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The role of exosomes in the promotion of epithelial-to-mesenchymal transition and metastasis

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1. ABSTRACT

The progression of a solid cancer from a localised disease to metastatic stages is a key reason for mortality in patients. Amongst the drivers of cancer progression, **E**pithelial-to-**M**esenchymal **T**ransition (EMT) has been shown to be of crucial importance. EMT results in the phenotypic shift of an immotile, treatment-sensitive epithelial cell into an elongated, metastatic and treatment-resistant mesenchymal cell. Depending on the cellular and molecular setting, a myriad of studies have demonstrated that EMT causes increased cancer cell motility, invasiveness, resistance to therapies, dormancy and cancer-stem cell phenotypes, all of which are prerequisites for metastasis. The alteration of non-canonical intercellular signalling events in cancer EMT is a phenomenon that is not completely understood. Recently, extracellular vesicles, especially small vesicles called exosomes, have shown to be involved in cancer cell EMT. Most intriguingly, across different cancer types, cancer-derived exosomes have demonstrated to be capable of transferring a mesenchymal phenotype upon recipient epithelial cells, including epithelial cancer cells. The uptake of EMT-inducing exosomes results in molecular changes, altering miRNA, mRNA, and protein levels, either through direct transfer of these components, or by altering gene expression networks involved in EMT. In this review, we are presenting the current state of research of exosomes in cancer EMT, highlight gaps in our current

knowledge and propose strategies for future experiments in this area.

2. INTRODUCTION

Cancer incidence is continually increasing, with 33% of men and 25% of women developing cancer in their lifetime (1). Cancer is one of the leading causes of death worldwide due to untreatable disease progression (2). Cancer cells display a wide array of phenotypes during cancer progression, which may be caused by epigenetic alterations, oncogenic transformation, or even altered environmental cues (3). Even within a cancer patient, a tumour is highly heterogeneous, reflected by various molecular alterations. These environmental cues and heterogeneous nature of cancers influence cancer cell plasticity, treatment resistance and the propensity of cancer cells to metastasise (3-5).

Metastasis is the most common cause of cancer morbidity and mortality, accounting for approximately 90% of cancer-related deaths (6, 7). Metastasis is a complex multistage process, in which cancer cells disseminate from the primary tumour, and travel via the vascular systems to neighbouring tissues and distant organs. Cancer cells evade immune attack and proliferate in distant tissues, establishing a microenvironment that enables the formation of metastatic deposits (7). Despite the progression and development of cancer therapies and treatments, there has been little impact in reducing morbidity and mortality rates for patients with metastatic cancer. This failure emphasises the need for a greater understanding of the biological mechanisms of the metastatic cascade in order to advance strategies that target metastasis (7, 8).

It has become clear that cancer cells can prime metastatic sites before the arrival of metastatic cells. We and others have demonstrated that primary tumours can condition the microenvironment of tissues prior to invasion by cancer cells through secreted factors (9-14). This supports the notion of Stephen Paget, who first proposed this phenomenon in 1889, the ‘seed and soil’ hypothesis (15). This concept described that cancer cells (the ‘seeds’) of the primary tumour interact and communicate with specific organ microenvironments (the ‘soil’) prior to colonisation by metastatic cancer cells (13, 16). These organ-specific microenvironments are called the pre-metastatic niche (13).

Although primary tumours enhance metastatic outgrowth by priming secondary sites, cancer cells have to obtain specific traits to initiate the metastatic cascade. It has been suggested that epithelial-to-mesenchymal transition (EMT) of cancer cells facilitates this phenotypic transition and plays a major role in metastasis (17). EMT is a biological process that describes the phenotypic shift of an epithelial cell into an elongated mesenchymal cell, due to a series of biochemical changes (18). The EMT process was first described by Gary Greenburg and Elizabeth Hay in 1982 (19), as an epithelial-to-mesenchymal *transformation* (20). However, subsequent studies revealed EMT to be a reversible process thus “transformation” was replaced with “transition” (20). EMT contributes to the phenotypic heterogeneity present within the primary tumour and can be induced by oncogenic transformation, as well as autocrine and paracrine signals within the primary tumour microenvironment (3, 21).

EMT is a multifaceted process, causing profound phenotypic changes within the cell thereby promoting cancer progression. However, EMT also perturbs the extracellular environment by altering the secretion of canonical and non-canonical factors from cells undergoing EMT. We have recently demonstrated that non-canonical extracellular signalling events can promote EMT and drive cancer progression (18). This non-canonical signalling is driven through secreted extracellular vesicles (EVs) that play a critical role in intercellular signalling. EVs are composed of large (100-1,000 nm) microvesicles and smaller (30-150 nm) vesicles termed exosomes. These EVs carry nucleic, protein and lipid information of the cell of origin they are derived from, and are capable of contributing to EMT, thereby promoting drug resistance, cancer recurrence and metastasis. This review will detail the complex events of EMT and how EVs can contribute to this process. Moreover, how EVs can inform about the

extent of EMT in a primary tumour and contribute to clinical management will be discussed.

3. THE PROCESS OF EMT

3.1. The epithelial phenotype

Epithelial cells are immotile, polarised cells arranged in a single-cell “cobblestone” monolayer or in multi-layered sheets (22). Epithelial cells are connected by intercellular junctions and interact with an intact basement membrane (BM) through integrin receptors, thus movement is quite restricted (23, 24). There are four different types of intercellular junctions; (I) adherens; (II) tight; (III) gap; and (IV) desmosomes (25), and the expression of these junctions is critical in describing the epithelial phenotype (Table 1). Adherens junctions play a role in regulating the cytoskeleton and stabilising adhesive connections for effective intercellular signalling (26). The formation of the adherens junction results in the establishment of the tight junction (26), which forms cell-cell barriers to limit paracellular transport of molecules (27). Gap junctions not only have adhesive qualities, but also allow intercellular passive transport of ions and small molecules (28). Desmosomes attach to the cytoskeleton, thus provide strength to tissues for resistance against mechanical stress (29, 30). The intercellular junctions provide the structure and rigidity required for the primary function of epithelial cells to line the surfaces of body cavities (31). In addition to contributing to structural integrity, intercellular junctions are composed of key protein complexes that control epithelial function (24). The expression of these key proteins maintains epithelial cell integrity and adhesive properties, and prevents differentiation (32, 33). Importantly, these biochemical traits of an epithelial cell restrict cancer cells from entering into the metastatic cascade, and it is the loss and destabilisation of these key proteins that contributes to EMT and thereby cancer metastasis (3-5, 34).

A significant event that occurs during EMT is the downregulation of epithelial cadherin (E-cadherin). E-cadherin is a major transmembrane glycoprotein of the adherens-type junction. E-cadherin is a critical component in intercellular adhesion, inducing the formation of both the adherens junction and desmosomes by pairing cadherins in lateral epithelial cells (24, 26, 35, 36). E-cadherin also binds proteins of the cytoplasm called catenins, including p120 catenin, β-catenin, and α-catenin (26). This allows cadherins to connect to the cytoskeleton and be involved in signalling pathways (24, 26). Cleavage and subsequent degradation of E-cadherin prevents interaction with β-catenin. As a result, β-catenin may translocate to the nucleus with p120 catenin for transcriptional activation of Wnt genes, which drives EMT (25, 37, 38). Desmosomes are very similar to adherens junctions, with desmosomal cadherin proteins connected to intermediate filaments through desmoplaskin, which are disrupted during EMT (25). The main components of tight junctions are the family of transmembrane proteins, occludin and claudins, and the intracellular scaffold protein, zonula occludens 1 (ZO-1) (27). Occludin and claudins regulate ion selection and permeability of the intercellular pathway connecting adjacent cells, whereas ZO-1 binds to the cytoskeleton and proteins of the adherens and tight junctions (26). Downregulation of these proteins in EMT results in the loss of the epithelial cell polarity (39). Furthermore EMT decreases the expression of connexin – a major protein in gap junctions – which causes a loss of junction integrity (25). The inhibition of the expression of these proteins disrupts the epithelial phenotype and leads to the onset of EMT.

3.2. The epithelial-to-mesenchymal transition

EMT is associated with normal, homeostatic events that are spatially and temporally regulated (24, 40). EMT occurs in normal developmental processes such as embryogenesis (22), embryo implantation during pregnancy (41) and organ development (36). EMT also occurs in wound healing, tissue regeneration, and organ fibrosis (36). These processes are initiated to recruit and activate fibroblasts to aid in the healing of tissues that have undergone trauma and inflammation (36). However, in the state of disease, EMT is hijacked and results in disturbing epithelial integrity and producing mesenchymal cells that sustain and exacerbate the disease (24). In the cancer setting, EMT is activated

Table 1. Function of EMT markers and regulators

EMT markers and regulators	Function
Epithelial	
E-cadherin	Regulates the formation of adherens junction and desmosomes, and has an important role in intercellular adhesion
β-catenin	Connects cadherins to cytoskeleton
Occludin	Stabilises tight junctions
Claudins	Determine tight junction barrier properties
ZO-1	Scaffold protein
Mesenchymal	
N-cadherin	Facilitates transition of cell towards a mesenchymal phenotype, increasing migration and invasion
Vimentin	Cytoskeletal intermediate filament that induces changes in cell morphology, migration and adhesion
Fibronectin	Extracellular glycoproteins that acts as a scaffold for the fibrillar ECM of mesenchymal cells
α-SMA	Controls cell motility and differentiation
Transcription factors	
SNAIL	Transcriptionally represses epithelial markers such as E-cadherin, and activates mesenchymal markers such as N-cadherin
SLUG	
TWIST	
ZEB1	
ZEB2	
Regulators	
TGF-β	Induces EMT by controlling regulation of EMT transcription factors
HIF1α	Promotes EMT by modulating genes associated with EMT

in order to produce cancer cells that exhibit both epithelial and mesenchymal qualities or cells with only a mesenchymal phenotype to propel cell invasion and metastasis (36).

Prior to EMT initiation, cells that will undergo EMT must be primed and conditioned towards a mesenchymal phenotype. For example, cell division may cease so that the cytoskeleton can be used to drive the changes in cell morphology and motility required for EMT (42). This induces major changes in gene expression necessary for EMT initiation (42). Temporal and spatial patterning of the epithelial region encourages morphogenic rearrangement to enable cell transportation to the EMT site (43). It also ensures that the integrity of the remaining epithelium is uncompromised (42). Following this, intercellular junctions and cell-BM connections must be disrupted (24). Dissolution of adherens, tight, gap junctions and desmosomes results in the loss of BM integrity (44). The disruption of these connections allows cells undergoing EMT to detach from the epithelial structure and for the remaining cells to close the gap (24). The detached cells then undergo cytoskeletal changes and differentiate into spindle-shaped mesenchymal cells (42).

Transformation into a mesenchymal phenotype results in the loss of apical and basal polarity, and the acquisition of an elongated morphology allows for fluid cellular movement, thus enables migration (45). A complete transition is characterised by changes in (i) cell morphology; (ii) functionality markers; and (iii) differentiation. Classical mesenchymal markers include N-cadherin, vimentin and fibronectin (Table 1). Downregulation of E-cadherin results in the upregulation of the mesenchymal N-cadherin, facilitating the transition of the cell towards a mesenchymal phenotype, increasing migration and invasion (25). This is commonly referred to as ‘cadherin switching’ and is

an important stage in EMT-driven metastasis. Vimentin is a cytoskeletal intermediate filament protein that induces changes in cell morphology, migration and adhesion (46). Fibronectin is an extracellular glycoprotein that acts as a scaffold for the fibrillar ECM of mesenchymal cells (47). EMT results in enhanced cell motility, migratory potential, invasiveness, resistance to apoptosis and alterations of cell-ECM interactions and ECM components (20, 24). The degradation of the BM and formation of a mesenchymal cell marks the completion of an EMT (20).

Depending on the tissue or signalling mechanisms, a 'partial' or 'quasi' EMT of epithelial cells may take place. This is when epithelial cells lose only some of their traits or exhibit both epithelial and mesenchymal traits. Cancer cells that exhibit this partial EMT phenotype have the ability to move as clusters, which can become more aggressive than the cancer cells that have undergone complete EMT (48). Cells in the clusters exhibit enhanced tumour-promoting properties as they are resistant to apoptotic mechanisms, can exit the bloodstream in a more efficient manner and increase plasticity (49). This poses a problem for detection of partial EMT cancer cells as epithelial and mesenchymal markers may be expressed equally or at varying levels.

4. EMT AND METASTASIS

It has been suggested that EMT is a critical mechanism responsible for the malignant transformation of epithelial cancer cells as well as metastasis (40). Numerous *in vitro* and *in vivo* studies have demonstrated that epithelial cancer cells undergoing EMT exhibit decreased expression of epithelial markers, such as E-cadherin, occludin, claudins, ZO-1, connexins, and the acquisition of mesenchymal markers such as N-cadherin, vimentin and fibronectin (50-57). These morphological and molecular alterations correlate with more aggressive cancer cell phenotypes and metastatic potential (58). The acquisition of a mesenchymal phenotype increases the invasiveness and motility of cancer cells, allowing them to escape apoptosis, cellular senescence and immune system activation (36).

A significant amount of research has been directed in characterising the events of EMT in the primary tumour and how this contributes toward cancer progression (50-57). In fact, EMT has been linked to subpopulations of cancer cells within a tumour, referred to as cancer stem cells (CSCs), which exploit EMT mechanisms to promote metastasis, resist current treatments, and drive cancer recurrence (59). Chemokines and cytokines, generated by either the transformed cancer cells themselves or stromal constituents of the primary tumour microenvironment, are thought to promote the CSC phenotype (60). CSCs exhibit self-renewal properties and the ability to differentiate (61). CSCs are thought to display a partial EMT phenotype. Moreover, CSCs are characterised by a low proliferation rate, $CD24^{low}/CD44^{high}$ phenotype, and are able to escape the harmful effects of chemo- and radiotherapy due to the high levels of drug export systems (61, 62). CSCs are able to undergo EMT to extravasate and invade target tissues, then induce mesenchymal-to-epithelial transition (MET) in order to produce secondary epithelia and establish metastatic tumour sites (20, 61).

It is thought that cancer cells that have undergone substantial genetic modifications during primary tumour formation are hypersensitive to EMT signalling compared to untransformed cells (39). Interestingly, it has been observed that the secondary tumour cells established by supposed EMT-derived migratory cells are similar to the primary tumour site, meaning they do not resemble the mesenchymal phenotype proposed for the transitional stage (40). This implies that cancer cells undergo phenotypical changes equivalent to MET in order to allow secondary tumour formation. This may occur due to the loss of EMT transcription factor signalling that are present in the primary tumour (41). EMT signalling has predominantly focussed on classically secreted factors such as transforming growth factor beta (TGF-β) or microenvironmental conditions that induce EMT transcription factors that promote the phenotypic depolarisation of epithelial cells. However, it is becoming clear that there are several non-canonical intercellular processes that contribute to

EMT and cancer progression. In particular, the secretion of EVs can either inhibit or promote EMT through the transfer of nucleic acids or protein information from one cell to the other.

The effects of TGF-β signalling depend on the stage of cancer progression. In the early stages of tumour formation, TGF-β can act to inhibit tumour development by preventing cancer cell proliferation and activating apoptotic pathways (63). However, as cancer progresses, TGF-β promotes tumour progression by regulating the pathways that activate the EMT transcription factors (64). TGF-β activates Smad2 and Smad3, which then bind Smad4 to form complexes that regulate transcription of pro-metastatic genes. TGF-β can also induce signalling via activation of phosphatidylinositol 3-kinase (PI3K)/AKT/mitogen activated protein kinase (MAPK) pathways (63). Both the SMAD and PI3K/AKT/MAPK pathways control the activation of EMT transcription factors SNAIL and SLUG (64). SNAIL downregulates epithelial markers like claudins, and also interacts with EMT transcription factors, TWIST and ZEB1 to enhance EMT metastasis (63).

Hypoxia is a crucial feature of the tumour microenvironment that plays a significant role in mediating the promotion of EMT and metastasis in multiple cancers (65). Most tumours have an inadequate blood supply, hence the tumour microenvironment becomes hypoxic (65, 66). Hypoxia-induced EMT causes an increase in CSC formation during cancer development, which further stimulates invasive and metastatic properties (65). Importantly, this has been linked to poor patient outcome (65). Pro-EMT signalling is maintained through hypoxia inducible factor 1 alpha (HIF1α), an important regulator of EMT (65, 66). HIF1α modulates the expression of EMT transcription regulators in order to promote metastasis (67). In addition, intermittent hypoxia - common in solid malignancies - has been linked to EMT in breast cancer (68). EMT transcription regulators induced by hypoxia repress E-cadherin, resulting in a shift of gene expression that favours the EMT state (25). HIF activity switches cancer cell metabolism in order to benefit proliferation, expansion and survival. A major sign of altered metabolism is increased glucose consumption due to the use of aerobic glycolysis (69). Aerobic glycolysis is the conversion of glucose to ultimately form lactic acid (70, 71). In order to counteract the intracellular acidification, cancer cells export lactic acid and H^+ ions into the extracellular space. This results in the acidification of the tumour microenvironment (71). The acidity of the tumour microenvironment has shown to alter cancer cell phenotype. One study demonstrated that an acidic pH facilitated EMT in melanoma cells. This was accompanied by an increase in invasiveness, acquisition of mesenchymal morphology, apoptotic resistance and activation of mesenchymal markers N-cadherin, vimentin and TWIST (72).

The relevance of EMT in metastasis has been questioned by many, as there is limited *in vivo* evidence demonstrating that cancer cells undergoing EMT within the primary tumour are responsible for metastatic growths. A recent study conducted in mice with pancreatic ductal adenocarcinoma revealed that suppressing EMT had no effect on cancer cell dissemination and metastasis (73). This study designed an *in vivo* model of EMT inhibition by knocking down the expression of *TWIST1* and *SNAI1*. Knockdown of *TWIST1* and *SNAI1* resulted in the suppression of *ZEB1, ZEB2, SOX4* and *SNAI2*. This had no significant effect on the rate of tumour progression, proliferation, invasion and systemic dissemination of tumour cells to lung and liver (73). Also, *in vivo* studies are typically conducted in rodents, thus clinicians and pathologists express uncertainty on the relevance of EMT and its contribution to cancer in the clinical setting (74). Further studies that experimentally validate the relationship between EMT and metastasis *in vivo* in humans need to be conducted to comprehensively address this. Despite these doubts, there is a growing amount of evidence for the role of EMT in cancer progression (74). The induction of EMT and its role in the metastatic cascade has been reported in lung, breast, prostate, colorectal cancer and many more (75-78). It is important that the results obtained from *in vitro* experiments are validated in *in vivo* and clinical settings, thereby providing greater understanding of the necessary approaches for cancer therapies and improving clinical outcome.

Measuring EMT markers in primary tumours may reveal the processes that drive

metastasis and may also act as a determining factor in establishing a patient's risk for developing metastatic disease (79). Currently, tumour tissue biopsies are the standard method used to obtain molecular information of the tumour (80). There are a variety of methods used on tissue biopsies for the confirmation of cancer diagnosis. These include immunohistochemical (IHC) staining, flow cytometry, transmission electron microscopy (TEM), and genetic testing. IHC staining is used to evaluate cancer cell type and the site of origin of a metastatic cancer cell (81). Flow cytometry can quantitatively analyse cancer cell phenotype and content (82). TEM is typically used as an additional measure to provide further information about the tumour that other methods failed to uncover. TEM assesses aspects such as intercellular interactions and localisation of proteins (83). Assays for genetic testing evaluates gene expression, mutational signatures, DNA damage and much more (84). Biopsies have the potential to improve diagnosis, discover other primary cancers and confirm the expression/absence of biomarkers which impact choice of therapy (85). Tissue biopsies have been clinically validated, however, they can be very invasive and are potentially risky surgical procedures to perform that may be painful for patients (80). Additional tissue biopsies are ideal for additional analysis or subsequently during therapies, but are difficult to repeat due to the potential danger for patients and limited cancer material (80, 86). In addition to this, tissue biopsies may provide an inaccurate representation of tumour heterogeneity and generally fail to detect distant metastatic sites, requiring additional imaging studies (85). Tumour cells undergoing EMT can be observed in tissue biopsies by IHC staining to study for the expression of EMT markers (87). However, it is debatable as to whether the cells observed can be readily and accurately differentiated from the mesenchymal stromal cells in the tumour microenvironment (88). Also, there is great variation in the methods employed for measuring EMT markers in tumour cells (79). However, given these limitations of sampling tumour biopsies, an alternative approach is to sample liquid biopsies, which is gradually becoming a reliable, fast and non-invasive diagnostic approach.

5. EXTRACELLULAR VESICLES

EVs are membrane-bound lipid vesicles secreted by most cell types into the extracellular space (89). They are present in most bodily fluids such as blood, urine and saliva (90). The lipid bilayer structure of EVs is enriched in cholesterol, phosphatidylserine and glycosphingolipids, which confers increased stability, unlike the more fluid nature of cellular plasma membranes (91). This aids efficient transport of EVs through bodily fluids and ensures the protection of complex cargo (91). EVs can be categorised into different subtypes, based on the biogenesis, size, morphology, cargo and method of isolation (92). There are three main subtypes; apoptotic bodies, microvesicles and exosomes (93). EV release is a normal, homeostatic process, however, an increase in EV production has been described for various pathophysiologies, including certain cancers (94). The unique molecular content of EVs and its elicited effects on recipient cells, makes cancer-derived EVs promising candidates as potential cancer biomarkers (92). EV cargo includes lipids, proteins, genetic materials (miRNA, lncRNA, mRNA, RNA, DNA, etc.), metabolites and other molecules derived from the parental cell (95). EV cargo is reflective of the cell-of-origin and its biological status (96, 97). Once secreted from cells, EVs transport their cargo to recipient cells for uptake, which can result in the alteration of the recipient cell's function and physiology (18, 92, 97). Thus, EVs play an important role in intercellular communication (98). The communication function employed by EVs may be attributed to its diverse components (99). Thus, it has been suggested that cancer-derived EVs can be involved in intercellular communication to promote EMT and metastasis (100).

Cells undergoing apoptosis randomly assort their contents into vesicles, which are known as apoptotic bodies. Therefore, the content of apoptotic bodies secreted from the same cell can vary greatly, consisting of cytoplasmic molecules and organelles, with phosphatidylserine as the only characterising marker (101, 102). Apoptotic bodies are the largest of the extracellular vesicles as they can range from 800-5,000 nm in size (103). Once in the circulation, they are quickly degraded by phagocytosis, thus apoptotic bodies seem to have no

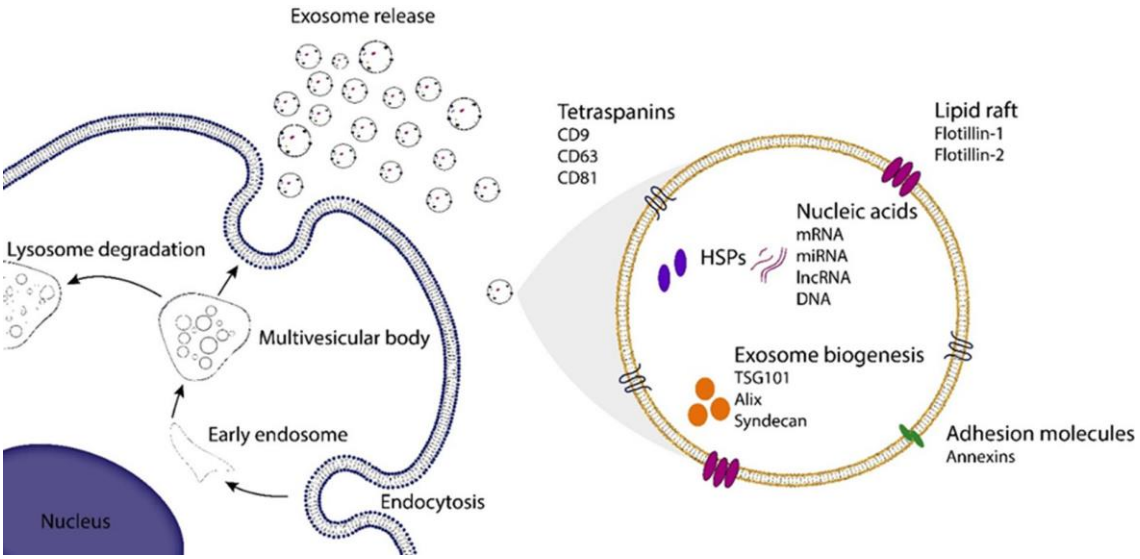

Figure 1. Exosome biogenesis begins with invagination of the plasma membrane to form early endosomes. Early endosomes mature into multivesicular bodies (MVBs), with invagination of the membrane generating intraluminal vesicles. MVBs either fuse with lysosomes for degradation, or fuse with the plasma membrane, thus releasing the intraluminal vesicles as exosomes. Exosomes carry proteins, lipids and genetic materials such as mRNA, miRNA, lncRNA and DNA. Exosomes are characterised by the presence of marker proteins, such as tetraspanins (CD9, CD63, and CD81), heat shock proteins (HSPs), lipid raft proteins (flotillin-1, flotillin-2), adhesion molecules (annexins) and by endosomal sorting complexes required for transport (ESCRT) proteins (TSG101, Alix, and Syndecan).

significant role in intercellular communication (101). Microvesicle populations display incredible heterogeneity as they are irregular in shape, range from 100-1,000 nm in size and are formed from the budding of the plasma membrane. They express surface markers such as CD40, integrin-β and selectins (104). Exosomes are the smallest of the EV subtypes and are more of a homogenous population compared to microvesicles (102). Exosomes have a size range of 30-150 nm and are of endocytic origin (105, 106). Exosome biogenesis begins with the formation of early endosomes. Early endosomes mature into multivesicular bodies (MVBs), as intraluminal budding by invagination of the membrane generates intraluminal vesicles. MVBs either fuse with lysosomes for degradation, or fuse with the plasma membrane, thus releasing its contents as exosomes (107, 108) (Figure 1). Exosomes are characterised by the presence of marker proteins, such as tetraspanins (CD63, CD9, CD81), HSP70, flotillin-1 and by ESCRT proteins TSG101 and Alix (97) (Figure 1). Furthermore, the absence of cell organelle marker proteins, such as calnexin and GM130, is used to assist in characterising the purity of exosomes (109). There is evidence that exosome biogenesis can occur in either an ESCRT-dependent or ESCRT-independent manner (110), however, further research is required to understand the exact mechanisms involved. For uptake by recipient cells, it has been suggested to occur via mechanisms such as endocytosis, receptor-mediated endocytosis, direct fusion with the plasma membrane and phagocytosis (111).

Although the EV subtypes differ in physical properties and mode of biogenesis, there is a grey area due to the overlap in characteristics, with a heavy emphasis on the lack of tools to accurately differentiate EVs from each other. The specified size range of the EV subtypes differs greatly amongst researchers in the field. Current methods of EV isolation, such as ultracentrifugation and filtration, rely heavily on separation by density and size, respectively. However, relying on density and size may exclude potential EV populations that are of interest, which can alter results based on the isolation method used (112). Factors such as yield, purity and quality must be taken into consideration for the effective concentration and isolation of exosomes (109, 113). We have developed an optimised protocol for the isolation of human- and cell culture-derived exosomes (109). When comparing

exosome yield from cell culture supernatant, concentrating devices driven by ultracentrifugation produced a greater yield than devices driven by pressure. In comparison to ultracentrifugation, ultrafiltration was more effective for particle yield and recovery, as well as time efficiency. For the purification of exosomes from concentrated cell culture media, size exclusion chromatography (SEC) proved to be the most efficient method, compared to that of polymer-based precipitation reagents. Exosome precipitation reagents produce high particle yields but also result in the co-isolation of larger, contaminating particles. SEC selects particles based on size, providing a pure exosome sample in a reasonable time-frame that can be used to accurately assess the specific content of exosomes (109).

Tumour heterogeneity can make the isolation of cancer-derived exosomes slightly difficult, which can alter final results and hinder translation to the clinical field (114). Hence universal biomarkers of cancer-derived exosomes would assist in the proper detection of the desired cancer exosome populations and distinguish non-cancer from cancer. Many studies have shown the increased expression of particular genetic materials that serve as biomarkers of cancer-derived exosomes (115).Currently, a global consensus has yet to be reached on specific EV markers. One study revealed that exosomal protein markers HSP70, flotillin-1, MHCI and MHCII were not only expressed in what was considered the “exosomal” fraction, but was also highly enriched in fractions containing larger EVs (99). This implies that these exosomal markers may be non-specific and cannot truly define this subset of vesicles. Also, with the lack of detailed knowledge on exosome biogenesis, markers are not ubiquitously expressed (116). Therefore, studies that utilise methods that solely focus on the presence of certain markers may be inaccurate. Developing a method that can identify the pathway of EV biogenesis of the isolated EVs would be a better approach for differentiation; however, it is extremely challenging and only somewhat feasible for *in vitro* studies (112). Another issue with focusing on one EV subtype is that the effects measured in that particular EV may also occur in other EVs. The International Society of Extracellular Vesicles suggests that researchers quantitatively compare EV fractions to determine whether the results are specific and truly representative of the EV type of choice (112). Lack of methodological consistency prevents comparison between studies. Thus, a large focus is on establishing appropriate EV markers and improving methods of isolation. Many publications group EVs together, or use terms like ‘EVs’, ‘microvesicles’ and ‘exosomes’ interchangeably (105, 117-120). However, grouping EV subtypes together provides no clarity due to the diverse and heterogeneous nature of EVs. Therefore, this review will only refer to exosomal studies that have confirmed exosome isolation by size, morphology and presence of marker proteins.

6. EXOSOMES

Exosomes were once thought to merely function as vesicles for the disposal of unwanted cellular material (121). Recent findings have shown that exosomes play an important role in maintaining both homeostatic and pathological states through intercellular communication (122). Exosomes are involved in normal physiological processes, such as the immune response, neuronal synaptic function and lactation, as well as being involved in the pathophysiology of diseases, such as cancer (123, 124). Cancer cells can sort oncogenic material, including miRNA and proteins, into exosomes, which can then be transferred to neighbouring or distant recipient cells, contributing to tumour growth and the transformation of cells to pro-metastatic phenotypes (53, 94, 122). Exosomes act in an autocrine, paracrine and endocrine fashion, enabling horizontal transfer of proteins, lipids and genetic information (122, 125). Cancer-derived exosomes have shown to play a major role in the promotion of metastasis, from the initial stages of dissemination, to formation of the pre-metastatic niche, and to the development of secondary tumours (100). The cargo, function, stability and abundance of exosomes in a variety of bodily fluids make them ideal targets for uncovering EMT-related and metastatic mechanisms during cancer progression (122).

Cancer-derived exosomes assist in shielding tumour cells from the immune system and promoting pro-metastatic processes, including cell invasion, migration, proliferation and EMT (53, 126). Recently, it has been revealed that cancer-derived exosomes carry EMT factors to recipient cells, resulting in alterations in morphology, phenotype and

function, thereby enabling metastatic progression in a variety of cancer types (50-57, 111). These pro-EMT factors include TGF-β, HIF1α, β-catenin and vimentin, all of which facilitate tumour progression, partly through pre-metastatic niche formation (127, 128). Pre-metastatic niches are permissive changes to tissues promoting the growth of subsequently arriving circulating tumour cells (CTCs) (129-131). Although the phenotypic and functional alterations that occur during the EMT process have been characterised, there are many gaps in the literature that require further investigation.

6.1. *In vitro* models of exosome-induced EMT and metastasis

There is a significant association between metastatic, mesenchymal cell-derived exosomes and EMT initiation in epithelial cells, which has been demonstrated by numerous *in vitro* studies (52-57, 93) (Table 2, Figure 2). A study on hepatocellular carcinoma (HCC) demonstrated that exosomes derived from highly metastatic HCC cells were taken up by HCC cells with low metastatic propensity (54). This resulted in the recipient cells undergoing EMT through the activation of the MAPK/ERK pathway, associated with a more malignant phenotype and facilitating HCC progression (54). The ability of the low metastatic cells to migrate, form colonies, follow chemotaxis and invade was significantly increased, co-occurring with high expression of the mesenchymal markers α-SMA and vimentin, and a low expression of the epithelial marker E-cadherin (54). Similarly, another study found that both melanoma and lung cancer-derived exosomes increased the migratory and invasive capacity of primary melanocytes, suggesting that effects of cancer-derived exosomes is not limited to certain cancer types (55). The invasive phenotype of exosome-treated melanocytes is regulated by *let-7i*, which may induce its effects through LIN28B and HMGA2 (55). These two targets have been suggested to contribute to the EMT process (55, 132). Two EMT-related miRNAs, *miR-191* and *let-7a*, were significantly upregulated in the serum exosomes of stage I melanoma patients, compared to healthy control patients, suggesting that these miRNAs are potential biomarkers for early-stage melanoma (55). This study also showed treatment of primary melanocytes with melanoma-derived exosomes caused an upregulation of *SNAI2* and *ZEB2*, which led to the subsequent downregulation of E-cadherin and upregulation of vimentin (55). Furthermore, in lung cancer, it has been established that treatment of epithelial lung cancer cells with exosomes derived from mesenchymal lung cancer cells resulted in their transition to a metastatic, mesenchymal phenotype (52, 53). The epithelial cells gained an elongated, spindle-like shape, and had exhibited increased migratory and invasive abilities. Also, the downregulation of E-cadherin, and upregulation of N-cadherin and vimentin was observed (52, 53). In addition to these findings, numerous miRNA were differentially expressed in the mesenchymal cell-derived exosomes (52). Interestingly, it was found that the most enriched pathways represented by the miRNA were significantly associated with EMT factors, such as TGF-β and intercellular junctions (52). This study suggests that these differentially expressed miRNAs could serve as EMT biomarkers in lung cancer (52).

The EMT process and the transformation of lung cancer cells into a metastatic phenotype has also been induced in human bronchial epithelial cells (HBECs) by exosomes derived from the serum of late stage lung cancer patients (53). *In vitro* application of the serum-derived exosomes resulted in increased migration and invasion of the HBECs along with decreased expression of E-cadherin and ZO-1, and increased activity of N-cadherin and vimentin. Knockdown of exosomal vimentin reduced cell migration which suggests that vimentin may behave as an activator of exosome-mediated metastasis in lung cancer (53). Similar findings have been reported in a study that assessed the risk of pregnancy-associated breast cancer (56). Exosomes derived from healthy human milk were found to express significantly increased concentrations of TGF-β2, which, when incubated with benign and malignant epithelial breast cancer cells, led to the initiation of EMT (56). Morphological changes were observed in the benign and malignant cells, with the loss of the cytoskeletal structure and disruption of the intercellular junctions. This was accompanied by

Table 2. The effects of exosomes in the promotion of EMT in cancer

Cancer Type	Exosomal Source	Recipient Cell/ Animal	Biological Effects		References
Breast	Serum of tumour-bearing mice	Wildtype Mice	• Increased IL-6, IL-17	• Tumour formation • Increased tumour metastasis	(60)
	Healthy human milk	Benign and malignant epithelial breast cancer cells	• Decreased E-cadherin • Increased α-SMA, vimentin	• Loss of cytoskeletal structure • Disruption of intercellular junctions	(56)
	Breast CSCs, and breast cancer cells resistant to tamoxifen, metformin, doxorubicin and paclitaxel	Sensitive breast cancer cells	• Decreased E-cadherin, TGF-β, FOXO-3a • Increased SLUG, SNAIL, SOX9, BMI1, EZH2 • Activation of NF-κB, SNAI1, AKT	• Increased resistance to tamoxifen, metformin, doxorubicin and paclitaxel	(145), (149)
Liver	Highly metastatic HCC cells	Low metastatic HCC cells, and mice	• Decreased E-cadherin • Increased α-SMA, vimentin • Activation of MAPK/ERK pathway	• Increased migration, invasion, colony formation, chemotaxis • Tumour recurrence in the liver • Increased tumour size, weight	(54)
Lung	Mesenchymal lung cancer cells, and serum of late stage lung cancer patients	Epithelial lung cancer cells	• Decreased E-cadherin, ZO-1 • Increased N-cadherin, vimentin • Increased ZEB1, TWIST1	• Acquisition of an elongated, spindle-like shape • Shift towards $CD24^{low}/CD44^{high}$ phenotype • Increased migration, invasion • Increased resistance to gemcitabine, and cisplatin/gemcitabine	(52), (18), (53)
Oesophageal	Irradiated T cells	Oesophageal cancer cells	• Increased NF-κB, SNAIL, β-catenin	• Increased migration, invasion	(148)
Ovarian	Hypoxic macrophages	Epithelial ovarian cancer cells, and mice	• Activation of PTEN-PI3K/AKT pathway	• Increased resistance to cisplatin	(146)
Skin	Melanoma and lung cancer cells	Primary melanocytes	• Decreased E-cadherin • Increased SLUG, ZEB2, vimentin	• Increased migration, invasion	(55)

the loss of E-cadherin and increase in α-SMA and vimentin (56). These results suggest that women who secrete high amounts of TGF-β2 in their breast milk-derived exosomes may be at an elevated risk of breast cancer (56). Increased concentrations of TGF-β2 have also been described in exosomes derived from hypoxic prostate cancer cells compared to exosomes derived from normoxic prostate cancer cells. In addition to TGF-β2, pro-EMT factors IL-6 and β-catenin were also significantly expressed in the hypoxic exosomes. This resulted in the downregulation of E-cadherin and upregulation of β-catenin in recipient prostate cancer cells along with increased invasiveness, movement and stemness (127).

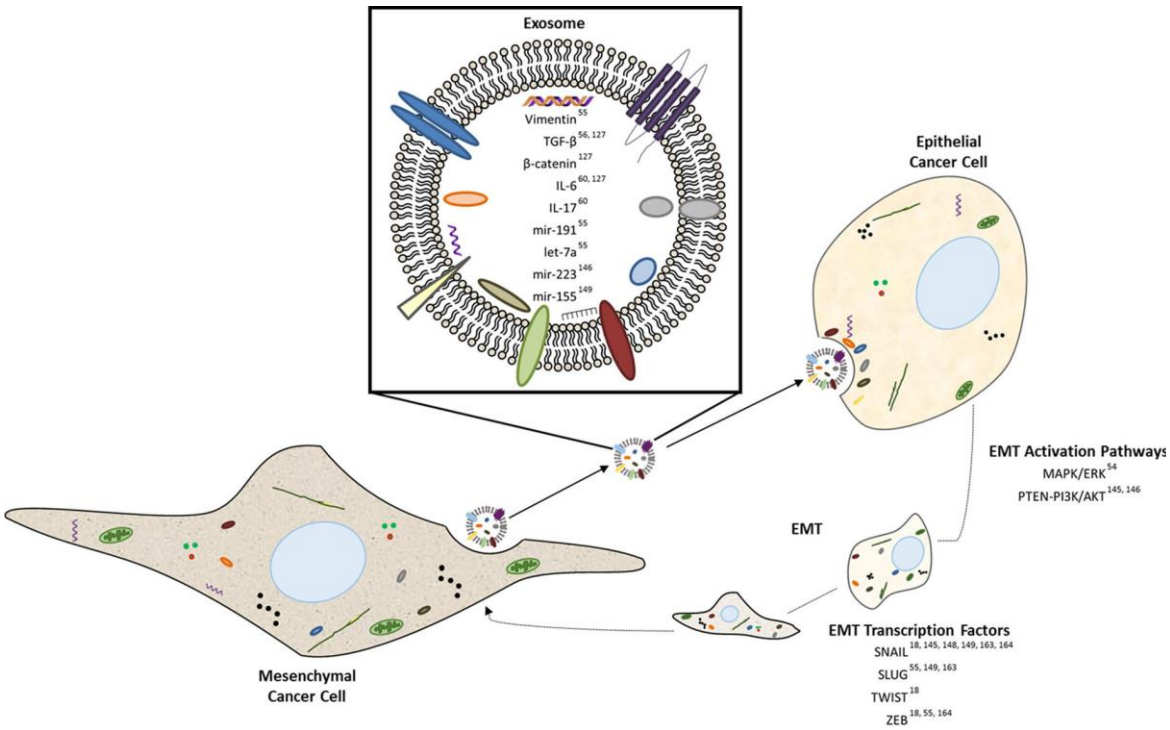

Figure 2. Exosomes derived from metastatic, mesenchymal cells carry pro-EMT factors to recipient epithelial cells, consequently inducing EMT. Pro-EMT factors include Vimentin, TGF-β, β-catenin, interleukins-6 and -17, and several miRNA. Uptake of these factors result in the activation of EMT pathways and subsequently EMT transcription factors. Numbers listed refer to citations in the reference list.

6.2. *In vivo* models of exosome-induced EMT and metastasis

Currently, there is a paucity of *in vivo* studies and reports in the literature showcasing the effects of cancer-derived exosomes on EMT and metastasis. It has been shown that exosomes derived from a highly metastatic pancreatic cancer cell line can cause an increase in primary tumour volume in mice (133). Injection of these exosomes also caused a greater metastatic burden and cancer cell metastasis to various organs compared to control mice and mice injected with exosomes derived from poorly metastatic cells (133). In breast cancer, infusion of exosomes derived from the serum of tumour-bearing mice into wildtype mice resulted in tumour formation and increased metastasis of the tumour (60). The tumours themselves and the tumour-derived exosomes displayed an altered cytokine profile compared to exosomes derived from the wildtype mice, with IL-6 and IL-17 significantly upregulated (60). Inhibition of IL-6 and IL-17 resulted in the attenuation of exosome-induced micrometastases in the lung and draining lymph nodes (60). It has been demonstrated in *in vitro* studies that IL-6 and IL-17 drive EMT in breast, oesophageal, lung and brain cancer (134-140). This growing body of *in vitro* and *in vivo* evidence demonstrating exosomes as key mediators of EMT and metastasis suggests a direction for potential translation into the clinical field. However, there is a need for more extensive *in vivo* investigations, as it is imperative to understand the role of exosomes in physiological settings before clinical application aimed at the improvement of cancer treatments.

7. EXOSOMES CONFER THERAPY RESISTANCE AND CANCER RECURRENCE THROUGH INDUCTION OF EMT

Therapy resistance and recurrence have become complicated obstacles to overcome in the treatment of cancer, despite initial successful attempts at treating the primary tumour by either

surgical resection, chemotherapy, radiotherapy or adjuvant therapy (141-143). Tumour cell resistance to therapy can be attributed to genetic mutations and/or mechanisms employed by elements of the tumour microenvironment that induce protection against treatment (142). Cancer-derived exosomes exploit their intercellular signalling function in order to manipulate both parent and recipient cells to confer a therapy-resistant phenotype through EMT (142). EMT is strongly linked with therapy resistance and cancer recurrence (144). Tumour cells resistant to therapy often enter a dormant state, then exit this state causing clinical recurrence (54). Tumour recurrence is frequently caused by metastasis with secondary tumours exhibiting decreased sensitivity to the effects of chemo- and radiotherapy compared to their corresponding primary lesions (54, 141).

7.1. Exosomes Promote EMT-Induced Resistance to Chemotherapy and Radiation

Research has shown that exosome uptake can modify recipient cells to adopt a therapy-resistant phenotype (18, 142, 145-150). A study on human breast cancer cells demonstrated that exosomes derived from cells resistant to the drugs tamoxifen (MCF-7/T) and metformin (MCF-7/M), induced resistance to these drugs in the parental MCF-7 cells (145). Exosome-induced resistant MCF-7 cells were characterised by the downregulation of E-cadherin, and activation of NF-κB, SNAI1 and AKT. Interestingly, addition of parental MCF-7-derived exosomes had no effect on the resistant properties of MCF-7/T and MCF-7/M cells (145). Another study on epithelial ovarian cancer (EOC) showed that exosomes derived from hypoxic macrophages increased the resistance of EOC cells to cisplatin, linking the impact of the primary tumour microenvironment on the interaction between infiltrating immune cells and cancer cells (146). These exosomes were highly enriched with *miR-223*, which increased cisplatin resistance through the PTEN-PI3K/AKT pathways, both *in vivo* in mice, and *in vitro.* In EOC patients, those with a high expression of HIF-1α had higher intertumoural levels of *miR-223.* Furthermore, circulating exosomal *miR-223* levels were closely associated with EOC recurrence. Intriguingly, it has been shown that EMT is regulated by the *miR-223* pathway (146). In pancreatic cancer cells, downregulation of *miR-223* reverses EMT in cells resistant to gemcitabine (147). Overall, these studies suggest that exosomal content can influence chemotherapy responses in cancer by modifying EMT.

Another interesting phenomenon is that radiation triggers an immune response that causes immune-derived exosomes to promote metastasis. Irradiated T cell-derived exosomes caused oesophageal cancer cells to gain a migratory and invasive phenotype (148). The higher the radiation dose, the more invasive the cancer cells were. The metastatic-like phenotype of the cells was associated with an upregulation of NF-κB, SNAIL, and β-catenin (148). Activation of NF-κB is associated with the stabilisation of SNAIL, which is known to suppress E-cadherin expression (151). The onset of EMT is induced by activation of Wnt signaling which prevents GSK-3β from phosphorylating β-catenin and SNAIL. The combined effect of these two factors promotes cancer cell survival during dissemination and invasion (152). The findings of these studies suggest that exosomes induce EMT to facilitate therapeutic resistance to radio- and chemotherapies.

Many studies demonstrating therapy resistance are strongly associated with CSCs (18, 142, 143). A key attribute of CSCs is their ability to enter dormancy, then re-emerge into the circulation, metastasise and form a secondary tumour by undergoing MET (142). Our previous work was first to demonstrate that exosomes derived from oncogenically-transformed, mesenchymal HBECs can transfer chemoresistant traits to, and induce a CSC-like phenotype in recipient untransformed HBECs (18). The mesenchymal HBECs displayed an elongated, spindle-like morphology, along with a decrease in the expression of *CDH1*, and an increase in the expression of *SNAI1*, *SNAI2*, *TWIST*, *ZEB1* and *ZEB2*. Additionally, the mesenchymal HBECs exhibited significantly elevated resistance to commonly used lung cancer therapies, cisplatin, gemcitabine, and a combination of cisplatin and gemcitabine treatment, compared to the epithelial HBECs. Exosomes derived from the chemoresistant, mesenchymal oncogenic HBECs promoted resistance to gemcitabine and the combination of cisplatin and gemcitabine, in the epithelial,

untransformed HBECs. The treatment of exosomes also increased expression of *ZEB1* and *TWIST1*, and promoted "stemness" by shifting the cells towards a CSC-like $CD24^{low}/CD44^{high}$ phenotype (18). Another study showed that exosomes derived from breast CSCs and cells resistant to doxorubicin and paclitaxel promoted EMT-mediated chemoresistance of the recipient sensitive breast cancer cells (149). The exosomes derived from both the CSCs and chemoresistant cells were highly enriched with *miR-155*, which was transferred to the recipient cells. It has been suggested that *miR-155* acts as a regulator of EMT and CSCs as it targets FOXO3a and regulates the loss of C/EBP-β, which can result in the loss of TGF-β (149, 153). These exosomes also induced an increase in the mRNA levels of *SLUG*, *SNAIL*, *SOX9*, *BMI1* and *EZH2*, alongside a decrease in *E-CAD*, TGF-β and FOXO-3a in the recipient sensitive cells. BMI1 and EZH2 are stemness-related transcription factors (149). These results show that the acquisition of a CSC-like phenotype is a major contributing factor of chemoresistance.

Another causative element of chemoresistance is tumour microenvironment pH. An acidic microenvironment has been associated with poor patient prognosis, suppressing the function of cytotoxic lymphocytes and NK cells, and a therapy-resistant phenotype (70, 142). Acidic environments are thought to significantly increase exosome release and facilitate uptake of exosomes by recipient cells *in vitro* (154-156). Extracellular acidity affects the mechanisms of anticancer therapies that are weak base drugs (157). Cellular uptake of weak base drugs is reduced as a high intracellular pH causes an influx of H^+ ions from the extracellular space into the cell (157, 158). Weak bases are ionised in acidic environments which reduces its ability to permeate cell membranes (157). The acidic tumour microenvironment also assists exosomes in promoting therapy resistance (142). Some cancer-derived exosomes express ATP-binding cassette (ABC) transporters (159). Exosomal ABC transporters have shown to sequester chemotherapeutic drugs into exosomes (142). The chemotherapeutic drug docetaxel, used for the treatment of breast and prostate cancer, can actually increase the number of exosomal ABC transporters (159). It has also been revealed that cisplatin is sequestered into melanoma exosomes in a pH-dependent manner (160). Chemoresistance is often seen in breast cancer as the multidrug pump ABCG2 is localised in the membrane of breast cancer-derived exosomes (150). Expression of ABCG2 mediates multidrug resistance as it enables sequestration of the drugs mitoxantrone and topotecan into the exosomal lumen. The PI3K-AKT signalling pathway regulates ABCG2, as inhibition of this pathway causes ABCG2 to relocalise to the cytoplasm, thus restores breast cancer cell drug sensitivity (150).

7.2. Exosomes promote EMT-induced cancer recurrence

There are not many studies on the relationship between exosomes, EMT and cancer recurrence. One study looked at the effects of highly metastatic exosomes on tumour recurrence in hepatic cellular carcinoma (HCC) (54). Surgical resection is the primary treatment for HCC patients who do not have cirrhosis (54, 161). Despite resection, the five-year risk of recurrence is 70%, which often arises within two years after surgery (162). Injection of highly metastatic HCC cell-derived exosomes into the tail vein of mice resulted in recurrence in the remnant liver in 100% of the mice, compared to the control group in which only 40% experienced recurrence (54). Tumour size and weight was also significantly higher in the group injected with the exosomes compared to the control group. As mentioned earlier these exosomes induced EMT in HCC cells via MAPK/ERK signalling (54). Furthermore, a study on colorectal cancer uncovered that there was a significantly higher count of $GPC1^+$ plasma exosomes in CRC patients with relapse, compared to patients without relapse (163). Moreover, patients that died with relapse compared to patients that survived with relapse, and patients that survived with relapse compared to patients that survived without relapse had altered levels of $GPC1^+$ plasma exosomes (163). There was also an increasing trend with $GPC1^+$ plasma exosomes in patients who relapsed nine months post-surgery. In order to investigate the role of *GPC1* in cancer recurrence, *GPC1* was overexpressed in CRC cells,

which resulted in decreased E-cadherin, increased vimentin and upregulated SNAI1 and SLUG expression, ultimately causing increased migratory and invasion abilities (163). These findings suggest that the upregulation of GPC1 in plasma exosomes may be involved in CRC relapse through induction of EMT (163). A study on urothelial bladder cancer (UBC) found that exosomes derived from the urine of UBC patients had significantly increased expression of the lncRNA HOX transcript antisense RNA (*HOTAIR*) (164). *HOTAIR* aids tumour initiation and progression, and is closely linked with poor prognosis in various cancers (165-167). Knockdown of *HOTAIR* decreased migration and invasion of UBC cell lines (164). It also resulted in the reduction of *SNAI1* and *ZEB1*, *TWIST1*, *MMP1*, *LAMB3* and *LAMC2* and increased expression of *ZO1* (164). Previous studies have shown that a high level of expression of *HOTAIR* is associated with cancer recurrence and even has the potential to act as a biomarker for recurrence in HCC, bladder cancer (165-167). These retrospective studies examining patient-derived exosomal cargo are beneficial for understanding the pathogenesis of cancer recurrence and there is a great urgency for additions to the literature.

Together, these studies have highlighted the involvement of cancer-derived exosomes in the initiation and promotion of EMT, metastasis, therapy-resistance and cancer recurrence (Table 2). Whether exosomes are the driving force behind these factors still requires more research, however, it is evident that exosomes are important contributing factors. In order to determine this, future studies will need to confirm that the effects observed are a true representation of exosomes and not of other elements of the tumour microenvironment, for example by inhibiting exosome release. It is essential that more animal and patient studies are conducted in order to determine the alterations in exosomal cargo induced by cancer. Identifying these changes in exosomal cargo may provide insight into the disease and act as potential biomarkers of cancer to guide prospective patient studies. Early detection of cancer onset, metastatic progression, therapy-resistance and recurrence would allow for early intervention and tailored therapies, thus the requirement for accurate biomarkers is essential. The rapid progression of cancer going undetected can be attributed to the current tissue biopsy and imaging methods used for diagnosis and prognosis. Real-time detection of exosomes using liquid biopsies promises being a suitable, better alternative.

8. LIQUID BIOPSY

Liquid biopsy in the cancer setting is a process that involves isolating and analysing biomarkers present in bodily fluids, such as blood, urine, saliva and ascites, in order to provide information about the tumour (168, 169). Currently, liquid biopsies based on cancer marker proteins (e.g. CA125 for ovarian cancer (170)) and cytokine responses to therapies (171) are used in cancer diagnostics. Unlike tissue biopsies, liquid biopsies promises the detection of metastasis and cancer responses to therapies in real-time (172). Due to the non-invasiveness of liquid biopsies it is safe for patients, rapid to perform and easily repeatable. Importantly, liquid biopsies may provide a more accurate representation of tumour heterogeneity, as it is assumed that the mutant molecules derived from the circulation originate from the variety of cancer cells present in the lesion (173). The abundance of exosomes in blood and other body fluids, and the fact that their content is reflective of their parent cells, make exosomes an ideal target for liquid biopsy approaches (174). However, in addition to exosomes, liquid biomarkers are also based on a variety of other entities, such as circulating tumour cells (CTCs) and circulating tumour DNA (ctDNA) (168).

8.1. CTCs and ctDNA

Circulating tumour cells are cancer cells that detach from the primary tumour, invade the BM and surrounding tissues, and disseminate into blood vessels (6, 175). CTCs are considered “predestined sources” of metastasis (175), representing the stage between the acquisition of an invasive phenotype and the formation of metastatic sites (176). EMT transcription factors, such as SNAIL, SLUG, TWIST and SIP1 promote the survival and formation of CTCs by preventing apoptosis, escaping senescence, and enhancing invasiveness and intravasation (175, 176). Circulating tumour DNA (ctDNA) is released by apoptotic and necrotic tumour cells (177). ctDNA

therefore contains the entire tumour genome, serving as reservoirs of genetic mutations and alterations (177). It has been proposed that ctDNA may induce oncogenic alterations and promote transformation of normal, non-cancer cells, thus contributing to metastasis (178). Therefore, CTCs and ctDNA have become of interest for their potential to act as diagnostic, prognostic and predictive biomarkers (172). Although CTCs and ctDNA have potential as liquid biopsy biomarkers, there are many limitations.

CTCs and ctDNA are difficult to detect as they are rapidly cleared from bodily fluids due to their short half-lives of 1-2.5 hours and less than 1.5 hours, respectively (179, 180). Up to 99.9% of CTCs go undetected by the current CTC assay methods available, as CTCs are only released into the blood at low concentrations (1-10 CTC/mL), often enter dormancy and are easily clogged in small blood vessels (181, 182). Typically, 7.5 mL of blood is extracted from patients to be used for CTC experimentation. One study analysed the differences in the detection of CTCs derived from 7.5 mL of blood and 30 mL of blood, in 15 patients with colorectal liver metastasis (183). Using the CellSearch® System, it was revealed that a median of 1 CTC was detected in the 7.5mL samples and a median of only 2 CTCs was detected in the 30mL sample (183). The CellSearch® System recommends a minimum CTC count for certain types of cancer for assay specificity and prognostic relevance (184). Therefore, patients with a low CTC count are excluded for clinical application, although they may have clinical relevance. During early stage disease, few cancer cells are dying, hence a very low level of ctDNA circulates in the blood (185). This poses a major problem for early cancer detection (186). Similarly to CTC detection methods, ctDNA assays can generate false-positive and false-negative errors (187-189). CTCs and ctDNA abundances are often below detection thresholds after cancer therapies, however, this is not necessarily an indicator of a complete removal of the cancer (190). Although CTCs and ctDNA may act as an alternative to the traditional tissue biopsy, they require validation in large for clinical application of these biomarkers in advanced cancer and numerous obstacles are yet to be overcome.

8.2. Exosomes

Exosomes provide significant advantages over CTCs and ctDNA, making them a good candidate for liquid biopsy methods (174). The most important feature of exosomes is that they sensitively reflect the phenotype of the primary tumour in real-time, thus are an accurate representation of tumour heterogeneity (174, 191). Unlike CTCs and ctDNA, exosomes are present in most bodily fluids at high concentrations during all stages of cancer, as exosome release is an active process (174, 182, 192). This allows for disease monitoring over extended time periods (182). Exosomes are stable and can be preserved and maintained in blood *ex vivo.* Their stability allows for the protection of their complex cargo derived from the tissue of origin (168, 182). This stability, and the presence of EMT associated nucleic acids and proteins within exosomes provides a unique insight into EMT and potential metastasis of the primary tumour, allowing for potentially earlier and more targeted therapy (191). Only a small volume of blood is required for their highly sensitive detection in early-stage disease (168, 182). Studies have identified exosome content derived from cancer patients as potential cancer biomarkers. One study reported elevated levels of GPC1 in exosomes derived from the serum of pancreatic ductal adenocarcinoma patients, compared to healthy donors. These $GPC1^{+}$ exosomes had a sensitivity and specificity of 100% for all stages of pancreatic cancer, demonstrating its potential as a liquid biopsy biomarker for early cancer detection (193). As mentioned earlier, GPC1 plays a role in the progression of EMT, which correlates with the mesenchymal phenotype often found in pancreatic tumours (163, 194). The unique features of exosomes make them a promising source of cancer biomarkers for early diagnosis and prognosis, monitoring metastatic progression and assessing treatment responses (191).

9. CONCLUSION

Functionally, cancer-derived exosomes carry EMT factors capable of promoting

metastasis, and facilitating therapy resistance and recurrence. The tumour microenvironment is an important contributor of altering exosomal intercellular communication, which often contributes to the pathogenesis of cancer. Although a general consensus of the definition of exosomes and its isolation methods have yet to be reached, it is evident that these extracellular vesicles are important mediators in a variety of cancer-related processes. Because of their specific EMT cargo, exosomes are predestined sources for liquid biopsy approaches which in the future will lead to the improvement of cancer monitoring, and thereby decrease cancer-related morbidity and mortality.

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Abbreviations: BM: basement membrane; CBD: common bile duct; cfDNA: cell-free DNA; CRC: colorectal cancer; CSC: cancer stem cell; CTC: circulating tumour cell; ctDNA: circulating tumour DNA; DOX:doxorubicin; ECM: extracellular matrix; EMT: epithelial-to-mesenchymal transition; ERK: extracellular signal-regulated kinase; ESCRT: endosomal sorting complex required for transport; EV: extracellular vesicle; HCC: hepatocellular carcinoma; HIF1α: hypoxia inducible factor 1 alpha; HSP70: heat shock protein 70; IHC: immunohistochemical; IL-17: interleukin-17; IL-6: interleukin-6; ISEV: international society of extracellular vesicles; lncRNA: long non-coding RNA; MAPK: mitogen activated protein kinase; MET: mesenchymal-to-epithelial transition; MHC: major histocompatibility complex; miRNA: microRNA; mRNA: messenger RNA; MVB: multivesicular body; NF-κB: nuclear factor kappa B; PI3K: phosphatidylinositol 3-kinase; TEM: transmission electron microscopy; TGF-β: transforming growth factor beta; TSG101: tumour susceptibility gene 101; UBC: urinary bladder cancer; ZO-1: zonula occludens 1; α-SMA: alpha-smooth muscle actin.

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