Exosomes and microvesicles: extracellular vesicles for genetic information transfer and gene therapy

Yi Lee[1], Samir EL Andaloussi[1,2] and Matthew J.A. Wood[1,*]

[1]Department of Physiology, Anatomy and Genetics, University of Oxford, South Parks Road, Oxford OX1 3QX, UK
[2]Department of Laboratory Medicine, Karolinska Institutet, Huddinge SE-141 86, Sweden

Exosomes and microvesicles are extracellular nanovesicles released by most but not all cells. They are specifically equipped to mediate intercellular communication via the transfer of genetic information, including the transfer of both coding and non-coding RNAs, to recipient cells. As a result, both exosomes and microvesicles play a fundamental biological role in the regulation of normal physiological as well as aberrant pathological processes, via altered gene regulatory networks and/or via epigenetic programming. For example, microvesicle-mediated genetic transfer can regulate the maintenance of stem cell plasticity and induce beneficial cell phenotype modulation. Alternatively, such vesicles play a role in tumor pathogenesis and the spread of neurodegenerative diseases via the transfer of specific microRNAs and pathogenic proteins. Given this natural property for genetic information transfer, the possibility of exploiting these vesicles for therapeutic purposes is now being investigated. Stem cell-derived microvesicles appear to be naturally equipped to mediate tissue regeneration under certain conditions, while recent evidence suggests that exosomes might be harnessed for the targeted delivery of human genetic therapies via the introduction of exogenous genetic cargoes such as siRNA. Thus, extracellular vesicles are emerging as potent genetic information transfer agents underpinning a range of biological processes and with therapeutic potential.

INTRODUCTION

Genetic information can be transferred through two proposed mechanisms: vertical gene transfer, gene exchange from parent to the next generation, and horizontal gene transfer, induced through, for example, bacteriophages (1) or viruses (2). Recently, another mechanism of horizontal gene transfer has emerged: naturally occurring cell-derived vesicles such as exosomes and microvesicles. These are extracellular vesicles produced constitutively by most, but not all, cell types and, interestingly, contain both mRNAs and non-coding RNAs such as small regulatory microRNAs (miRNAs) as well as proteins that can be functionally delivered between different cell types and across species (3). As a result, such vesicles have a significant impact on natural physiological processes including the regulation of stem cell plasticity.

However, this natural ability of exosomes and microvesicles to transfer genetic information might instead facilitate the spread of disease through the delivery of genetic material and/or pathogenic proteins (4). For example, it has been noted that greater numbers of extracellular vesicles can be isolated from diseased patients, some of which contain elevated levels of specific miRNAs, which may be involved in the cause and spread of diseases such as cancer (5). Recently, similar evidence has been found for neurodegenerative diseases, raising the possibility that the local spread of neuropathology could be exosome-mediated (6). Hence, an increasingly attractive hypothesis is that extracellular vesicles play crucial roles in genetic information transfer in both normal and diseased states.

In addition to their natural role in genetic information transfer, several groups have now attempted to exploit the potential of extracellular vesicles for therapeutic applications. Microvesicles derived from injured tissues can induce phenotypic changes in local stem cells through epigenetic reprogramming with miRNAs to stimulate tissue repair and regeneration (7), while the natural ability of exosomes as agents for the delivery therapeutic genetic materials has also recently been demonstrated (8,9).

In this review, we discuss the fundamental role that extracellular vesicles play in the regulation of normal physiological and aberrant pathological processes through the transfer of

*To whom correspondence should be addressed. Tel: +44 1865272419; Fax: +44 1865 272420; Email: matthew.wood@dpag.ox.ac.uk

Table 1. Table summarizing the properties and biogenesis of the different extracellular vesicles described in literature

Nomenclature	Properties	Biogenesis	Reference
Exosome	Homogenous population with a size of 40–100 nm in diameter	End of endocytic pathway, released from cells when multivesicular bodies fuse with the plasma membrane	(16,103,117)
	Exosomal markers include CD9, CD63, Alix, flotillin-1 and Tsg101	ESCRT is involved	
Microvesicle	Heterogeneous population with a size of 50–1000 nm in diameter	Budding off/fission directly from the plasma membrane	(116)
	No definite unique markers		
Apoptotic bodies	Variable size, 500–2000 nm in diameter	Extensive plasma membrane blebbing occurs followed by karyorrhexis and separation of cell fragments during a process called 'budding'	(118,119)
	Consist of cytoplasm with tightly packed organelles		
Ectosomes	Neutrophil- or monocyte-derived MVs	Small shedding membrane vesicles, which bud directly from the cell membrane	(120)

Table 2. Table summarizing some of the different tissue/cell-specific microvesicle/exosomes that have been described to date

Name	Type of vesicle	Function	Reference
Cardiosome	Microvesicles/exosomes from cardiomyocytes	Contain RNAs that are involved in a metabolic course of events in the microenvironment of the heart	(26)
Prostasome	Nanosized microvesicles secreted by acinar epithelial cells of the prostate gland	Intercellular communication by direct interaction primarily between the immobile acinar cells of the prostate gland and the mobile spermatozoa	(121)
Vexosome	Microvesicles/exosomes that are associated with adeno-associated virus vectors	Proposed to be an efficient and novel gene delivery system	(122)

genetic information. We also describe how these vesicles may be utilized in the context of gene therapy. Lastly, we touch on the challenges and potential future directions for studying extracellular vesicle biology and therapy.

EXTRACELLULAR VESICLES: EXOSOMES AND MICROVESICLES

The notion of extracellular vesicles first arose in 1983, when researchers in Stahl's (10) and Johnstone's (11) groups described the observation of multivesicular late endosomes releasing vesicles from reticulocytes into the extracellular environment. These vesicles were subsequently named 'exosomes' (12), not to be confused with the identically named ribonuclease complex (13).

Recently, the interest in extracellular vesicle biology has grown enormously and many have described different types of vesicles depending on their biophysical properties and biogenesis including several cell type-specific vesicles depending on their source of origin (Tables 1 and 2). Such vesicles are released from most cells and can be readily isolated from most body fluids such as serum, plasma, urine and cerebrospinal fluid. Here, we focus the discussion on two specific types of extracellular vesicles: exosomes and microvesicles.
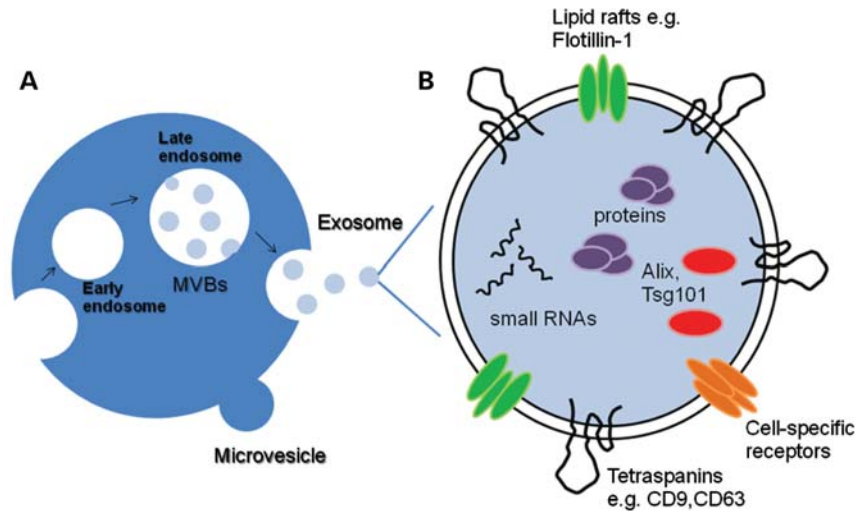
Both exosomes and microvesicles are membrane bound vesicles that differ based on their process of biogenesis and biophysical properties, including size and surface protein markers (Fig. 1). Exosomes are homogenous small particles ranging from 40 to 100 nm in size and are derived from the endocytic recycling pathway. In endocytosis, endocytic vesicles form at the plasma membrane and fuse to form early endosomes. These mature and become late endosomes where intraluminal vesicles bud off into an intra-cytoplasmic lumen. Instead of fusing with the lysosome, these multivesicular bodies directly fuse with the plasma membrane and release exosomes into the extracellular space (14). Interestingly, exosome biogenesis (15,16), protein cargo sorting (17,18) and release (19) involve the endosomal sorting complex required for transport (ESCRT complex) and other associated proteins such as Alix (20,21) and Tsg101 (22). In contrast, microvesicles are produced directly through the outward budding and fission of membrane vesicles from the plasma membrane, and hence, their surface markers are largely dependent on the composition of the membrane of origin. Further, they tend to constitute a larger and more heterogeneous population of extracellular vesicles, ranging from 50 to 1000 nm in diameter. However, both types of vesicles have been shown to deliver functional mRNA, miRNA and proteins to recipient cells. Hence, some reports have interchangeably used the terms 'exosomes' and 'microvesicles' to describe their role in genetic information transfer.

CELL–CELL COMMUNICATIONS VIA EXOSOMES AND MICROVESICLES

In order to maintain cellular homeostasis or to respond to pathogens in the extracellular milieu, cells often exchange information through the secretion of soluble factors, via ligand-receptor interactions or via cellular 'bridges' such as nanotubes (23). However, increasing evidence now indicates

Figure 1. (**A**) Exosome and microvesicle biogenesis. Exosomes are an end-product of the endocytic recycling pathway. First, endocytic vesicles form at the plasma membrane and fuse to form early endosomes. These mature and become late endosomes where intraluminal vesicles bud off into the lumen. These multi-vesicular bodies (MVBs) then directly fuse with the plasma membrane and release exosomes into the extracellular space. As for microvesicles, they bud off directly from the plasma membrane. (**B**) An enlarged exosome showing that there are a variety of common exosomal surface markers (e.g. tetraspanins such as CD9 and CD63 and lipid raft-associated proteins including flotillin-1) as well as internal markers such as Alix and Tsg101. Each exosome also contain and transfer small RNAs and other cytoplasmic proteins (purple) and cell-specific receptors (orange) which can be transferred to recipient cells.

that exosomes and microvesicles contribute significantly to genetic cross-talk between all cells.

Pioneering reports on vesicle-mediated genetic information transfer were on tumor-derived (24) and murine embryonic stem cell (ESC) (25)-derived microvesicles. The first study reported that tumor-derived microvesicles (TMVs) showed the presence of several surface determinants of tumor cells such as chemokine receptors (CCR6) and CD44v7/8 and contained mRNA for growth factors including vascular endothelial growth factor (VEGF) and interleukin-8 (IL-8). When TMVs were engulfed by monocytes, these surface determinants were transferred and activated Akt, resulting in anti-apoptotic effects in these monocytes. As for the latter study, it provided evidence that ESC-derived microvesicles could induce epigenetic reprogramming of hematopoietic progenitor cells (HPCs). The authors proposed that ESC microvesicles stimulated HPCs through the interaction of a surface ligand, Wnt3 and delivery of mRNAs encoding several pluripotency transcription factors. This mRNA transfer led to increased phosphorylation of the mitogen-activated protein kinase p42/44 and Akt, resulting in higher survival rates and increased expression of early pluripotent (e.g. Oct-4, Nanog and Rex-1) and haematopoietic stem cell (e.g. Scl, HoxB4 and GATA 2) markers. Subsequently, exosomes derived from human mast cell lines (3) were also shown to contain RNAs, aptly named 'exosomal shuttle RNAs (esRNAs)'. Interestingly, RNAs found in exosomes were annotated mainly as small RNAs, including miRNAs. Further microarray and DNA–ChIP analysis revealed that only ~8% of vesicle RNA corresponded to that found in the parental cells, with ~270 unique gene transcripts found in the exosomes. These results were corroborated in subsequent reports of non-coding RNAs and miRNAs in extracellular vesicles derived from other cells such as cardiomyocytes (26), a range of stem cells (27), tumor cells (28) and dendritic cells (29–31). Besides RNAs,

extracellular vesicles also contain and transfer important membrane and cytoplasmic protein components (32–34), some of which are involved in RNA stabilization and trafficking (35), translation and transcription, e.g. the RNA-induced silencing complex proteins such as Argonaute 2 and its interacting partner GW182 (36). Hence, exosomes and microvesicles are a potent source of genetic information transfer both between different cell types and even between cell types across a species barrier, e.g. genetic transfer from human liver stem cell-derived microvesicles to hepatectomized rats (37–39) (Fig. 2).

MICROVESICLE-MEDIATED INFORMATION TRANSFER FOR CELL PHENOTYPE MODULATION

An important, yet not well–understood, feature of microvesicle-mediated information transfer is cell phenotype modulation. This idea first arose when the Sharkis laboratory demonstrated that bone marrow cells began to express mRNA encoding albumin after being co-cultured with liver cells (40). Subsequently, Aliotta *et al.* (41) generated similar results when co-culturing injured lung tissues with bone marrow cells: microvesicles released from the lung cells induced epigenetic modifications in the recipient bone marrow cells, causing these cells to express pulmonary epithelial cell-specific genes and pro-surfactant B protein. Using microarray analysis, the transfer of tissue-specific mRNAs, miRNAs and protein-based transcription factors through the extracellular microvesicles was shown to induce this phenotype change (42). Interestingly, this microvesicle-induced phenotype change in bone marrow cells was not limited to extracellular vesicle transfer from lung tissues: they also demonstrated the expression of tissue-specific brain, heart and liver mRNAs in marrow cells when co-cultured with
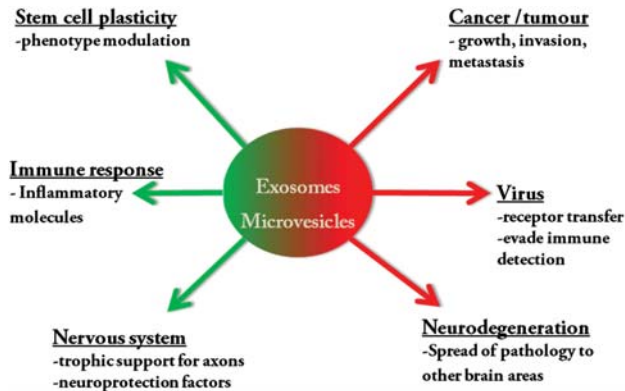
Figure 2. The different beneficial (green) and potentially detrimental (red) effects of exosome and microvesicle gene information transfer.

cells derived from these various tissues (43,44). However, they did notice that this phenotype modulation was dependent on cell cycle status (45). Microvesicles contain varied levels of adhesion molecules, such as integrins, when released by stem cells at different stages of the cell cycle and this could affect vesicle trafficking and uptake. Hence, a model of stem cell regulation termed 'the continuum model' was proposed where the plasticity of stem cells, both intra- and extra-haematopoietic, is mediated by two factors: the cell cycle status and the transfer of genetic information from microvesicles in the local environment (43).

ROLE OF EXTRACELLULAR VESICLES IN MAINTENANCE OF NORMAL PHYSIOLOGICAL PROCESSES

In many biological systems, extracellular vesicles are emerging as important mediators of cell–cell communication underpinning the maintenance of physiological function. Early studies in the immune system had shown that exosomes derived from a range of different immune cells can harbor immunologically relevant molecules such as major histocompatibility complex (MHC) class II, cluster of differentiation 86 (CD86), lymphocyte function-associated antigen 1 and intercellular adhesion molecule 1 that impact on a variety of immunological functions, including T cell activation (46,47), tolerance induction (48) and dendritic cell maturation (49). More recent studies have shown that the genetic transfer of esRNAs across immune cell types, e.g. between human mast cells and CD34+ progenitor cells, provides critical regulatory signals for appropriate cell maturation (50). Such genetic transfer may also be crucial for antigen recognition purposes, e.g. as shown by T cell-derived exosomes transferring miR-335 to antigen-presenting cells in an antigen-dependent, unidirectional manner, only during immune synapse (51). Besides immune cells, exosomes from other cell sources such as breast tissues have also been found to modulate immune responses including immune stimulation (52) and tolerance induction (48). Further, it was recently discovered that exosomes isolated from breast milk are highly enriched in immune- and developmental-related miRNAs (e.g. miR-148a-3p and let-7 family). Hence, it seems plausible

that breast milk exosomes play a role in the development of the immune system through post-transcriptional repression of various miRNA-regulated target genes in the cells of the newborn infant digestive tract (53,54).

Similarly in the nervous system, extracellular vesicles derived from neurones have been shown to transmit information in the form of proteins to facilitate neural circuit function. For example, cortical neurone-derived exosomes transfer newly synthesized proteins including α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor receptor subunits to the presynaptic terminals of connected neurones and contribute to the local synaptic plasticity (55,56). Further, increasing evidence of esRNA transfer within the nervous system suggests that mRNAs and miRNAs are also transferred (57) to regulate neuronal function. Importantly, membrane vesicles here provide an efficient form of exchange of biochemical information as these vesicles are sufficiently motile to carry their genetic contents and impact on static neuronal networks located at a distance (6).

SPREAD OF DISEASE PATHOLOGY BY EXOSOMES AND MICROVESICLES

Since extracellular vesicles are a potent source of information transfer to neighboring and distant cells, it is no surprise that viruses (58,59) and other pathogens would exploit this system to assist transmission. Indeed, many studies have noted that the production of extracellular vesicles rises sharply in diseased when compared with non-diseased states (5,60–62). One mechanism of disease spreading is through the vesicle-mediated receptor transfer, e.g. transfer of chemokine receptors to aid the spread of the human immunodeficiency virus (63–65). Another mechanism could involve the transfer of miRNAs and oncogenic proteins through microvesicles to facilitate local or metastatic tumor spread. For example, glioblastoma-derived microvesicles contain elevated levels of let-7a, miR-15b and oncogenic receptors such as EGFRvIII, all of which can be transferred to other cells in the tumor environment, leading to further tumor growth and metastasis (34). Moreover, neighboring non-tumor cells such as tumor-associated macrophages can secrete microvesicles with high levels of miR-223. miR-223 can bind to target sites in the 3′-UTR of Mef2c (66), causing an increased accumulation of β-catenin in the nuclei of breast cancer cells to encourage local invasion (67). Further, microvesicles have been postulated to re-shape the local tumor environment into a more favorable niche for tumor growth, invasion and spread of metastasis (60,68–70). For example, microvesicles from lung cancer cells can activate and stimulate expression of several pro-angiopoietic factors (e.g. IL-8, VEGF, LIF, oncostatin M, IL-11 and matrix metalloproteinase 9) in surrounding stromal cells, effectively supporting the microenvironment to encourage lung cancer cell metastasis (68).

Besides cancer, extracellular vesicles are also implicated in the local spread of neurodegenerative diseases as increasing evidence indicates that exosomes released from neurones can be transferred to other brain cells locally and at a distance. For example in Alzheimer's disease, processing of amyloid-β results in the release of secreted amyloid precursor protein and

a membrane-associated fragment [beta-C-terminal fragment (β-CTF)] (71). The latter fragment can be trafficked into endosomal compartments and become encapsulated in exosomes (72,73). Subsequently, exosomes containing toxic proteins can transport these and lead to pathogenic amyloid deposition in other parts of the brain (4,74–79). Similarly, oligomeric and monomeric α-synuclein species have also been detected in extracellular vesicles. These vesicles can then transfer these toxic inclusions to assist with the propagation of Parkinson's disease-related pathology (80–82). Another brain pathogen that exploits exosome-mediated transfer is the prion protein. Exosomes from prion-infected cells contain both the host-encoded prion protein (PrP(C)) and the abnormal pathogenic prion protein isoform (PrP(Sc)) (83). When applied, these exosomes can efficiently initiate prion propagation in uninfected recipient cells and even to non-neuronal cells. Hence, it is increasingly evident in a range of diseases and disease models that extracellular vesicles assist disease propagation through the genetic transfer.

THERAPEUTIC POWER OF EXOSOMES AND MICROVESICLES

With the natural ability of exosomes and microvesicles to transfer genetic material both locally and systemically, some groups have investigated ways to exploit these vesicles as therapeutic agents. In 2007, Camussi's group (84) isolated microvesicles from endothelial progenitor cells (EPCs) which they later deduced had contained proangiogenic miR-126 and miR-296 (85). Transfer of these miRNAs triggered the activation of the PI3K/Akt signaling pathway and phosphorylation of endothelial nitric oxide synthases and directed endothelial cells to undergo angiogenic and anti-apoptotic Programme, shown initially *in vitro* and later *in vivo* (86). Interestingly, the same miRNAs (miR-126 and miR-296) in microvesicles derived from EPCs were also shown to induce therapeutic effects in other cell types. For example, EPC microvesicles were able to reprogram hypoxic resident renal cells to regenerate and protect them from ischaemia-reperfusion injury (87) or activate an angiogenic Programme in islet endothelium to sustain revascularization and β-cell function, potentially useful for increasing efficacy of insulin production after islet transplantation (86). Subsequently, microvesicles from different sources including mesenchymal stem cells (MSCs) and liver stem cells were also found to confer therapeutic benefit in a range of different diseases; enhancing survival in acute (37,88) and chronic (89) kidney injuries and peripheral arterial disease (90) as well as accelerating hepatic regeneration (38). Similarly, MSC-derived exosomes were also able to provide protection against myocardial ischaemia (91) and to treat myocardial infarction (92) through the expression of higher levels of precursor forms of hsa-let-7b and hsa-let-7g miRNAs (93). These findings led to the hypothesis that microvesicle-mediated therapeutic effects may occur through two different mechanisms involving gene information transfer (7,23,94) (Fig. 3). First, microvesicles released from injured tissues can act on (local) stem cells and promote the release of 'regenerative' microvesicles for tissue repair; second, local stem cells in
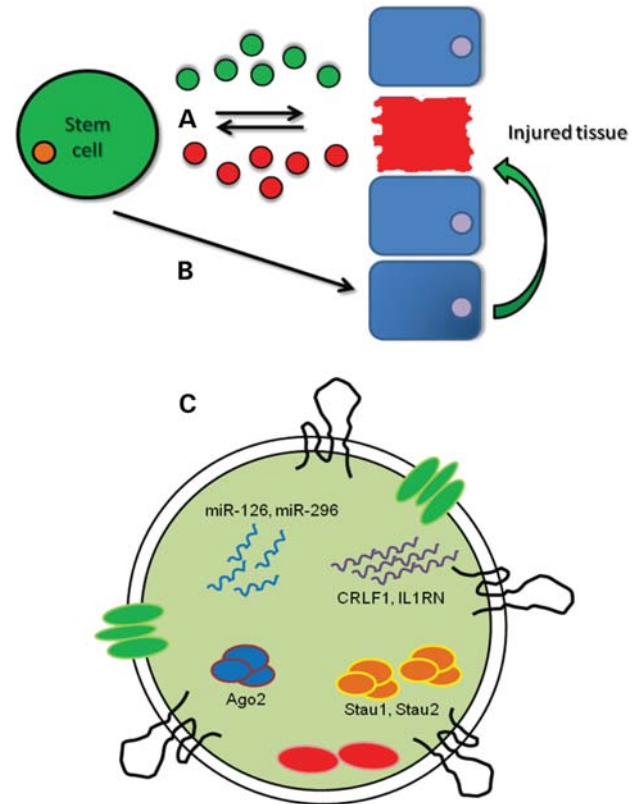
Figure 3. The two mechanisms of stem cell exosome/microvesicle-mediated regeneration of injuried tissues. (**A**) Microvesicles and exosomes can be released from injured tissues and act locally on the stem cells to prime them to release exosomes/microvesicles that naturally contain a variety of beneficial cargoes to help in repair and regeneration directly. (**B**) Microvesicles and exosomes can be released from injured tissue and act on the stem cells. These stem cells can then de-differentiate neighbouring cells at the injuired site to replace the damaged cells. (**C**) Enlarge view of a stem cell-derived extracellular vesicle, showing its cargo contents for repair and regeneration. These cargoes include proangiogenic miRNAs such as miR-126 and miR-296, mRNAs for immune regulation including cytokine receptor-like factor 1 (CRLF1) and interleukin 1 receptor antagonist (IL1RN), transport proteins that assist in the transport and stability of mRNA such as Staufen1 (Stau1) and 2 (Stau2) and factors involved in miRNA transport and processing like Argonaute2 (Ago2).

the vicinity of injured or degenerating tissues produce microvesicles that induce de-differentiation and re-entry into the cell cycle of cells neighboring the injured tissues to stimulate regeneration.

An alternative therapeutic approach is to re-engineer naturally derived exosomes for targeted gene therapy. Exosomes are potentially ideal gene therapy delivery vectors as they are comprised of natural non-synthetic and non-viral components. Further, their small size and flexibility enables them to cross major biological membranes, while their bi-lipid structure protects the RNA and protein cargo from degradation, facilitating delivery to its target (95). In 2011, Alvarez-Erviti *et al.* (8) published the first study using modified murine exosomes to successfully deliver exogenous genetic cargo (siRNA) resulting in gene-specific silencing in the brain. They proved that by expressing a rabies virus glycoprotein peptide (96), which specifically targets the brain, on these exosomes, they were able to get target gene knockdown

in a number of brain regions following systemic intravenous delivery, with little effect in peripheral organs such as the liver and kidneys. Further, these modified exosomes could be repeatedly injected into healthy mice without adverse immune response, indicating that this might be a relatively safe form of therapy. Recently, Valadi's group was able to validate exosomes from peripheral blood as genetic delivery agents (9) for heterologous siRNA against MAPK-1. These exosomes could be delivered to human blood mononuclear cells including monocytes and lymphocytes, to result in efficient gene knockdown. These exciting early findings have laid the groundwork for developing extracellular vesicles as intelligent, targeted gene therapeutic agents and extending the repertoire of cargoes to other therapeutic macromolecules including oligonucleotides and proteins.

IMPORTANCE AND CHALLENGES IN STUDYING EXOSOMES AND MICROVESICLES

Exosomes and microvesicles are beginning to emerge as crucial vectors aiding genetic information transfer in both health and disease. Moreover, new evidence showing the therapeutic relevance of these vesicles in both unmodified and modified forms make them attractive therapeutic agents for further study. However, there remain fundamental challenges in the field of extracellular vesicle research. These include development of robust, reproducible methods for extracellular vesicle isolation and characterization as well as developing greater fundamental knowledge on exosome biogenesis and function; all of which will serve to enhance our overall understanding on the role of such vesicles in gene information transfer.

The derivation of highly pure and well-characterized vesicular populations is crucial to establishing a detailed understanding of genetic information transfer; how such information is packaged and transferred and how its functions are mediated within the host cell. There are currently various methods to isolate specific extracellular vesicle populations; from ultracentrifugation protocols (97), to newer alternative methods such as filtration (98), immunoaffinity capture with beads (99) and microfluidics approaches (100). Sucrose density gradients can be used to derive pure populations (97), but this method is time-consuming with low yield. At present, there is a lack of consensus as to the optimal methods for the isolation of pure vesicular preparations.

Regarding characterization of extracellular vesicles, there are several common methods used including electron microscopy (EM), western blotting and fluorescence-activated cell sorting (FACS) with beads. In addition, new technologies such as the Nanosight (101), new FACS (102) protocols and curation of an exosome marker database like exocarta.org (103) have emerged recently to further supplement current characterization studies. However, some methods have significant limitations; for example, the original EM classification of exosomes as 'cup-shaped' vesicles is incorrect as this is now known to be an artefact of EM preparation (61). Moreover, it is important to note that none of these methods singly allows for complete biophysical and biochemical characterization of vesicles and their genetic content. Robust and reproducible methods for elucidating vesicular genetic contents will be crucial to underpin our understanding of vesicle biology and for the exploitation of such contents as disease biomarkers (34,104–106). Hence, establishing appropriate and comprehensive methods for isolation and characterization of extracellular vesicles is critical to ensuring the reliability of genetic data derived from analysing different vesicle populations.

Understanding the specificity and mechanism by which genetic information is inserted into extracellular vesicles prior to release will be central to understanding their role in information transfer (3). Numerous reports have speculated that plasma membrane anchors such as a myristoylation tags (107), conserved glycan signatures (108), a 25-nucleotide zip code (109) or short nucleotide patterns (110) can shuttle specific RNA and protein cargo into exosomes but none of these data have been repeated for exosomes from all cell types. Thus, it remains unclear whether the RNA and protein content in vesicles is the result of a highly selective or stochastic process. Another idea gaining favour is that the type of cargo entering vesicles is dependent on the external environment of the cell. For example, it has been shown that exosomes derived from mast cells under oxidative stress have a RNA content distinct from those grown under normal conditions and that these exosomes have the ability to induce tolerance to oxidative stress in recipient cells (111).

Lastly, the actual mode of trafficking and uptake of vesicles into recipient cells is still poorly understood. Some have hypothesized that exosomes and microvesicles can be phagocytosed by recipient cells (112,113) or fuse directly with the plasma membrane (114). Others have speculated that this could be a receptor-mediated process (33,115,116), which suggests that cells could take up extracellular vesicles selectively based on their surface receptor repertoires. Also, upon uptake of vesicles into recipient cells, there are further unanswered questions on how genetic information such as miRNA are released and localized to the cytoplasmic or nuclear compartments in which they are functional. Gaining a deeper understanding of extracellular vesicle trafficking, targeting and uptake will help to answer fundamental questions relating to the function and importance of the genetic signals encapsulated and transferred within such natural vesicles.

CONCLUSION

Extracellular vesicles are emerging as potent sources of genetic information transfer between mammalian cells and tissues resulting in both beneficial (cell communication, stem cell plasticity and repair of injured tissues) and potentially detrimental (spread of disease) outcomes. Such vesicles also have therapeutic potential as gene therapy tools, and hence increasing efforts will be made in the coming years to better understand their biology and function.

Conflict of Interest statement. None declared.

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