species. Arrows are accompanied by the most important effect exosomes elicit in the recipient species or most common use.

apoplastic fluid of sunflower seeds contains microvesicles carrying GTPase Rab cargo.[134] Liang et al discovered circulating plant miRNA (watermelon) in human plasma, speculating about the presence of microvesicles.[135]

However Ju et al were the first to investigate the effect of plant exosomes on the mammalian digestive system. Exosome-like nanoparticles were isolated from grapes (GELN) and their effect on intestinal stem cells was assessed in vitro, as well as in a colitis mouse model in vivo. GELN were found to not only be taken up by intestinal cells, but also to increase proliferation and organoid formation in vitro. In a dextran sulphate sodium-induced colitis model, mice ingesting grape exosomes revealed a decreased onset of colitis, indicating the regenerative and protective effect of these exosomes.[136] In a follow-up study exosomes from ginger, carrot, grapefruit as well as grape were analyzed concerning pathways for interspecies communication. It was shown that those exosomes were taken up by macrophages and intestinal stem cells, and furthermore that exosomes from different plant sources activated different pathways in mammalian cells. While ginger mainly induced interleukin 10 and heme-oxygenase 1 expression in macrophages, grape, and grapefruit were found to induce Wnt/TCF4 expression. Furthermore, grapefruit, ginger, and carrot promoted activation of nuclear factor (erythroid-derived 2)-like 2. The authors of the study conclude that "the data suggest a role for EPDEN mediated interspecies communication by inducing expression of genes for anti-inflammation cytokines, antioxidation, and activation of Wnt signaling, which are crucial for maintaining intestinal homeostasis."[137] It is noteworthy that communication between plants and animals can be classified as "interkingdom" communication, rather than interspecies (Fig 2). Zhou et al provided new insight into interkingdom crosstalk in their 2017 review, pointing out the importance of miRNA as well as sRNA, which they argue to travel through the organism via two potential mechanisms: on the one hand sRNA are taken up by intestinal cells and subsequently packaged into exosomes and secreted, and on the other hand—referring to[137]—within plant exosomes themselves.[138] Interestingly, plant exosomes have not only been shown to interact with fungal and mammalian cells,

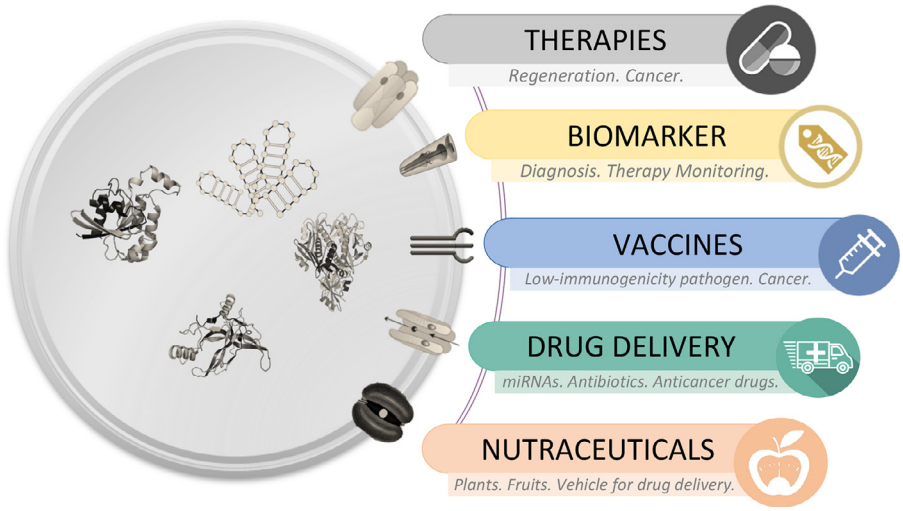

Fig 3. Exosomes identified from the different tissues or species can be used in a plethora of different biomedical applications. The administration of exosomes can be applied as cell-based therapies, vaccine or as nutraceuticals. The identification of exosomes in body fluids can be utilized to identify diseases and monitor therapy progression (biomarkers). Finally, the loading of exosomes with miRNA, proteins or small molecules represents a new delivery system for drugs and antibiotics.

but also with bacteria. Yu et al discovered that commensal bacteria such as *Escherichia coli* MG1655 and *Lactobacillus plantarum* take up exosomes derived from coconut water (*Cocos nuciferi*).[139]

A reoccurring future perspective is the use of plant exosomes in a therapeutic setting, either utilizing known therapeutic properties of plants or package plant exosomes with a therapeutic cargo. In a preclinical study, Wang et al utilized grapefruit-derived exosomes to deliver doxorubicin 2 to different cancer models, showing a decreased growth of the tumors. Furthermore, the same exosomes were loaded with curcumin and tested in a colitis model, revealing a protective effect in DSS colitis.[140] Zhuang et al investigated the effect of intranasal administration of micro RNA 17 encapsulated into folic acid coated grapefruit vesicles on brain tumors and found a selective uptake into FL-26 tumor cells in vitro and delayed tumor growth in a mouse model.[141] Li et al reported a tumor-inhibiting effect of ginger-derived exosomes, when decorated with orientable arrowtail RNA for siRNA delivery.[142]

Another interesting aspect in plant exosomes are pollen-derived exosomes, or pollensomes. Prado et al first analyzed protein content of *Olea europaea* pollen-derived exosomes (as well as *Betula verrucosa, Pinus sylvestris* and *Lolium perenne*), to then further investigate their role in allergy. They found proteins associated to a number of cellular functions, such as metabolism and signaling (eg, fructokinase), protein synthesis and processing (eg, peptidyl-prolyl-isomerase), but also cell wall expansion (eg, PME) or membrane transport (eg, H +-ATPase 6), and concluded that the interplay of those play a crucial role in pollen tube growth and successful fertilization. They also found proteins related to defense responses (eg, phenylcoumaran benzylic ether reductase, heat shock protein 70), and allergen-associated proteins (Ole e 1, Ole e 11 (a PME), and Ole e 12).[143] In a subsequent clinical study, they investigated allergenic potential of Olea pollensomes and found increased patients IgE-binding, human basophil activation, and positive skin reactions. To address the question whether pollensomes are a laboratory phenomenon or naturally occurring, they collected aerobiological samples and isolated pollensomes, concluding that pollensomes could be vehicles for pollen allergens, potentially playing crucial roles in allergic reactions.[144]

APPLICATIONS AND CHALLENGES

Over the last years, research on potential applications for exosomes has caught the attention of a number of clinical fields. The proposed benefits range from easily accessible to versatile and safe cell-free therapy, and due to their known regenerative potential, MSCs have been a popular source for exosomes.

However, as mentioned throughout the review, other sources appear to offer interesting opportunities in medicine. Understanding the role of exosomes in pathology might augment in developing treatments, but also associate symptoms to pathogens (eg, P. gingivalis OMVs in arteriosclerosis). Therefore, throughout the following section we will describe several potential applications for exosomes with direct benefit in clinics and medicine (Fig 3).

Therapy: Due to their innate role in tissue regeneration, MSCs have been used as a source of regenerative exosomes for a variety of conditions, such as wound healing,[145,146] ischemic pathologies such as stroke[147,148] and heart infarct,[149,150] as well as liver fibrosis[16] and sepsis.[151] Promising anticancer therapies include exosomes derived from DCs, but also chimeric antigen presenting T cells[21,25] and ginger-derived exosomes.[142] Exosomes derived from microbiota bacteria, helminth parasites, and grapes have shown to alleviate symptoms in intestinal pathologies such as colitis.[79,129,130,136]

Vaccines: OMVs have offered an opportunity to develop vaccines for pathogens with low immunogenicity, such as *N. meningitidis* serogroup B (MenB), which traditionally bears the risk of autoimmunity due to the low immunogenicity of its capsular polysaccharides. Since the 1970s, parenteral vaccines using wildtype OMVs are in use in several countries (Norway, Cuba, New Zealand), with an efficacy of 70%-83%. Other examples for wildtype OMVs include *Vibrio cholerae* ($dOMV_C$), *Bordetella pertussis* ($dOMV_{BP}$), and *Mycobacterium smegmatis*.[152] In a new trend, genetically modified bacteria are used to improve vaccine efficacy. In case of MenB, a strain was genetically engineered to have constitutive expression of the outer membrane protein FetA, which again has been shown to induce bacteriocidal antibodies in humans.[153] Interestingly, OMV based vaccines are also being considered for vaccinating fish against diseases such as francisellosis.[154]

Over the years several studies have investigated exosomes as anticancer vaccines. Zitvogel et al in 1998 showed DC-derived exosomes bear functional MHC I and II molecules able to induce an antitumor immune responses, which has led to several clinical trials.[22-24] However, further research is necessary in this field in order to transfer these therapies into everyday clinical therapies.

Drug delivery: Exosomes display a number advantages as nanocarriers for drug delivery, such as penetration into deep tissues, a characteristic zeta potential (measure of electric charge in disperse nanoparticle systems)[155] allowing prolonged circulation as well as their intrinsic cell-targeting properties.[156] Mouse lymphoma cell line-derived exosomes loaded with curcumin have been shown to decrease inflammation in septic mice.[157] Loaded with doxorubicin, DC-derived exosomes lead to inhibition of breast tumor growth.[158] Yang et al were able to demonstrate that exosomes derived from cancer cell lines transport doxorubicin and paclitaxel across the blood brain barrier in an interkingdom model using zebrafish (*Danio Rerio*).[33] Macrophage and monocyte-derived exosomes were shown to be able to transport the antioxidant catalase to the brain in an attempt to treat Parkinson's disease in a mouse model.[159]

Biomarkers: Cancer-derived exosomes as well as body−fluid-derived exosomes have shown great potential for the use as biomarkers in early diagnosis and therapy monitoring.[43,160,161] Analysis of urinary exosome contents have been extensively investigated for their use as potential biomarkers for renal dysfunction and injury (eg, polycystic kidney disease[162] or diabetic nephropathy).[163] Furthermore, placental exosomes are of interest for detection of pre-eclampsia, an obstetric disorder associated to severe complications during pregnancy.[43] Also, serum-derived exosomes have been shown to assist in diagnosis of glioblastoma, Parkinson's disease but also Alzheimer's disease.[164-166]

Nutraceuticals: are an emerging field, and exosomes derived from whey and edible plants such as grape or grapefruit, which have been shown to be taken up by mammalian cells and exert beneficial effects on the digestive tract. Furthermore they were shown to be modifiable in their cargo (eg, adding doxorubicin or curcumin), altering their properties[136,140] and presenting a cost-efficient and versatile alternative to cell−culture-derived exosomes.

Challenges: Currently, the use of exosomes in the clinics is facing a number of challenges in the manufacturing process, as reviewed by Colao et al.[167] The main method used for labscale isolation of exosomes—ultracentrifugation−has been demonstrated to isolate both, microvesicles and exosomes without discriminating between the 2 types without extensive processing.[168] Furthermore, changing from labscale ultracentrifugation to more scalable isolation techniques such as tangential flow filtration resulted in different exosome cargos and functional outcomes.[169,170] Aside from manufacturing, Yang et al identified drug loading and delivery to target cells as potential challenges for exosome therapy.[171]

POTENTIAL SOURCES AND PERSPECTIVES

While numerous sources have already been examined for the presence and biological role of exosomes, others—even though the presence of exosomes can be assumed—appear to be understudied. Carneiro et al as well as Ogawa et al discovered exosomes in snake venom, which is secreted by venom glands and related to salivary glands. Consequently, other secretes produced by salivary-related glands could be a potential source for exosomes. Examples include Bombyx mori silk, Aerodramus saliva (which hardens when in contact with air), puffer fish secrete, octopus mucus, shrew saliva as well as lizard and iguana venom.[172] Furthermore it can be

hypothesized that bee products such as honey or royal jelly may contain exosomes not just due to their origin (hypopharyngeal and mandibular glands), but also because of their lipid and membrane-derived fatty acids contents.[173,174] Given that human placenta has been demonstrated to produce exosomes, placental tissue throughout species could be a source of exosomes, such as, bird eggs, but also fish or amphibian eggs. Several animals with remarkable characteristics have been thoroughly studied to identify underlying molecular mechanisms, however have not been evaluated for the presence of exosomes yet. This includes the axolotl due to its ability to regenerate limbs,[175] animals known to produce bioadhesives,[176] as well as snail mucus as it has been shown to exert regenerative effects.[177]

CONCLUSIONS

Exosomes have been found in all taxonomic kingdoms and offer numerous opportunities to study physiological processes and pathologies, as well as regeneration. As exosomal communication is not confined to interspecies interaction, the potential to discover new pathologic mechanisms (eg, participation of OMVs in Alzheimer's disease) as well as novel therapies appears endless. Until now only a few nonmammalian sources have been tested in preclinical or clinical settings and the potential of exosomes has not been exhaustively studied. Several probable exosomes sources such as bee products or indigenous medicinal plants have not been investigated yet. If exosomes are proven to be the active compounds of natural products then their isolation from those sources could offer the opportunity of bringing traditional medicine into the 21st century. Aside from their innate cargo, exosomes from several taxonomic kingdoms have been shown to be loadable with therapeutic agents such as curcumin, doxorubicin or paclitaxel, acting as nanocarrier drug delivery systems in mammals. Medical applications of exosomes include therapeutic approaches such as anticancer therapies, vaccines against microbes with low immunogenicity but also cancer, drug delivery systems, and biomarkers for several conditions. Alternative sources of exosomes such as bacteria, parasites or plants offer cost-effective and easily scalable alternatives to conventional therapeutic exosome sources such as cultivated MSCs.

ACKNOWLEDGMENTS

This work was supported by CONICYT FONDECYT grant No. 11180406, and CORFO grant No. 17CH-83954.

We confirm that all authors have read the journal's authorship agreement, and that the manuscript has been reviewed by and approved by all named authors. Furthermore, confirm that all authors have read the journal's policy on disclosure of potential conflicts of interest. MK is the CSO of Cells for Cells and Regenero, FAM and JC received stipends from Regenero. CS declares no conflicts of interest.

REFERENCES

1. Trams EG, Lauter CJ, Norman Salem J, Heine U. Exfoliation of membrane ecto-enzymes in the form of micro-vesicles. BBA - Biomembr 1981;645:63–70. https://doi.org/10.1016/0005-2736(81)90512-5.
2. Pan BT, Johnstone RM. Fate of the transferrin receptor during maturation of sheep reticulocytes in vitro: selective externalization of the receptor. Cell 1983;33:967–78. https://doi.org/10.1016/0092-8674(83)90040-5.
3. Raposo G. B lymphocytes secrete antigen-presenting vesicles. J Exp Med 1996;183:1161–72. https://doi.org/10.1084/jem.183.3.1161.
4. Valadi H, Ekström K, Bossios A, Sjöstrand M, Lee JJ, Lötvall JO. Exosome-mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells. Nat Cell Biol 2007;9:654–9. https://doi.org/10.1038/ncb1596.
5. Lï¿½tvall 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. https://doi.org/10.3402/jev.v3.26913.
6. 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. https://doi.org/10.1080/20013078.2018.1535750.
7. Ratajczak J, Miekus K, Kucia M, et al. Embryonic stem cell-derived microvesicles reprogram hematopoietic progenitors: evidence for horizontal transfer of mRNA and protein delivery. Leukemia 2006;20:847–56. https://doi.org/10.1038/sj.leu.2404132.
8. Alcayaga-Miranda F, Varas-Godoy M, Khoury M. Harnessing the angiogenic potential of stem cell-derived exosomes for vascular regeneration. Stem Cells Int 2016: 34091. https://doi.org/10.1155/2016/3409169.
9. Jing H, He X, Zheng J. Exosomes and regenerative medicine: state of the art and perspectives. Transl Res 2018. https://doi.org/10.1016/j.trsl.2018.01.005.
10. Lee J-K, Park S-R, Jung B-K, et al. Exosomes derived from mesenchymal stem cells suppress angiogenesis by down-regulating VEGF expression in breast cancer cells. PLoS One 2013;8:e84256. https://doi.org/10.1371/journal.pone.0084256.
11. Baglio SR, Rooijers K, Koppers-Lalic D, et al. Human bone marrow- and adipose-mesenchymal stem cells secrete exosomes enriched in distinctive miRNA and tRNA species. Stem Cell Res Ther 2015;6:127. https://doi.org/10.1186/s13287-015-0116-z.
12. Alcayaga-Miranda F, González PL, Lopez-Verrilli A, Aguila-Díaz C, Contreras L, Khoury M. Prostate tumor-induced angiogenesis is blocked by exosomes derived from menstrual stem cells through the inhibition of reactive oxygen species. Oncotarget 2016;7:44462–77. https://doi.org/10.18632/oncotarget.9852.
13. Shabbir A, Cox A, Rodriguez-Menocal L, Salgado M, Van Badiavas E. Mesenchymal stem cell exosomes induce proliferation and migration of normal and chronic wound fibroblasts, and enhance angiogenesis in vitro. Stem Cells Dev 2015;24:1635–47. https://doi.org/10.1089/scd.2014.0316.

14. Lopez-Verrilli MA, Caviedes A, Cabrera A, Sandoval S, Wyneken U, Khoury M. Mesenchymal stem cell derived exosomes from different sources selectively promote neuritic outgrowth. Neuroscience 2016;320:129–39. https://doi.org/10.1016/j.neuroscience.2016.01.061.
15. Bruno S, Grange C, Deregibus MC, et al. Mesenchymal stem cell-derived microvesicles protect against acute tubular injury. J Am Soc Nephrol 2009;20:1053–67. https://doi.org/10.1681/ASN.2008070798.
16. Li T, Yan Y, Wang B, et al. Exosomes derived from human umbilical cord mesenchymal stem cells alleviate liver fibrosis. Stem Cells Dev 2012;22. https://doi.org/10.1089/scd.2012.0395 120924123440009.
17. Khan M, Nickoloff E, Abramova T, et al. Embryonic stem cell-derived exosomes promote endogenous repair mechanisms and enhance cardiac function following myocardial infarction. Circ Res 2015;117:52–64. https://doi.org/10.1161/CIRCRESAHA.117.305990.
18. Hu GW, Li Q, Niu X, et al. Exosomes secreted by human-induced pluripotent stem cell-derived mesenchymal stem cells attenuate limb ischemia by promoting angiogenesis in mice. Stem Cell Res Ther 2015;6. https://doi.org/10.1186/scrt546.
19. Nong K, Wang W, Niu X, et al. Hepatoprotective effect of exosomes from human-induced pluripotent stem cell−derived mesenchymal stromal cells against hepatic ischemia-reperfusion injury in rats. Cytotherapy 2016;18:1548–59. https://doi.org/10.1016/j.jcyt.2016.08.002.
20. Zhang B, Yin Y, Lai RC, Lim SK. Immunotherapeutic potential of extracellular vesicles. Front Immunol 2014;5. https://doi.org/10.3389/fimmu.2014.00518.
21. Zitvogel L, Regnault A, Lozier A, et al. Eradication of established murine tumors using a novel cell-free vaccine: dendritic cell-derived exosomes. Nat Med 1998;4:594–600. https://doi.org/10.1038/nm0598-594.
22. Escudier B, Dorval T, Chaput N, et al. Vaccination of metastatic melanoma patients with autologous dendritic cell (DC) derived-exosomes: results of thefirst phase I clinical trial. J Transl Med 2005;3:10. https://doi.org/10.1186/1479-5876-3-10.
23. Morse MA, Garst J, Osada T, et al. A phase I study of dexosome immunotherapy in patients with advanced non-small cell lung cancer. J Transl Med 2005;3. https://doi.org/10.1186/1479-5876-3-9.
24. Besse B, Charrier M, Lapierre V, et al. Dendritic cell-derived exosomes as maintenance immunotherapy after first line chemotherapy in NSCLC. Oncoimmunology 2016;5. https://doi.org/10.1080/2162402X.2015.1071008.
25. Tang X-J, Sun X-Y, Huang K-M, et al. Therapeutic potential of CAR-T cell-derived exosomes: a cell-free modality for targeted cancer therapy. Oncotarget 2015;6:44179–90. https://doi.org/10.18632/oncotarget.6175.
26. King HW, Michael MZ, Gleadle JM. Hypoxic enhancement of exosome release by breast cancer cells. BMC Cancer 2012;12. https://doi.org/10.1186/1471-2407-12-421.
27. Wolfers J, Lozier A, Raposo G, et al. Tumor-derived exosomes are a source of shared tumor rejection antigens for CTL cross-priming. Nat Med 2001;7:297–303. https://doi.org/10.1038/85438.
28. Skog J, Würdinger T, van Rijn S, et al. Glioblastoma microvesicles transport RNA and proteins that promote tumour growth and provide diagnostic biomarkers. Nat Cell Biol 2008;10:1470–6. https://doi.org/10.1038/ncb1800.
29. Lau C, Kim Y, Chia D, et al. Role of pancreatic cancer-derived exosomes in salivary biomarker development. J Biol Chem 2013;288:26888–97. https://doi.org/10.1074/jbc.M113.452458.
30. Gangoda L, Liem M, Ang CS, et al. Proteomic profiling of exosomes secreted by breast cancer cells with varying metastatic potential. Proteomics 2017;17. https://doi.org/10.1002/pmic.201600370.
31. Safaei R. Abnormal lysosomal trafficking and enhanced exosomal export of cisplatin in drug-resistant human ovarian carcinoma cells. Mol Cancer Ther 2005;4:1595–604. https://doi.org/10.1158/1535-7163.MCT-05-0102.
32. Chen WX, Liu XM, Lv MM, et al. Exosomes from drug-resistant breast cancer cells transmit chemoresistance by a horizontal transfer of MicroRNAs. PLoS One 2014;9. https://doi.org/10.1371/journal.pone.0095240.
33. Yang T, Martin P, Fogarty B, et al. Exosome delivered anticancer drugs across the blood-brain barrier for brain cancer therapy in Danio Rerio. Pharm Res 2015;32:2003–14. https://doi.org/10.1007/s11095-014-1593-y.
34. Théry C. Exosomes: secreted vesicles and intercellular communications. F1000 Biol Rep 2011;3:1–8. https://doi.org/10.3410/B3-15.
35. Bobrie A, Colombo M, Raposo G, Théry C. Exosome secretion: molecular mechanisms and roles in immune responses. Traffic 2011;12:1659–68. https://doi.org/10.1111/j.1600-0854.2011.01225.x.
36. Bretz NP, Ridinger J, Rupp A-K, et al. Body fluid exosomes promote secretion of inflammatory cytokines in monocytic cells via Toll-like receptor signaling. J Biol Chem 2013;288:36691–702. https://doi.org/10.1074/jbc.M113.512806.
37. Ogawa Y, Kanai-Azuma M, Akimoto Y, Kawakami H, Yanoshita R. Exosome-like vesicles with dipeptidyl peptidase IV in human saliva. Biol Pharm Bull 2008;31:1059–62. https://doi.org/10.1248/bpb.31.1059.
38. Ogawa Y, Miura Y, Harazono A, et al. Proteomic analysis of two types of exosomes in human whole saliva. Biol Pharm Bull 2011;34:13–23. https://doi.org/10.1248/bpb.34.13 [pii].
39. Berckmans RJ, Sturk A, Van Tienen LM, Schaap MCL, Nieuwland R. Cell-derived vesicles exposing coagulant tissue factor in saliva. Blood 2011;117:3172–80. https://doi.org/10.1182/blood-2010-06-290460.
40. Hiemstra TF, Charles PD, Gracia T, et al. Human urinary exosomes as innate immune effectors. J Am Soc Nephrol 2014;25:2017–27. https://doi.org/10.1681/ASN.2013101066.
41. Kwon TH, Frøkiær J, Nielsen S. Regulation of aquaporin-2 in the kidney: a molecular mechanism of body-water homeostasis. Kidney Res Clin Pract 2013;32:96–102. https://doi.org/10.1016/j.krcp.2013.07.005.
42. Street JM, Birkhoff W, Menzies RI, Webb DJ, Bailey MA, Dear JW. Exosomal transmission of functional aquaporin 2 in kidney cortical collecting duct cells. J Physiol 2011;589:6119–27. https://doi.org/10.1113/jphysiol.2011.220277.
43. Salomon C, Torres MJ, Kobayashi M, et al. A gestational profile of placental exosomes in maternal plasma and their effects on endothelial cell migration. PLoS One 2014;9:e98667. https://doi.org/10.1371/journal.pone.0098667.
44. Pillay P, Maharaj N, Moodley J, Mackraj I. Placental exosomes and pre-eclampsia: maternal circulating levels in normal pregnancies and, early and late onset pre-eclamptic pregnancies. Placenta 2016;46:18–25. https://doi.org/10.1016/j.placenta.2016.08.078.
45. Salomon C, Guanzon D, Scholz-Romero K, et al. Placental exosomes as early biomarker of preeclampsia: potential role of exosomal MicroRNAs across gestation. J Clin Endocrinol Metab 2017;102:3182–94. https://doi.org/10.1210/jc.2017-00672.
46. Tan KH, Tan SS, Ng MJ, et al. Extracellular vesicles yield predictive pre-eclampsia biomarkers. J Extracell Vesicles 2017;6:1408390. https://doi.org/10.1080/20013078.2017.1408390.

47. Admyre C, Johansson SM, Qazi KR, et al. Exosomes with immune modulatory features are present in human breast milk. J Immunol 2007;179:1969–78.
48. Lässer C, Seyed Alikhani V, Ekström K, et al. Human saliva, plasma and breast milk exosomes contain RNA: uptake by macrophages. J Transl Med 2011;9. https://doi.org/10.1186/1479-5876-9-9.
49. Torregrosa Paredes P, Gutzeit C, Johansson S, et al. Differences in exosome populations in human breast milk in relation to allergic sensitization and lifestyle. Allergy 2014;69:463–71. https://doi.org/10.1111/all.12357.
50. Santonocito M, Vento M, Guglielmino MR, et al. Molecular characterization of exosomes and their microRNA cargo in human follicular fluid: bioinformatic analysis reveals that exosomal microRNAs control pathways involved in follicular maturation. Fertil Steril 2014;102:1751–61,. https://doi.org/10.1016/j.fertnstert.2014.08.005 e1.
51. Poliakov A, Spilman M, Dokland T, Amling CL, Mobley JA. Structural heterogeneity and protein composition of exosome-like vesicles (prostasomes) in human semen. Prostate 2009;69:159–67. https://doi.org/10.1002/pros.20860.
52. Sullivan R, Saez F. Epididymosomes, prostasomes, and liposomes: their roles in mammalian male reproductive physiology. Reproduction 2013;146:R21–35. https://doi.org/10.1530/REP-13-0058.
53. Ronquist GK, Larsson A, Stavreus-Evers A, Ronquist G. Prostasomes are heterogeneous regarding size and appearance but affiliated to one DNA-containing exosome family. Prostate 2012;72:1736–45. https://doi.org/10.1002/pros.22526.
54. Vojtech L, Woo S, Hughes S, et al. Exosomes in human semen carry a distinctive repertoire of small non-coding RNAs with potential regulatory functions. Nucleic Acids Res 2014;42:7290–304. https://doi.org/10.1093/nar/gku347.
55. Ronquist KG, Ronquist G, Carlsson L, Larsson A. Human prostasomes contain chromosomal DNA. Prostate 2009;69:737–43. https://doi.org/10.1002/pros.20921.
56. Ronquist G. Prostasomes are mediators of intercellular communication: from basic research to clinical implications. J Intern Med 2012;271:400–13. https://doi.org/10.1111/j.1365-2796.2011.02487.x.
57. Arienti G, Carlini E, Saccardi C, Palmerini CA. Role of human prostasomes in the activation of spermatozoa. J Cell Mol Med 2004;8:77–84. https://doi.org/10.1111/j.1582-4934.2004.tb00261.x.
58. Aalberts M, van Dissel-Emiliani FMF, van Adrichem NPH, et al. Identification of distinct populations of prostasomes that differentially express prostate stem cell antigen, annexin A1, and GLIPR2 in humans. Biol Reprod 2012;86:82. https://doi.org/10.1095/biolreprod.111.095760.
59. Reinhardt TA, Lippolis JD, Nonnecke BJ, Sacco RE. Bovine milk exosome proteome. J Proteomics 2012;75:1486–92. https://doi.org/10.1016/j.jprot.2011.11.017.
60. Samuel M, Chisanga D, Liem M, et al. Bovine milk-derived exosomes from colostrum are enriched with proteins implicated in immune response and growth. Sci Rep 2017;7. https://doi.org/10.1038/s41598-017-06288-8.
61. Reinhardt TA, Sacco RE, Nonnecke BJ, Lippolis JD. Bovine milk proteome: quantitative changes in normal milk exosomes, milk fat globule membranes and whey proteomes resulting from Staphylococcus aureus mastitis. J Proteomics 2013;82:141–54. https://doi.org/10.1016/j.jprot.2013.02.013.
62. Mobley CB, Mumford PW, McCarthy JJ, et al. Whey protein-derived exosomes increase protein synthesis and hypertrophy in C 2−C 12 myotubes. J Dairy Sci 2017;100:48–64. https://doi.org/10.3168/jds.2016-11341.
63. Johnstone MB, Gohad N V, Falwell EP, Hansen DC, Hansen KM, Mount AS. Cellular orchestrated biomineralization of crystalline composites on implant surfaces by the eastern oyster, Crassostrea virginica (Gmelin, 1791). J Exp Mar Bio Ecol 2015;463:8–16. https://doi.org/10.1016/j.jembe.2014.10.014.
64. Zhou W, Woodson M, Neupane B, et al. Exosomes serve as novel modes of tick-borne flavivirus transmission from arthropod to human cells and facilitates dissemination of viral RNA and proteins to the vertebrate neuronal cells. PLoS Pathog 2018;14. https://doi.org/10.1371/journal.ppat.1006764.
65. Carneiro SM, Fernandes W, Sant'Anna SS, Yamanouye N. Microvesicles in the venom of Crotalus durissus terrificus (Serpentes, Viperidae). Toxicon 2007;49:106–10. https://doi.org/10.1016/j.toxicon.2006.04.020.
66. Ogawa Y, Kanai-Azuma M, Akimoto Y, Kawakami H, Yanoshita R. Exosome-like vesicles in Gloydius blomhoffii blomhoffii venom. Toxicon 2008;51:984–93. https://doi.org/10.1016/j.toxicon.2008.02.003.
67. Carregari VC, Rosa-Fernandes L, Baldasso P, et al. Snake Venom Extracellular vesicles (SVEVs) reveal wide molecular and functional proteome diversity. Sci Rep 2018;8:12067. https://doi.org/10.1038/s41598-018-30578-4.
68. Kuehn MJ, Kesty NC. Bacterial outer membrane vesicles and the host-pathogen interaction. Genes Dev 2005;19:2645–55, doi:19/22/264519/22/2645 [pii]\r10.1101/gad.1299905.
69. MacDonald IA, Kuehn MJ. Stress-induced outer membrane vesicle production by Pseudomonas aeruginosa. J Bacteriol 2013;195:2971–81. https://doi.org/10.1128/Jb.02267-12.
70. 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. https://doi.org/10.1128/jb.177.14.3998-4008.1995.
71. Weiner A, Mellouk N, Lopez-Montero N, et al. Macropinosomes are key players in early shigella invasion and vacuolar escape in epithelial cells. PLoS Pathog 2016;12. https://doi.org/10.1371/journal.ppat.1005602.
72. Lewis W. Pinocytosis. John Hopkins Hosp Bull 1931;49:17–27.
73. Norbury CC, Hewlett LJ, Prescott AR, Shastri N, Watts C. Class I MHC presentation of exogenous soluble antigen via macropinocytosis in bone marrow macrophages. Immunity 1995;3:783–91. https://doi.org/10.1016/1074-7613(95)90067-5.
74. Cañas MA, Giménez R, Fábrega MJ, Toloza L, Baldomà L, Badia J. Outer membrane vesicles from the probiotic Escherichia coli Nissle 1917 and the commensal ECOR12 enter intestinal epithelial cells via clathrin-dependent endocytosis and elicit differential effects on DNA damage. PLoS One 2016;11. https://doi.org/10.1371/journal.pone.0160374.
75. Vercauteren D, Vandenbroucke RE, Jones AT, et al. The use of inhibitors to study endocytic pathways of gene carriers: optimization and pitfalls. Mol Ther 2010;18:561–9. https://doi.org/10.1038/mt.2009.281.
76. Lim JS, Shin M, Kim HJ, Kim KS, Choy HE, Cho KA. Caveolin-1 mediates salmonella invasion via the regulation of SopE-dependent Rac1 activation and actin reorganization. J Infect Dis 2014;210:793–802. https://doi.org/10.1093/infdis/jiu152.
77. Bomberger JM, MacEachran DP, Coutermarsh BA, Ye S, O'Toole GA, Stanton BA. Long-distance delivery of bacterial virulence factors by pseudomonas aeruginosa outer membrane vesicles. PLoS Pathog 2009;5. https://doi.org/10.1371/journal.ppat.1000382.
78. Shen Y, Torchia MLG, Lawson GW, Karp CL, Ashwell JD, Mazmanian SK. Outer membrane vesicles of a human

commensal mediate immune regulation and disease protection. Cell Host Microbe 2012;12:509–20. https://doi.org/10.1016/j.chom.2012.08.004.
79. sung Kang C, Ban M, Choi EJ, et al. Extracellular vesicles derived from gut microbiota, especially Akkermansia muciniphila, protect the progression of dextran sulfate sodium-induced colitis. PLoS One 2013;8. https://doi.org/10.1371/journal.pone.0076520.
80. Donato GM, Goldsmith CS, Paddock CD, Eby JC, Gray MC, Hewlett EL. Delivery of Bordetella pertussis adenylate cyclase toxin to target cells via outer membrane vesicles. FEBS Lett 2012;586:459–65. https://doi.org/10.1016/j.febslet.2012.01.032.
81. Jha C, Ghosh S, Gautam V, Malhotra P, Ray P. In vitro study of virulence potential of Acinetobacter baumannii outer membrane vesicles. Microb Pathog 2017;111:218–24. https://doi.org/10.1016/j.micpath.2017.08.048.
82. Kadurugamuwa JL, Beveridge TJ. Bacteriolytic effect of membrane vesicles from *Pseudomonas aeruginosa* on other bacteria including pathogens: conceptually new antibiotics. J Bacteriol 1996;178:2767–74, doi: .
83. Dutta S, Iida KI, Takade A, Meno Y, Nair GB, Yoshida SI. 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;48:965–9. https://doi.org/10.1111/j.1348-0421.2004.tb03626.x.
84. 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.
85. Ricci V, Chiozzi V, Necchi V, et al. Free-soluble and outer membrane vesicle-associated VacA from Helicobacter pylori: two forms of release, a different activity. Biochem Biophys Res Commun 2005;337:173–8. https://doi.org/10.1016/j.bbrc.2005.09.035.
86. Li J, Azam F, Zhang S. Outer membrane vesicles containing signalling molecules and active hydrolytic enzymes released by a coral pathogen Vibrio shilonii AK1. Environ Microbiol 2016;18:3850–66. https://doi.org/10.1111/1462-2920.13344.
87. Evans AGL, Davey HM, Cookson A, et al. Predatory activity of Myxococcus xanthus outer-membrane vesicles and properties of their hydrolase cargo. Microbiol (United Kingdom) 2012;158:2742–52. https://doi.org/10.1099/mic.0.060343-0.
88. Ciofu O, Beveridge TJ, Kadurugamuwa J, Walther-Rasmussen J, Høiby N. Chromosomal beta-lactamase is packaged into membrane vesicles and secreted from Pseudomonas aeruginosa. J Antimicrob Chemother 2000;45:9–13. https://doi.org/10.1093/jac/45.1.9.
89. Devos S, Van Oudenhove L, Stremersch S, et al. The effect of imipenem and diffusible signaling factors on the secretion of outer membrane vesicles and associated Ax21 proteins in Stenotrophomonas maltophilia. Front Microbiol 2015;6. https://doi.org/10.3389/fmicb.2015.00298.
90. Lee J, Lee EY, Kim SH, et al. Staphylococcus aureus extracellular vesicles carry biologically active β-lactamase. Antimicrob Agents Chemother 2013;57:2589–95. https://doi.org/10.1128/AAC.00522-12.
91. Rumbo C, Fernández-Moreira E, Merino M, et al. Horizontal transfer of the OXA-24 carbapenemase gene via outer membrane vesicles: a new mechanism of dissemination of carbapenem resistance genes in Acinetobacter baumannii. Antimicrob Agents Chemother 2011;55:3084–90. https://doi.org/10.1128/AAC.00929-10.
92. Lapinet JA, Scapini P, Calzetti F, Pérez O, Cassatella MA. Gene expression and production of tumor necrosis factor alpha, interleukin-1β (IL-1β), IL-8, macrophage inflammatory protein 1α (MIP-1α), MIP-1β, and gamma interferon-inducible protein 10 by human neutrophils stimulated with group B meningococcal outer me. Infect Immun 2000;68:6917–23. https://doi.org/10.1128/IAI.68.12.6917-6923.2000.
93. Cecil JD, O'Brien-Simpson NM, Lenzo JC, et al. Outer membrane vesicles prime and activate macrophage inflammasomes and cytokine secretion in vitro and in vivo. Front Immunol 2017;8. https://doi.org/10.3389/fimmu.2017.01017.
94. Schultz H, Hume J, Zhang DS, Gioannini TL, Weiss JP. A novel role for the bactericidal/permeability increasing protein in interactions of gram-negative bacterial outer membrane blebs with dendritic cells. J Immunol 2007;179:2477–84. https://doi.org/10.4049/jimmunol.179.4.2477.
95. Grenier D, Bertrand J, Mayrand D. Porphyromonas gingivalis outer membrane vesicles promote bacterial resistance to chlorhexidine. Oral Microbiol Immunol 1995;10:319–20. https://doi.org/10.1111/j.1399-302X.1995.tb00161.x.
96. Waller T, Kesper L, Hirschfeld J, et al. Porphyromonas gingivalis outer membrane vesicles induce selective tumor necrosis factor tolerance in a Toll-like receptor 4- and mTOR-dependent manner. Infect Immun 2016;84:1194–204. https://doi.org/10.1128/IAI.01390-15.
97. Furuta N, Takeuchi H, Amano A. Entry of Porphyromonas gingivalis outer membrane vesicles into epithelial cells causes cellular functional impairment. Infect Immun 2009;77:4761–70. https://doi.org/10.1128/IAI.00841-09.
98. Sheets SM, Robles-Price AG, McKenzie RME, Casiano CA, Fletcher HM. Gingipain-dependent interactions with the host are important for survival of Porphyromonas gingivalis. Front Biosci 2008;13:3215–38. https://doi.org/10.2741/2922.
99. Popadiak K, Potempa J, Riesbeck K, Blom AM. Biphasic effect of gingipains from Porphyromonas gingivalis on the human complement system. J Immunol 2007;178:7242–50. https://doi.org/10.4049/jimmunol.178.11.7242.
100. Lai W-T, Krishnappa V, Phinney DG. Fibroblast growth factor 2 (Fgf2) inhibits differentiation of mesenchymal stem cells by inducing Twist2 and Spry4, blocking extracellular regulated kinase activation, and altering Fgf receptor expression levels. Stem Cells 2011;29:1102–11.
101. Yang WW, Guo B, Jia WY, Jia Y. Porphyromonas gingivalis-derived outer membrane vesicles promote calcification of vascular smooth muscle cells through ERK1/2-RUNX2. FEBS Open Bio 2016;6:1310–9. https://doi.org/10.1002/2211-5463.12151.
102. Hong SW, Kim MR, Lee EY, et al. Extracellular vesicles derived from Staphylococcus aureus induce atopic dermatitis-like skin inflammation. Allergy Eur J Allergy Clin Immunol 2011;66:351–9. https://doi.org/10.1111/j.1398-9995.2010.02483.x.
103. Solé M, Scheibner F, Hoffmeister AK, et al. Xanthomonas campestris pv. vesicatoria secretes proteases and xylanases via the Xps type II secretion system and outer membrane vesicles. J Bacteriol 2015;197:2879–93. https://doi.org/10.1128/JB.00322-15.
104. Bahar O, Mordukhovich G, Luu DD, et al. Bacterial outer membrane vesicles induce plant immune responses. Mol Plant Microbe Interact 2016;29:374–84. https://doi.org/10.1094/MPMI-12-15-0270-R.
105. Wolf JM, Espadas-Moreno J, Luque-Garcia JL, Casadevall A. Interaction of cryptococcus neoformans extracellular vesicles with the Cell Wall. Eukaryot Cell 2014;13:1484–93. https://doi.org/10.1128/EC.00111-14.
106. Joffe LS, Nimrichter L, Rodrigues ML, Del Poeta M. Potential roles of fungal extracellular vesicles during infection. mSphere 2016;1. https://doi.org/10.1128/mSphere.00099-16 e00099-16.
107. 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;10:1695–710. https://doi.org/10.1111/j.1462-5822.2008.01160.x.
108. 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;11:1676–85. https://doi.org/10.1021/pr200872s.
109. Leone F, Bellani L, Muccifora S, et al. Analysis of extracellular vesicles produced in the biofilm by the dimorphic yeast Pichia fermentans. J Cell Physiol 2018;233:2759–67. https://doi.org/10.1002/jcp.25885.
110. Vargas G, Rocha JDB, Oliveira DL, et al. Compositional and immunobiological analyses of extracellular vesicles released by Candida albicans. Cell Microbiol 2015;17:389–407. https://doi.org/10.1111/cmi.12374.
111. Ikeda MAK, de Almeida JRF, 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. https://doi.org/10.3389/fmicb.2018.02286.
112. Bowman SM, Free SJ. The structure and synthesis of the fungal cell wall. BioEssays 2006;28:799–808. https://doi.org/10.1002/bies.20441.
113. 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. https://doi.org/10.1371/journal.pone.0011113.
114. 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. https://doi.org/10.1128/EC.00370-07.
115. Bielska E, Sisquella M, Aldeieg M, et al. Pathogen-derived extracellular vesicles mediate virulence in the fatal human pathogen Cryptococcus gattii. Nature communications 2018. https://doi.org/10.1038/s41467-018-03991-6.
116. 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;13:467–77. https://doi.org/10.2147/IJN.S151110.
117. Nantakomol D, Dondorp AM, Krudsood S, et al. Circulating red cell-derived microparticles in human malaria. J Infect Dis 2011;203:700–6. https://doi.org/10.1093/infdis/jiq104.
118. 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. https://doi.org/10.1038/s41598-018-19149-9.
119. Regev-Rudzki N, Wilson DW, Carvalho TG, et al. Cell-cell communication between malaria-infected red blood cells via exosome-like vesicles. Cell 2013;153:1120–33. https://doi.org/10.1016/j.cell.2013.04.029.
120. Silverman JM, Reiner NE. Leishmania exosomes deliver preemptive strikes to create an environment permissive for early infection. Front Cell Infect Microbiol 2012. https://doi.org/10.3389/fcimb.2011.00026 1.
121. 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;123:842–52. https://doi.org/10.1242/jcs.056465.
122. Silverman JM, Clos J, Horakova E, et al. Leishmania exosomes modulate innate and adaptive immune responses through effects on monocytes and dendritic cells. J Immunol 2010;185:5011–22. https://doi.org/10.4049/jimmunol.1000541.
123. Gomez MA, Contreras I, Hallé M, Tremblay ML, McMaster RW, Olivier M. Leishmania GP63 alters host signaling through cleavage-activated protein tyrosine phosphatases. Sci Signal 2009;2. https://doi.org/10.1126/scisignal.2000213.
124. 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. https://doi.org/10.1111/pim.12426.
125. Evans-Osses I, Mojoli A, Monguió-Tortajada M, et al. Microvesicles released from Giardia intestinalis disturb host-pathogen response in vitro. Eur J Cell Biol 2017;96:131–42. https://doi.org/10.1016/j.ejcb.2017.01.005.
126. Fisher C, Grahovac TL, Schafer ME, Shippert RD, Marra KG, Rubin JP. Comparison of harvest and processing techniques for fat grafting and adipose stem cell isolation. Plast Reconstr Surg 2013;132:351–61. https://doi.org/10.1097/PRS.0b013e3182958796.
127. Summers RW, Elliott DE, Qadir K, Urban JF, Thompson R, Weinstock JV. Trichuris suis seems to be safe and possibly effective in the treatment of inflammatory bowel disease. Am J Gastroenterol 2003;98:2034–41. https://doi.org/10.1111/j.1572-0241.2003.07660.x.
128. Barranco C. Experimental arthritis: Helminth infection ameliorates arthritis. Nat Rev Rheumatol 2016;12:373. https://doi.org/10.1038/nrrheum.2016.95.
129. 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;19:1545–57. https://doi.org/10.1016/j.celrep.2017.05.001.
130. Buck AH, Coakley G, Simbari F, et al. Exosomes secreted by nematode parasites transfer small RNAs to mammalian cells and modulate innate immunity. Nat Commun 2014;5. https://doi.org/10.1038/ncomms6488.
131. Baldrich P, Rutter BD, Zand Karimi H, Podicheti R, Meyers BC, Innes RW. Plant extracellular vesicles contain diverse small RNA species and are enriched in 10 to 17 Nucleotide "Tiny" RNAs. Plant Cell January 2019. https://doi.org/10.1105/tpc.18.00872 tpc.00872.2018.
132. Rutter BD, Innes RW. Extracellular vesicles isolated from the leaf apoplast carry stress-response proteins. Plant Physiol 2017;173:728–41. https://doi.org/10.1104/pp.16.01253.
133. An Q, Hückelhoven R, Kogel KH, van Bel AJE. Multivesicular bodies participate in a cell wall-associated defence response in barley leaves attacked by the pathogenic powdery mildew fungus. Cell Microbiol 2006. https://doi.org/10.1111/j.1462-5822.2006.00683.x.
134. Regente M, Corti-Monzón G, Maldonado AM, Pinedo M, Jorrín J, de la Canal L. Vesicular fractions of sunflower apoplastic fluids are associated with potential exosome marker proteins. FEBS Lett 2009;583:3363–6. https://doi.org/10.1016/j.febslet.2009.09.041.
135. Liang H, Zhang S, Fu Z, et al. Effective detection and quantification of dietetically absorbed plant microRNAs in human plasma. J Nutr Biochem 2015. https://doi.org/10.1016/j.jnutbio.2014.12.002.
136. Ju S, Mu J, Dokland T, et al. Grape exosome-like nanoparticles induce intestinal stem cells and protect mice from DSS-induced colitis. Mol Ther 2013;21:1345–57. https://doi.org/10.1038/mt.2013.64.
137. Mu J, Zhuang X, Wang Q, et al. Interspecies communication between plant and mouse gut host cells through edible plant derived exosome-like nanoparticles. Mol Nutr Food Res 2014;58:1561–73. https://doi.org/10.1002/mnfr.201300729.
138. Zhou G, Zhou Y, Chen X. New insight into inter-kingdom communication: horizontal transfer of mobile small RNAs. Front Microbiol 2017;8. https://doi.org/10.3389/fmicb.2017.00768.

139. Yu S, Zhao Z, Xu X, Li M, Li P. Characterization of three different types of extracellular vesicles and their impact on bacterial growth. Food Chem 2019;272:372–8 https://doi.org/10.1016/j.foodchem.2018.08.059.
140. Wang Q, Ren Y, Mu J, et al. Grapefruit-derived nanovectors use an activated leukocyte trafficking pathway to deliver therapeutic agents to inflammatory tumor sites. Cancer Res 2015;75:2520–9. https://doi.org/10.1158/0008-5472.CAN-14-3095.
141. Zhuang X, Teng Y, Samykutty A, et al. Grapefruit-derived nanovectors delivering therapeutic miR17 through an intranasal route inhibit brain tumor progression. Mol Ther 2016;24:96–105. https://doi.org/10.1038/mt.2015.188.
142. Li Z, Wang H, Yin H, Bennett C, Zhang H, Guo P. Arrowtail RNA for ligand display on ginger exosome-like nanovesicles to systemic deliver siRNA for cancer suppression. Sci Rep 2018;8:14644. https://doi.org/10.1038/s41598-018-32953-7.
143. Prado N, De Dios Alché J, Casado-Vela J, et al. Nanovesicles are secreted during pollen germination and pollen tube growth: a possible role in fertilization. Mol Plant 2014;7:573–7. https://doi.org/10.1093/mp/sst153.
144. Prado N, De Linares C, Sanz ML, et al. Pollensomes as natural vehicles for pollen allergens. J Immunol 2015;195:445–9. https://doi.org/10.4049/jimmunol.1500452.
145. Fang S, Xu C, Zhang Y, et al. Umbilical cord-derived mesenchymal stem cell-derived exosomal MicroRNAs suppress myofibroblast differentiation by inhibiting the transforming growth factor-β/SMAD2 pathway during wound healing. Stem Cells Transl Med 2016;5:1425–39. https://doi.org/10.5966/sctm.2015-0367.
146. Zhang J, Guan J, Niu X, et al. Exosomes released from human induced pluripotent stem cells-derived MSCs facilitate cutaneous wound healing by promoting collagen synthesis and angiogenesis. J Transl Med 2015;13. https://doi.org/10.1186/s12967-015-0417-0.
147. Kim D-K, Nishida H, An SY, Shetty AK, Bartosh TJ, Prockop DJ. Chromatographically isolated CD63+CD81+ extracellular vesicles from mesenchymal stromal cells rescue cognitive impairments after TBI. Proc Natl Acad Sci U S A 2015. https://doi.org/10.1073/pnas.1522297113 1522297113.
148. Doeppner TR, Herz J, Görgens A, et al. Extracellular vesicles improve post-stroke neuroregeneration and prevent postischemic immunosuppression. Stem Cells Transl Med 2015;4:1131–43. https://doi.org/10.5966/sctm.2015-0078.
149. Teng X, Chen L, Chen W, Yang J, Yang Z, Shen Z. Mesenchymal stem cell-derived exosomes improve the microenvironment of infarcted myocardium contributing to angiogenesis and anti-inflammation. Cell Physiol Biochem 2015;37:2415–24. https://doi.org/10.1159/000438594.
150. Bian S, Zhang L, Duan L, Wang X, Min Y, Yu H. Extracellular vesicles derived from human bone marrow mesenchymal stem cells promote angiogenesis in a rat myocardial infarction model. J Mol Med (Berl) 2014;92:387–97. https://doi.org/10.1007/s00109-013-1110-5.
151. Wang X, Gu H, Qin D, et al. Exosomal MIR-223 contributes to mesenchymal stem cell-elicited cardioprotection in polymicrobial sepsis. Sci Rep 2015;5. https://doi.org/10.1038/srep13721.
152. Acevedo R, Fernández S, Zayas C, et al. Bacterial outer membrane vesicles and vaccine applications. Front Immunol 2014;5. https://doi.org/10.3389/fimmu.2014.00121.
153. Norheim G, Sanders H, Mellesdal JW, et al. An OMV vaccine derived from a capsular group b meningococcus with constitutive feta expression: preclinical evaluation of immunogenicity and toxicity. PLoS One 2015;10. https://doi.org/10.1371/journal.pone.0134353.
154. Brudal E, Lampe EO, Reubsaet L, et al. Vaccination with outer membrane vesicles from Francisella noatunensis reduces development of francisellosis in a zebrafish model. Fish Shellfish Immunol 2015;42:50–7 https://doi.org/10.1016/j.fsi.2014.10.025.
155. Beit-Yannai E, Tabak S, Stamer WD. Physical exosome:exosome interactions. J Cell Mol Med 2018;22:2001–6. https://doi.org/10.1111/jcmm.13479.
156. Gangadaran P, Hong CM, Ahn BC. An update on in vivo imaging of extracellular vesicles as drug delivery vehicles. Front Pharmacol 2018. https://doi.org/10.3389/fphar.2018.00169.
157. Sun D, Zhuang X, Xiang X, et al. A novel nanoparticle drug delivery system: the anti-inflammatory activity of curcumin is enhanced when encapsulated in exosomes. Mol Ther 2010;18:1606–14. https://doi.org/10.1038/mt.2010.105.
158. Tian Y, Li S, Song J, et al. A doxorubicin delivery platform using engineered natural membrane vesicle exosomes for targeted tumor therapy. Biomaterials 2014;35:2383–90. https://doi.org/10.1016/j.biomaterials.2013.11.083.
159. Haney MJ, Klyachko NL, Zhao Y, et al. Exosomes as drug delivery vehicles for Parkinson's disease therapy. J Control Release 2015;207:18–30. https://doi.org/10.1016/j.jconrel.2015.03.033.
160. Soung YH, Ford S, Zhang V, Chung J. Exosomes in cancer diagnostics. Cancers (Basel) 2017;9. https://doi.org/10.3390/cancers9010008.
161. Salih M, Zietse R, Hoorn EJ. Urinary extracellular vesicles and the kidney: biomarkers and beyond. Am J Physiol Renal Physiol 2014;306:F1251–9. https://doi.org/10.1152/ajprenal.00128.2014.
162. Pocsfalvi G, Raj DAA, Fiume I, Vilasi A, Trepiccione F, Capasso G. Urinary extracellular vesicles as reservoirs of altered proteins during the pathogenesis of polycystic kidney disease. PROTEOMICS - Clin Appl 2015;9:552–67. https://doi.org/10.1002/prca.201400199.
163. Kalani A, Mohan A, Godbole MM, et al. Wilm's tumor-1 protein levels in urinary exosomes from diabetic patients with or without proteinuria. Rastaldi MP, ed. PLoS One 2013;8:e60177. https://doi.org/10.1371/journal.pone.0060177.
164. Santangelo A, Imbrucè P, Gardenghi B, et al. A microRNA signature from serum exosomes of patients with glioma as complementary diagnostic biomarker. J Neurooncol 2018;136:51–62. https://doi.org/10.1007/s11060-017-2639-x.
165. Cao XY, Lu JM, Zhao ZQ, et al. MicroRNA biomarkers of Parkinson's disease in serum exosome-like microvesicles. Neurosci Lett 2017;644:94–9. https://doi.org/10.1016/j.neulet.2017.02.045.
166. Lugli G, Cohen AM, Bennett DA, et al. Plasma exosomal miRNAs in persons with and without Alzheimer disease: Altered expression and prospects for biomarkers. PLoS One 2015;10. https://doi.org/10.1371/journal.pone.0139233.
167. Colao IL, Corteling R, Bracewell D, Wall I. Manufacturing exosomes: a promising therapeutic platform. Trends Mol Med 2018;24:242–56 https://doi.org/10.1016/j.molmed.2018.01.006.
168. Konoshenko MY, Lekchnov EA, Vlassov AV, Laktionov PP. Isolation of extracellular vesicles: general methodologies and latest trends. Biomed Res Int 2018. https://doi.org/10.1155/2018/8545347.
169. Tauro BJ, Greening DW, Mathias RA, et al. Comparison of ultracentrifugation, density gradient separation, and immunoaffinity capture methods for isolating human colon cancer cell line LIM1863-derived exosomes. Methods 2012;56:293–304. https://doi.org/10.1016/j.ymeth.2012.01.002.
170. Haraszti RA, Miller R, Stoppato M, et al. Exosomes produced from 3D cultures of MSCs by tangential flow filtration show higher yield and improved activity. Mol Ther 2018. https://doi.org/10.1016/j.ymthe.2018.09.015.

171. Yang M, Wu SY. The advances and challenges in utilizing exosomes for delivering cancer therapeutics. Front Pharmacol 2018;9:735. https://doi.org/10.3389/fphar.2018.00735.
172. Tucker AS. Salivary gland adaptations: Modification of the glands for novel uses.. Salivary Glands: Development, Adaptations and Disease 2010;14:21–31. https://doi.org/10.1159/000313705.
173. Fratini F, Cilia G, Mancini S, Felicioli A. Royal Jelly: An ancient remedy with remarkable antibacterial properties. Microbiol Res 2016;192:130–41. https://doi.org/10.1016/j.micres.2016.06.007.
174. Angelov T, Hristov I. HPLC determination of pka value of 10-hydroxy-2-decenoic acid. J Liq Chromatogr Relat Technol 2018;41:87–92. https://doi.org/10.1080/10826076.2017.1408648.
175. Haas BJ, Whited JL. Advances in Decoding Axolotl Limb Regeneration. Trends Genet 2017;33:553–65. https://doi.org/10.1016/j.tig.2017.05.006.
176. Richter K, Grunwald I, von Byern J, Bioadhesives BT. Handbook of adhesion technology. In: Oechsner A, Adams R, eds. da Silva LFM, Cham: Springer International Publishing, 2018:1–45. https://doi.org/10.1007/978-3-319-42087-5_53-2.
177. Bonnemain B. Helix and drugs: snails for western health care from antiquity to the present. Evidence-based Complement Altern Med 2005;2:25–8. https://doi.org/10.1093/ecam/neh057.
178. Keller S, Ridinger J, Rupp AK, Janssen JWG, Altevogt P. Body fluid derived exosomes as a novel template for clinical diagnostics. J Transl Med 2011;9. https://doi.org/10.1186/1479-5876-9-86.
179. Stamer WD, Hoffman EA, Luther JM, Hachey DL, Schey KL. Protein profile of exosomes from trabecular meshwork cells. J Proteomics 2011;74:796–804. https://doi.org/10.1016/j.jprot.2011.02.024.
180. Dismuke WM, Challa P, Navarro I, Stamer WD, Liu Y. Human aqueous humor exosomes. Exp Eye Res 2015;132:73–7. https://doi.org/10.1016/j.exer.2015.01.019.
181. Tokuhisa M, Ichikawa Y, Kosaka N, et al. Exosomal miRNAs from peritoneum lavage fluid as potential prognostic biomarkers of peritoneal metastasis in gastric cancer. Dadras SS, ed. PLoS One 2015;10:e0130472. https://doi.org/10.1371/journal.pone.0130472.
182. Im H, Shao H, Park Il Y, et al. Label-free detection and molecular profiling of exosomes with a nano-plasmonic sensor. Nat Biotechnol 2014;32:490–5. https://doi.org/10.1038/nbt.2886.
183. Caivano A, Laurenzana I, De Luca L, et al. High serum levels of extracellular vesicles expressing malignancy-related markers are released in patients with various types of hematological neoplastic disorders. Tumor Biol 2015;36:9739–52. https://doi.org/10.1007/s13277-015-3741-3.
184. Nyalwidhe JO, Betesh LR, Powers TW, et al. Increased bisecting N-acetylglucosamine and decreased branched chain glycans of N-linked glycoproteins in expressed prostatic secretions associated with prostate cancer progression. Proteomics - Clin Appl 2013;7:677–89. https://doi.org/10.1002/prca.201200134.
185. Duijvesz D, Versluis CYL, Van Der Fels CAM, et al. Immunobased detection of extracellular vesicles in urine as diagnostic marker for prostate cancer. Int J Cancer 2015;137:2869–78. https://doi.org/10.1002/ijc.29664.
186. Rabinowits G, Gerçel-Taylor C, Day JM, Taylor DD, Kloecker GH. Exosomal microRNA: a diagnostic marker for lung cancer. Clin Lung Cancer 2009;10:42–6. https://doi.org/10.3816/CLC.2009.n.006.
187. Li J, Sherman-Baust CA, Tsai-Turton M, Bristow RE, Roden RB, Morin PJ. Claudin-containing exosomes in the peripheral circulation of women with ovarian cancer. BMC Cancer 2009;9:244. https://doi.org/10.1186/1471-2407-9-244.
188. Taylor DD, Gerçel-Taylor C. Tumour-derived exosomes and their role in cancer-associated T-cell signalling defects. Br J Cancer 2005;92:305–11. https://doi.org/10.1038/sj.bjc.6602316.
189. Graner MW, Alzate O, Dechkovskaia AM, et al. Proteomic and immunologic analyses of brain tumor exosomes. FASEB J 2009;23:1541–57. https://doi.org/10.1096/fj.08-122184.
190. Santangelo A, Imbrucè P, Gardenghi B, et al. A microRNA signature from serum exosomes of patients with glioma as complementary diagnostic biomarker. J Neurooncol 2018;136:51–62. https://doi.org/10.1007/s11060-017-2639-x.
191. Skog J, Wurdinger T, van Rijn S, et al. Glioblastoma microvesicles transport RNA and protein that promote tumor growth and provide diagnostic biomarkers. Nat Cell Biol 2008;10:1470–6. https://doi.org/10.1038/ncb1800.
192. Qu L, Ding J, Chen C, et al. Exosome-transmitted lncARSR promotes sunitinib resistance in renal cancer by acting as a competing endogenous RNA. Cancer Cell 2016;29:653–68. https://doi.org/10.1016/j.ccell.2016.03.004.
193. Khan S, Bennit HF, Turay D, et al. Early diagnostic value of survivin and its alternative splice variants in breast cancer. BMC Cancer 2014;14:176. https://doi.org/10.1186/1471-2407-14-176.
194. Yang S, Wang D, Li J, et al. Predictive role of GSTP1-containing exosomes in chemotherapy-resistant breast cancer. Gene 2017;623:5–14. https://doi.org/10.1016/J.GENE.2017.04.031.
195. Li J, Li B, Ren C, et al. The clinical significance of circulating GPC1 positive exosomes and its regulative miRNAs in colon cancer patients. Oncotarget 2017;8:101189–202. https://doi.org/10.18632/oncotarget.20516.
196. Li J, Chen Y, Guo X, et al. GPC1 exosome and its regulatory miRNAs are specific markers for the detection and target therapy of colorectal cancer. J Cell Mol Med 2017;21:838–47. https://doi.org/10.1111/jcmm.12941.
197. Melo SA, Luecke LB, Kahlert C, et al. Glypican-1 identifies cancer exosomes and detects early pancreatic cancer. Nature 2015;523:177–82. https://doi.org/10.1038/nature14581.
198. Song J, Kim D, Han J, Kim Y, Lee M, Jin E-J. PBMC and exosome-derived Hotair is a critical regulator and potent marker for rheumatoid arthritis. Clin Exp Med 2015;15:121–6. https://doi.org/10.1007/s10238-013-0271-4.
199. Bi S, Wang C, Jin Y, Lv Z, Xing X, Lu Q. Correlation between serum exosome derived miR-208a and acute coronary syndrome. Int J Clin Exp Med 2015;8:4275–80.
200. Hock A, Miyake H, Li B, et al. Breast milk-derived exosomes promote intestinal epithelial cell growth. J Pediatr Surg 2017;52:755–9. https://doi.org/10.1016/j.jpedsurg.2017.01.032.
201. Qin W, Tsukasaki Y, Dasgupta S, Mukhopadhyay N, Ikebe M, Sauter ER. Exosomes in human breast milk promote EMT. Clin Cancer Res 2016;22:4517–24. https://doi.org/10.1158/1078-0432.CCR-16-0135.
202. Kong F-L, Wang X-P, Li Y-N, Wang H-X. The role of exosomes derived from cerebrospinal fluid of spinal cord injury in neuron proliferation *in vitro*. *Artif Cells, Nanomedicine*. Biotechnol 2018;46:200–5. https://doi.org/10.1080/21691401.2017.1304408.
203. Akers JC, Ramakrishnan V, Kim R, et al. miR-21 in the Extracellular Vesicles (EVs) of Cerebrospinal Fluid (CSF): a platform for glioblastoma biomarker development. Chen M, ed. PLoS One 2013;8:e78115. https://doi.org/10.1371/journal.pone.0078115.
204. Diez-Fraile A, Lammens T, Tilleman K, et al. Age-associated differential microRNA levels in human follicular fluid reveal pathways potentially determining fertility and success of ***in***

vitro fertilization. Hum Fertil 2014;17:90–8. https://doi.org/10.3109/14647273.2014.897006.
205. Bard MP, Hegmans JP, Hemmes A, et al. Proteomic analysis of exosomes isolated from human malignant pleural effusions. Am J Respir Cell Mol Biol 2004;31:114–21. https://doi.org/10.1165/rcmb.2003-0238OC.
206. Palanisamy V, Sharma S, Deshpande A, Zhou H, Gimzewski J, Wong DT. Nanostructural and transcriptomic analyses of human saliva derived exosomes. PLoS One 2010;5. https://doi.org/10.1371/journal.pone.0008577.
207. Michael A, Bajracharya SD, Yuen PST, et al. Exosomes from human saliva as a source of microRNA biomarkers. Oral Dis 2010;16:34–8. https://doi.org/10.1111/j.1601-0825.2009.01604.x.
208. Sun Y, Huo C, Qiao Z, et al. Comparative proteomic analysis of exosomes and microvesicles in human saliva for lung cancer. J Proteome Res 2018;17:1101–7. https://doi.org/10.1021/acs.jproteome.7b00770.
209. Skriner K, Adolph K, Jungblut PR, Burmester GR. Association of citrullinated proteins with synovial exosomes. Arthritis Rheum 2006;54:3809–14. https://doi.org/10.1002/art.22276.
210. Kolhe R, Hunter M, Liu S, et al. Gender-specific differential expression of exosomal miRNA in synovial fluid of patients with osteoarthritis. Sci Rep 2017;7:2029. https://doi.org/10.1038/s41598-017-01905-y.
211. Domenis R, Zanutel R, Caponnetto F, et al. Characterization of the proinflammatory profile of synovial fluid-derived exosomes of patients with osteoarthritis. Mediators Inflamm 2017;2017:1–11. https://doi.org/10.1155/2017/4814987.
212. Grigor'eva AE, Tamkovich SN, Eremina AV, et al. Exosomes in tears of healthy individuals: isolation, identification, and characterization. Biochem Suppl Ser B Biomed Chem 2016;10:165–72. https://doi.org/10.1134/S1990750816020049.
213. Pathare G, Dhayat NA, Mohebbi N, et al. Changes in V-ATPase subunits of human urinary exosomes reflect the renal response to acute acid/alkali loading and the defects in distal renal tubular acidosis. Kidney Int January 2018. https://doi.org/10.1016/j.kint.2017.10.018.
214. Berrondo C, Flax J, Kucherov V, et al. Expression of the long non-coding RNA HOTAIR correlates with disease progression in bladder cancer and is contained in bladder cancer patient urinary exosomes. Castresana JS, ed. PLoS One 2016;11:e0147236. https://doi.org/10.1371/journal.pone.0147236.
215. Welton JL, Khanna S, Giles PJ, et al. Proteomics analysis of bladder cancer exosomes. Mol Cell Proteomics 2010;9:1324–38. https://doi.org/10.1074/mcp.M000063-MCP201.
216. Chen C-L, Lai Y-F, Tang P, et al. Comparative and targeted proteomic analyses of urinary microparticles from bladder cancer and hernia patients. J Proteome Res 2012;11:5611–29. https://doi.org/10.1021/pr3008732.
217. Butz H, Nofech-Mozes R, Ding Q, et al. Exosomal MicroRNAs are diagnostic biomarkers and can mediate cell−cell communication in renal cell carcinoma. Eur Urol Focus 2016;2:210–8. https://doi.org/10.1016/j.euf.2015.11.006.
218. Raimondo F, Morosi L, Corbetta S, et al. Differential protein profiling of renal cell carcinoma urinary exosomes. Mol Biosyst 2013;9:1220. https://doi.org/10.1039/c3mb25582d.
219. Royo F, Zuñiga-Garcia P, Sanchez-Mosquera P, et al. Different EV enrichment methods suitable for clinical settings yield different subpopulations of urinary extracellular vesicles from human samples. J Extracell Vesicles 2016;5:29497. https://doi.org/10.3402/jev.v5.29497.
220. Gracia T, Wang X, Su Y, et al. Urinary exosomes contain MicroRNAs capable of paracrine modulation of tubular transporters in kidney. Sci Rep 2017;7:40601. https://doi.org/10.1038/srep40601.
221. Moon P-G, Lee J-E, You S, et al. Proteomic analysis of urinary exosomes from patients of early IgA nephropathy and thin basement membrane nephropathy. Proteomics 2011;11:2459–75. https://doi.org/10.1002/pmic.201000443.
222. Keller S, Rupp C, Stoeck A, et al. CD24 is a marker of exosomes secreted into urine and amniotic fluid. Kidney Int 2007;72:1095–102. https://doi.org/10.1038/sj.ki.5002486.
223. Alvarez S, Suazo C, Boltansky A, et al. Urinary exosomes as a source of kidney dysfunction biomarker in renal transplantation. Transplant Proc 2013;45:3719–23. https://doi.org/10.1016/j.transproceed.2013.08.079.
224. Principe S, Jones EE, Kim Y, et al. In-depth proteomic analyses of exosomes isolated from expressed prostatic secretions in urine. Proteomics 2013;13:1667–71. https://doi.org/10.1002/pmic.201200561.
225. Perez-Hernandez J, Forner MJ, Pinto C, Chaves FJ, Cortes R, Redon J. Increased urinary exosomal MicroRNAs in patients with systemic lupus erythematosus. Alvarez ML, ed. PLoS One 2015;10:e0138618. https://doi.org/10.1371/journal.pone.0138618.
226. Solé C, Cortés-Hernández J, Felip ML, Vidal M, Ordi-Ros J. miR-29c in urinary exosomes as predictor of early renal fibrosis in lupus nephritis. Nephrol Dial Transplant 2015;30:1488–96. https://doi.org/10.1093/ndt/gfv128.