Exosomal integrins in tumor progression, treatment and clinical prediction (Review)

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Abstract. Integrins are a large family of cell adhesion molecules involved in tumor cell differentiation, migration, proliferation and neovascularization. Tumor cell-derived exosomes carry a large number of integrins, which are closely associated with tumor progression. As crucial mediators of intercellular communication, exosomal integrins have gained attention in the field of cancer biology. The present review examined the regulatory mechanisms of exosomal integrins in tumor cell proliferation, migration and invasion, and emphasized their notable roles in tumor initiation and progression. The potential of exosomal integrins as drug delivery systems in cancer treatment was explored. Additionally, the potential of exosomal integrins in clinical tumor prediction was considered, while summarizing their applications in diagnosis, prognosis assessment and treatment response prediction. Thus, the present review aimed to provide guidance and insights for future basic research and the clinical translation of exosomal integrins. The study of exosomal integrins is poised to offer new perspectives and methods for precise cancer treatment and clinical prediction.

Contents

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1. Introduction

Integrins are important cell surface adhesion receptors that bind to both extracellular matrix (ECM) ligands and cell surface ligands (1). As pivotal signaling molecules, integrins mediate cell migration and adhesion (2,3). Previous reports have shown that integrins are highly expressed in a variety of cancer types including lung cancer, hepatocellular carcinoma, pancreatic cancer and head and neck squamous cell carcinomas, and serve crucial roles in nearly every stage of cancer progression, including the initiation of primary tumor formation, subsequent growth and the metastatic cascade (4-8). Integrin-mediated sensing, stiffening and remodeling of the tumor stroma are key steps in supporting tumor cell invasion, acquiring cancer stem cell (CSC) characteristics and developing drug resistance during cancer progression (9,10). In addition, integrins have emerged as attractive targets for both predicting cancer prognosis and devising therapeutic strategies (11). Several integrin inhibitors, which disrupt the interaction between integrins and their respective ligands, hold notable therapeutic promise (12).

Exosomes are extracellular vesicles (EVs) secreted by cells, which serve a crucial role in regulating intercellular transport. Specifically, exosomes influence the state of both adjacent and distant cells by delivering nucleic acids, proteins and lipids (13). Tumor-derived exosomes (TDEs) are particularly important in angiogenesis, immune system regulation and the remodeling of surrounding tissues, thereby supporting tumor progression and metastasis to organs (14). As intercellular messengers, exosomes reflect the physiological state of various tumor cells, thus serving as biomarkers for clinical diagnosis and evaluation (15). Integrins have been identified as important components of exosomes. Accumulating evidence indicates that exosomal integrins assist in exosome homing, signal transduction and the phenotypic transformation of recipient cells (16-18). Research on exosomes

and integrins has been steadily advancing. However, there remains a lack of comprehensive reviews summarizing the role of exosomal integrins in tumor development. Exploring the role of exosomal integrins in tumors will enhance the understanding of tumor pathogenesis and help to identify new diagnostic and therapeutic strategies (10). In the present review, the roles of exosomal integrins in tumor migration, tumorigenesis [including epithelial-mesenchymal transition (EMT)], angiogenesis, formation of the pre-metastatic niche (PMN) and the development of tumor drug resistance were summarized. Additionally, the potential of exosomal integrins in tumor prediction and treatment were examined, which highlighted their prospects in improving the efficiency of these aspects.

2. Exosome biogenesis, composition and function

Cells release various types of EVs, including exosomes, microvesicles and apoptotic bodies. Exosomes are the smallest entities among EVs, with a diameter ranging 40-160 nm (average, ~100 nm), are secreted by almost all cell types and have been found in all biological fluids (19). The contents of exosomes vary and reflect the composition of the donor cells (20,21). Exosomes contain adhesion molecules, tetraspanins, major histocompatibility complex molecules, transmembrane proteins, cytosolic (such as heat shock proteins, cytoskeletal proteins and transporters) and nuclear proteins, lipids, nucleic acids (including DNA, mRNA and non-coding RNAs), amino acids and metabolites (such as bioactive lipids, glycosidases and nucleotides) (Fig. 1) (22,23).

The formation and secretion of exosomes is a complex process, which is typically divided into two pathways: The endosomal sorting complex required for transport (ESCRT)-dependent pathway and the ESCRT-independent pathway (24). The ESCRT system is a molecular machine that completes endosomal membrane invagination to form multivesicular bodies (MVBs) in eukaryotic cells. The ESCRT-dependent pathway involves a series of complexes such as ESCRT-0, -I, -II and -III (25). ESCRT-0 is responsible for the recognition of mono-ubiquitinated proteins. Then, ESCRT-I and -II bind to ESCRT-0 to induce endosomal membrane budding. Finally, ESCRT-III aggregates at the bud neck to pinch off the membrane, thereby releasing intraluminal vesicles (ILVs) into the lumen to form the MVBs (24,26). This process includes three steps: i) Extracellular substances, such as lipids, proteins and metabolites, enter cells through the initial plasma membrane invagination to form early-sorting endosomes (ESEs); ii) ESEs mature into late-sorting endosomes and then form MVBs. MVBs contain ILVs regulated by the ESCRT complex, which are the precursors to exosomes; and iii) MVBs either fuse with the plasma membrane to release exosomes or merge with autophagosomes and are degraded in the lysosomes (Fig. 1) (23,27). Studies have shown that, after the components of the ESCRT complex are depleted, exosome production is not completely blocked and a small number of exosomes are still formed (28,29). This suggests that exosomes can form in a manner independent of the ESCRT pathway. In the ESCRT-independent mechanism, the release of exosomes is dependent on sphingomyelinase. This involves the hydrolysis process of sphingomyelins into ceramides via neutral sphingomyelinase, which promotes inward budding of vesicles (30).

Exosomes carry a variety of bioactive molecules that have key roles in physiological and pathological processes through precise and dynamic intercellular communication. These processes include immune responses and infections, metabolic diseases, cardiovascular diseases, neurodegenerative diseases and cancer (31,32). Particularly, exosomes have gained attention in the field of cancer biology. Exosomes alter the fate of both the recipient and exosome-releasing cells through autocrine and paracrine signaling pathways (33). TDEs affect tumor growth, metastasis and drug resistance by interacting with tumor and stromal cells (34). Tumor stromal cells are primarily cancer-associated fibroblasts (CAFs) and immune cells (35). Exosomes have been recognized as crucial mediators in regulating the extracellular communication and metabolic reprogramming between CAFs and cancer cells (36,37). Furthermore, TDEs remodel the distant microenvironment at metastatic sites via blood and lymphatic circulation (38). Accumulating evidence indicates that TDEs are associated with angiogenesis and ECM remodeling in the tumor microenvironment (TME) (39-41).

3. Structure and function of integrin and exosomal integrin

Integrins are cell adhesion molecules that serve as membrane protein complexes, linking the ECM to the cytoskeleton, and regulate various cell behaviors, such as adhesion, proliferation and apoptosis, by triggering signal transduction through their extracellular connections to the cytoskeleton. This regulation provides the impetus and direction for cell migration and invasion (42,43). Integrins are ubiquitous in mammals, chickens, zebrafish and lower eukaryotes (44). In mammals, integrins are composed of α and β subunits bound by non-covalent bonds. To date, 18 α subunits and 8 β subunits have been identified, forming 24 αβ heterodimeric integrins with different properties and tissue distributions based on the various combinations. Both the α and β subunits are type I transmembrane proteins, each containing ectodomains, transmembrane domains and cytoplasmic domains (45,46). The integrin ectodomains are responsible for interacting with integrin ligands of the ECM (47). Due to the different characteristics of the integrin-ligand combinations, integrins can be clustered into four classes: Arginine-glycine-aspartate (RGD)-binding integrins (including αvβ1, αvβ3, αvβ5, αvβ6, αvβ8, α5β1, α8β1 and αIIbβ3) (48), leukocyte cell-adhesion integrins (including α4β1, α9β1, αLβ2, αMβ2, αXβ2, αDβ2, α4β7 and αEβ7) (49), collagen-binding integrins (which recognize the GFOGER binding site, including α1β1, α2β1, α10β1 and α11β1) (50) and laminin-binding integrins (including α3β1, α6β1, α6β4 and α7β1) (Fig. 2) (51,52).

Integrin-mediated transmembrane signals can exert their role through conformational transition. These transitions strictly regulate the transformation of integrins from a low-affinity state to a high-affinity state (53). Proteins such as talin, kindlin and tetraspanin trigger integrins to adopt an active open conformation, while integrin cytoplasmic domain-associated protein-1 and SHARPIN stabilize and inactivate integrins (54). Integrin-mediated transmembrane signals are bidirectional. During 'outside-in' signaling,

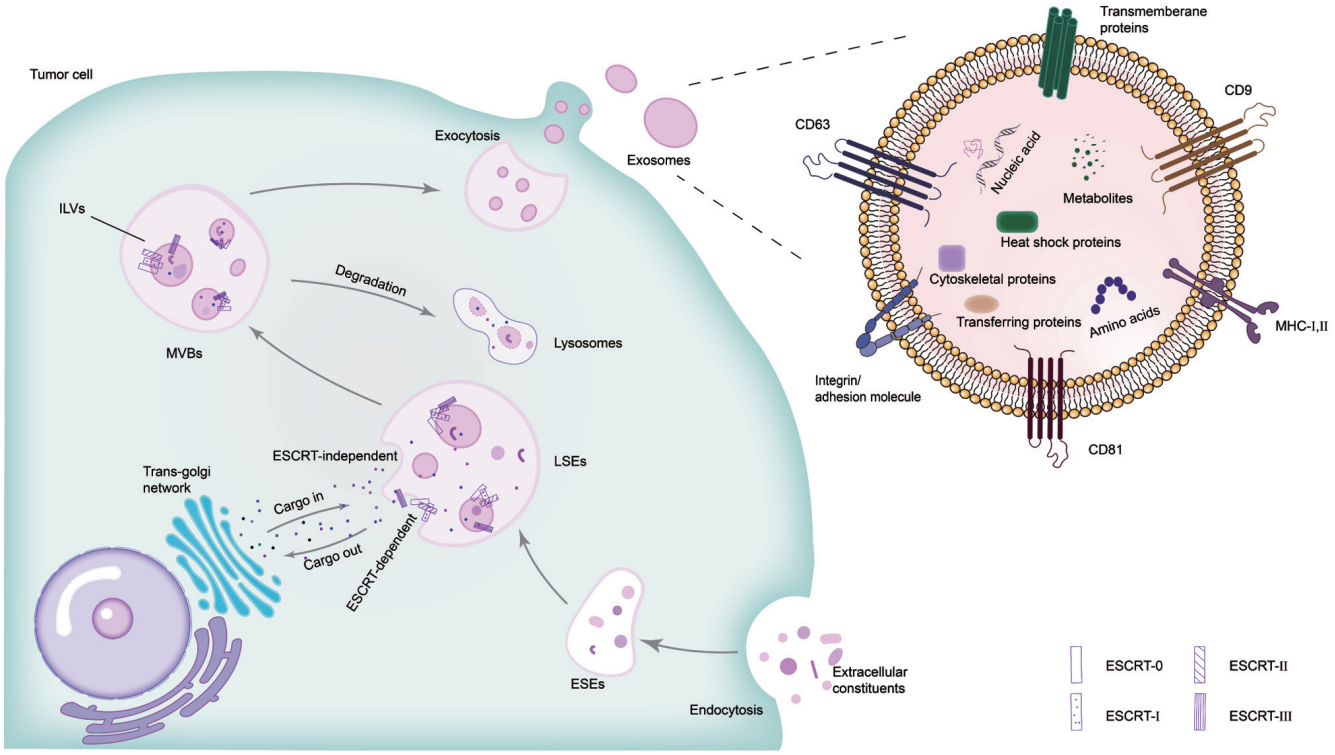

Figure 1. Exosome biogenesis and composition. The production of exosomes begins with the formation of ESEs through plasma membrane invagination of extracellular constituents. ESEs subsequently mature into LSEs. The second invagination of LSEs forms ILVs via the ESCRT-dependent and ESCRT-independent pathways, incorporating cytoplasmic components into the newly formed ILVs. LSEs then produce MVBs containing multiple ILVs, the precursors to exosomes. Finally, MVBs either fuse with the plasma membrane to release exosomes or are degraded within lysosomes. Exosomes have a lipid bilayer structure with adhesion molecules and tetraspanins, MHC molecules and transmembrane proteins attached to their surface. Exosomes are also enriched with various proteins (such as heat shock proteins, cytoskeletal proteins and transporters), lipids, nucleic acids, amino acids and metabolites. ESEs, early-sorting endosomes; LSEs, late-sorting endosomes; ILVs, intraluminal vesicles; ESCRT, endosomal sorting complex required for transport; MVBs, multivesicular bodies; MHC, major histocompatibility complex.

integrins exposed to exosomes recognize and bind to their specific ligands on the surface of the target cells, generating intracellular signals. These signals control a series of physiological functions, including regulating cell polarity, altering the cytoskeleton structure, as well as cell survival and proliferation (55). The affinity of cells to extracellular ligands is regulated by 'inside-out' signaling. As this affinity increases, the interaction between integrins and the ECM becomes strong enough to induce cells to migrate and the ECM to remodel (Fig. 2) (56).

Integrins are expressed on the surface of tumor cells. The expression of integrins αvβ3, αvβ5, α5β1, α6β4, α4β1 and αvβ6 on tumor cells may have an important role in the progression of lung, breast, prostate, pancreatic and colorectal cancers (4,57). The abnormal expression of integrins is involved in almost every stage of cancer development, from the formation of primary tumors to the establishment of metastatic niches (9). During tumor cell survival and proliferation, integrin β1 promotes the survival of cancer cells by activating different cell signaling proteins and enhances cell proliferation by phosphorylating focal adhesion kinase (FAK) (58). Additionally, integrin αvβ3 enhances the migration and invasion of non-small cell lung cancer (NSCLC) cells by triggering the FAK signaling pathway (59). A specific integrin subtype, αvβ6, is expressed in some types of malignant tumors, such as prostate, breast, colorectal and lung cancers, but not in normal epithelial cells or benign tumors (60). Furthermore, αvβ6 confers an invasive/metastatic phenotype to early colorectal cancer cells, promoting tumor metastasis and reducing patient survival (61). Integrins regulate the adhesion of tumor cells and the expression level of integrin is proportional to the adhesion (62). In the early stage of tumorigenesis, the expression of integrins is reduced, which is conducive to the growth and spread of tumors. Then, the tumor cells enter the blood circulation (63). Thereafter, the expression of integrin is increased, which is beneficial to the adhesion of tumor cells to the vascular endothelium. Specifically, integrins are the main adhesion molecule in the angiogenesis stage of tumorigenesis. Furthermore, integrins are expressed in the cavity and luminal surface of vascular endothelial cells, mediating endothelial cell migration and capillary lumen formation (64).

Exosomal integrins are a subset of integrins. Thus, cell membrane and exosomal integrins share similarities in that both are involved in cell-to-cell or cell-to-exosome communication. Currently, the understanding of the communication mechanism of exosomal integrins is still in its infancy. However, integrin function is considered to be regulated by talin in exosomes, as in other cellular systems (54). In addition to certain similarities in the communication mechanism, there are notable differences in the location and function of cell membrane and exosomal integrins (64,65). As aforementioned, cell membrane integrins mediate cell-ECM adhesion. In the occurrence, development and metastasis of tumors, this adhesion directly affects the physiological processes of

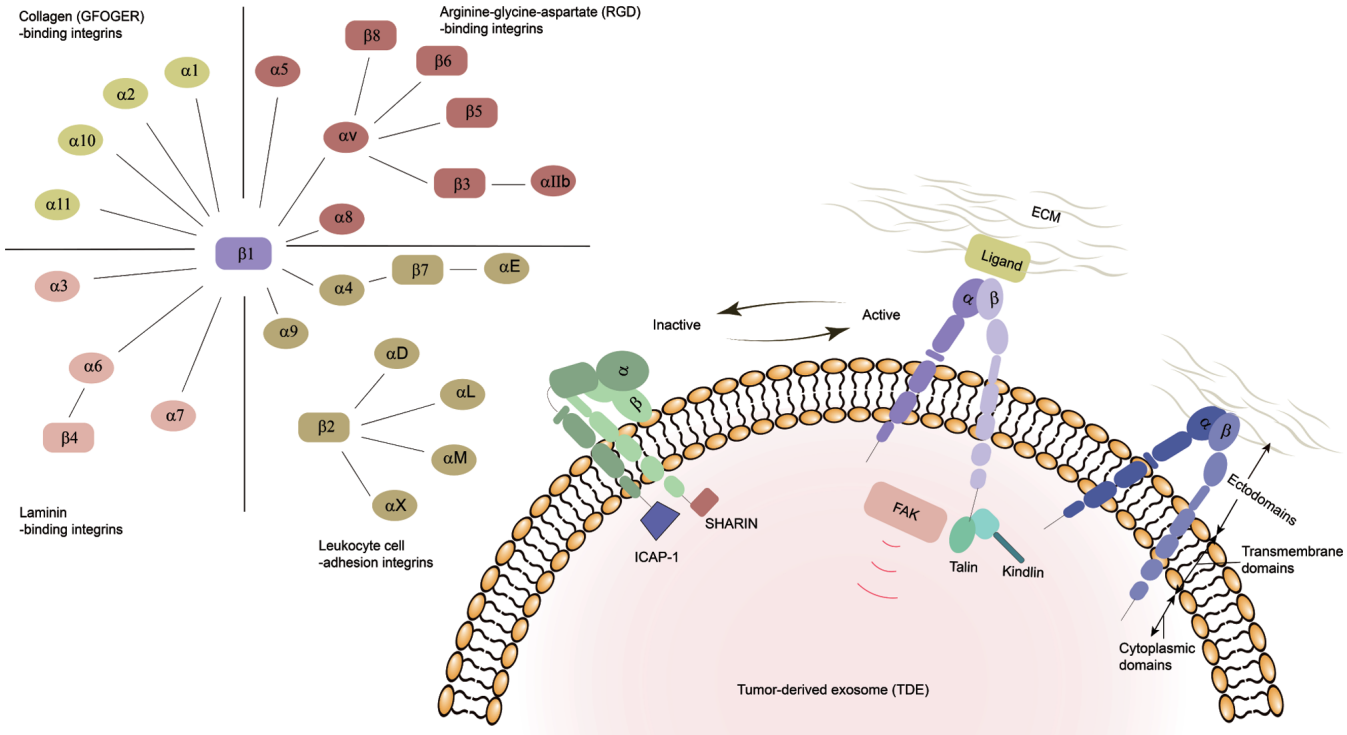

Figure 2. Structure and classification of tumor-derived exosomal integrins. A total of 18 α subunits and 8 β subunits have been identified, which form 24 αβ heterodimeric integrins. Each α or β subunit contains an ectodomain, a transmembrane domain and a cytoplasmic domain. Inactive integrins are inhibited by SHARPIN and ICAP-1, and the binding of talin and kindlin triggers the active state of the integrin conformation. FAK can receive signals from integrins and activate intracellular signaling pathways, thereby promoting tumorigenesis and metastasis. According to the different characteristics of integrin-ligand combinations, integrins can be divided into four categories: RGD-binding integrins, leukocyte cell-adhesion integrins, collagen-binding integrins (via the GFOGER motif) and laminin-binding integrins. ICAP-1, integrin cytoplasmic domain-associated protein-1; FAK, focal adhesion kinase; RGD, arginine-glycine-aspartate; ECM, extracellular matrix.

tumor cell migration, proliferation and survival. By contrast, exosomal integrins are embedded in the membrane of exosomes, which are small EVs that promote intercellular communication. These exosomal integrins serve a crucial role in targeting specific cells or tissues to achieve long-term signal transduction in processes such as cancer metastasis and immune regulation (16,65). Exosomal integrins also serve an important role in directing the tissue distribution of exosomes, thereby supporting long-range cellular interactions (16,66). In addition, exosomal integrins are involved in multiple steps of tumor formation as they enhance cell adhesion and migration, participate in PMN formation, and they modulate angiogenesis (54). It has been reported that exosomal integrins also confer drug resistance to tumors and impair drug efficacy (67).

4. Exosomal integrins in tumorigenesis and metastasis

Exosomal integrins in the TME. The TME is comprised of primary tumor lesions and their surrounding cellular and non-cellular components (68). Key features of the TME include low oxygen and nutritional levels, as well as an acidic environment. Cancer cells become increasingly invasive in such conditions, affecting tumor development and metastasis (69). TDEs, carrying molecules such as oncoproteins, lipids and various types of RNA (such as microRNA, mRNA and long non-coding RNA), induce changes in the TME phenotype (70). The cellular components of the TME include stromal cells (such as CAFs, mesenchymal stromal cells and pericytes) and immune cells [such as T and B lymphocytes, natural killer cells and tumor-associated macrophages (TAMs)] (71,72). CAFs serve a notable role in altering tumor mechanisms and are considered the most effective cells for the deposition and remodeling of the TME (73). TDEs induce the differentiation of fibroblasts (36). Integrin β4-overexpressing triple-negative breast cancer cells transfer integrin β4 protein to CAFs via exosomes, promoting cancer progression (74). In the lung metastasis niche of hepatocellular carcinoma (HCC), highly metastatic HCC cells secrete exosomal microRNA (miR)-1247-3p, activating the β1-integrin-NF-κB signaling pathway and transforming fibroblasts into CAF (75). In addition, macrophages are abundant in the TME, including both M1 and M2 polarized macrophages. TAMs are considered to promote tumor invasion (76,77). Exosomal integrin αvβ3 secreted by M2-like macrophages triggers the FAK signaling pathways in recipient cells and confers migration and invasion capabilities to NSCLC cells (59). The non-cellular components of the TME mainly include the ECM, including collagen and fibronectin, in which the ECM provides a biological scaffold for mechanical support (77). Integrin signal transduction drives intracellular signaling pathways through the interaction between cells and the ECM. Integrins are critical for cell anchorage to the ECM. Fibronectin matrix assembly is an integrin-dependent process. Integrin α5β1 induce initial fibronectin fibrillogenesis by transmitting cytoskeleton-generated tension to extracellular fibronectin molecules (78). Integrins α1β1, α2β1, α10β1 and α11β1 can bind to collagen (79). In the

basement membrane, α3β1, α6β1 and α6β4 integrins promote epithelial cell adhesion by recognizing the COOH-terminal globular domain of the laminin α subunit (80). Integrin αvβ3 and VEGF have synergistic signaling outputs during endothelial cell activation and angiogenesis, induced by the interaction of VEGF and ECM molecules (81). Based on the essential role of integrins in cells adhesion to the ECM, it could be suggested that tumor exosomal integrins serve a notable role in the TME by facilitating adhesion to adjacent cells, exosomes and the ECM. Abnormal adhesion functions can lead to diseases, including cancer progression (82). In summary, integrins, including exosomal integrins, affect the TME by regulating cell signaling pathways and interactions with surrounding matrices (Fig. 3A).

Exosomal integrins in EMT. Epithelium-derived tumor cells undergo a complex process termed EMT (83) to enhance their ability to disseminate from the original site, metastasize and invade other sites (84,85). EMT is a cellular developmental biology procedure that occurs during embryogenesis (83). Several key proteins, including E-cadherin, vimentin and N-cadherin, are involved in the EMT process (86). During EMT, epithelial cells lose their polarity and acquire mesenchymal characteristics by downregulating E-cadherin and upregulating vimentin and N-cadherin (87). Consequently, epithelial cells become invasive and attain stem cell-like properties (88). When hijacked by cancer cells, this process endows normal epithelial cells with malignant characteristics. CSCs, which possess stemness characteristics, have the initial capability for tumor metastasis and colonization. In fact, most cells maintain this ability through EMT (89). TDEs stimulate an EMT program through autocrine and paracrine signals within the tumor ecosystem (90). It has been demonstrated that diverse signaling pathways such as TGF-β, WNT, Notch and growth factor receptor tyrosine kinases induce the occurrence of EMT (91).

It has been shown that integrins serve an important role in regulating EMT and cancer stemness (89). Notably, integrins and TGF-β effectively synergistically induce the aberrant expression of EMT transcription factors, such as zinc finger E-box-binding homeobox 1 and snail2 (92,93). In a previous study, exosomes loaded with integrin β-like 1 (ITGBL1) from primary colorectal cancer (CRC) cells can convert fibroblasts in distal organs into CAFs by activating the TNFα-induced protein 3-mediated NF-κB signaling pathway. In this study, ITGBL1 overexpression enhanced the secretion of IL-6 and IL-8 from fibroblasts or stellate cells, thereby promoting the stemness and EMT of CRC cells (94). Additionally, CAF-derived IL-32 binds to integrin β3, thereby activating intracellular p38 MAPK signaling in breast cancer cells. This signaling increases the expression of EMT markers (including fibronectin, N-cadherin and vimentin) and promotes tumor cell invasion (95). These factors drive tumor cells to undergo EMT by various signaling pathways such as TGF-β, PI3K/AKT, MAPK and NF-κB (Fig. 3B) (52,96).

Exosomal integrins in tumor immunity. Previous studies have shown that TDEs have a pivotal role in regulating the TME by inducing immune suppressor cells and enabling cancer cells to evade immune effector cells (90,97). The antitumor ability of the human immune system is inhibited by TDEs through inflammatory signaling pathways (71). Exosomes secreted by cancer and immune cells deliver protein cargo similar to that of the primary tumor cells to specific tissues of the homing niche and alter the gene expression and molecular structure of the homing niche. Integrins regulate the tissue-specific homing pattern of exosomes (16). TDEs initiate immunosuppressive mechanisms at metastatic niches by triggering immune suppressor cells such as myeloid-derived suppressor cells, regulatory T cells (Tregs), tumor-associated neutrophils and TAMs (98).

Integrins on tumor cells are involved in the suppression of antitumor immunity throughout various stages of tumor formation and metastasis (99,100). Interferon (IFN)-γ-producing immune cells, mediated by α4β7, are recruited to CRC tissues where they exert an effective antitumor immune response (101). Immunologic targeting of integrin β4 significantly inhibited local tumor growth and metastases in both 4T1 mammary tumors and SCC7 head and neck squamous carcinoma models (102). Integrin αvβ3 regulates IFN-induced PD-L1 expression. In a mouse model, silencing αvβ3 expression reduced IFN-induced STAT1 phosphorylation, decreased PD-L1 expression and inhibited tumor growth (103). In addition, overexpression of integrin α2 increased the phosphorylation level of STAT3 in tumor cells to initiate PD-L1 transcription and thus upregulate PD-L1 expression (104). Integrin also regulates the activation of transforming growth factor-β (TGF-β) in immune cells, which may be another mechanism of tumor immune escape. In mouse melanoma and breast cancer models, Tregs (which express integrin αvβ8) are the predominant cell type that activate TGF-β produced by cancer cells (105). The activated TGF-β then protects the tumor from T cell attack by binding to and releasing αvβ8 on tumor cells or latent immune cells, thereby preventing T cell penetration into the tumor (106). The innate nature of integrins from cells to exosomes has implications for tumor immunity. Based on the inherent nature of exosomal integrins derived from tumor cell integrins, it is reasonable to speculate that exosomal integrins have similar tumor immune capabilities as tumor cell integrins. Indeed, chronic inflammation is known to contribute to cancer metastasis (107). Thus, integrin-guided preferential distribution of TDEs determines which specific organs may encounter TDE-mediated initiation of inflammation (108). Exosomal integrins not only target ECM proteins in distant tissues but are also delivered to the target cells themselves where they activate Src kinase signaling, leading to induction of the proinflammatory S-100 gene (16). The S100 proteins S100A8 and S100A9 are important mediators of various processes during chronic inflammation. The S100A8/9 proteins stimulate infiltration of inflammatory lesions by activated myeloid cells and are involved in leukocyte adhesion and migration (109). A tumor-bearing mouse model demonstrated that S100A8/A9 proteins participate in the activation and accumulation of MDSC cells during the induction of cancer T cell tolerance (110). S100A8/A9 proteins activate the NF-κB pathway in a positive feedback manner and ensure that the protein expression levels of S100A8/A9 are sufficient to maintain the immunosuppressive function of MDSC in the inflammatory tumor microenvironment (111). Therefore, the role of exosomal integrins in tumor immunosuppression

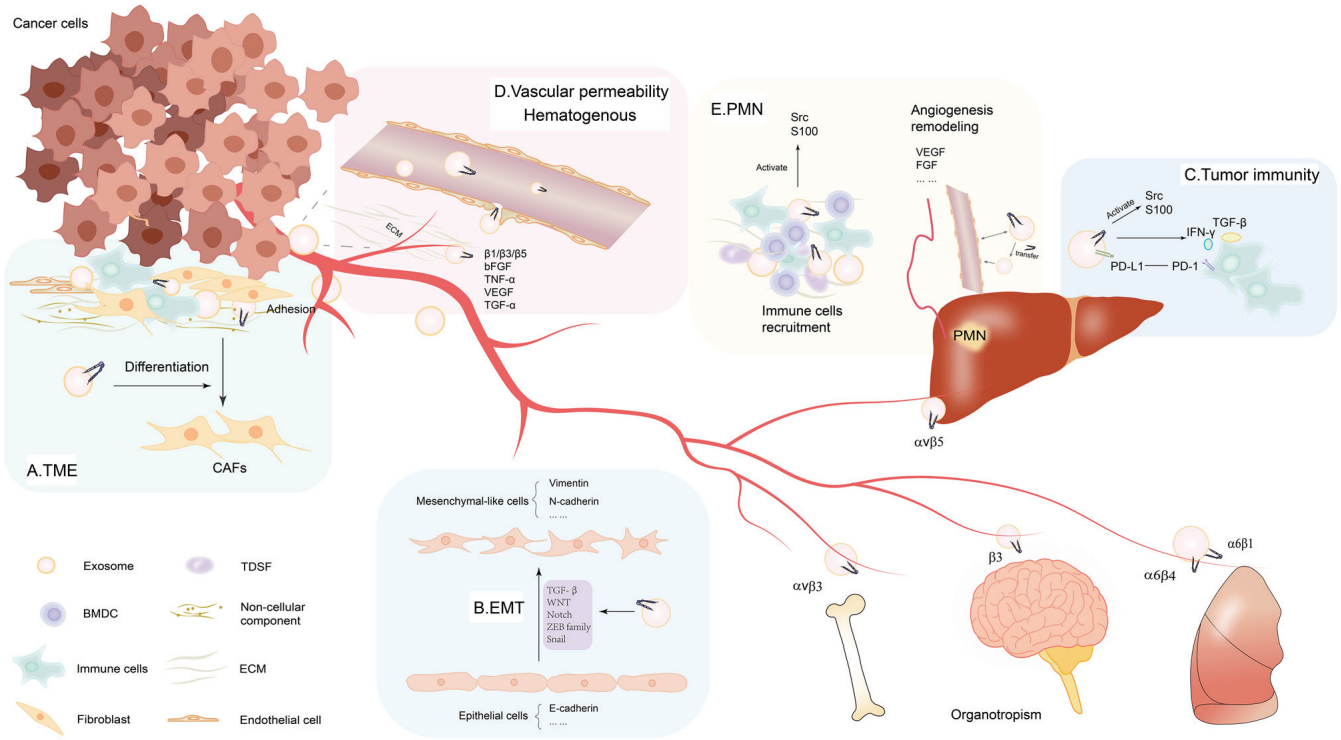

Figure 3. Role of exosomes/exosomal integrins in the TME, EMT, PMN formation, tumor immunity and metastasis. (A) Exosomes carrying proteins, nucleic acids and other substances in the TME induce the differentiation of fibroblasts and promote tumor growth. (B) Exosomal integrins promote epithelial cells to become mesenchymal-like cells through signaling pathways. (C) Exosomal integrins induce tumor immunity. (D) Increased vascular permeability in the TME leads to the entry of exosomes carrying integrins into the blood circulation, contributing to the distant metastasis of tumors. (E) Specific integrins carried by exosomes enable them to establish PMNs in the liver, bone, brain and lungs. In PMN formation, exosomes induce the mobilization and recruitment of multiple cell populations. Exosomes and VEGFs also induce vascular remodeling/formation. TME, tumor microenvironment; EMT, epithelial-mesenchymal transition; PMN, pre-metastatic niche; TDEs, tumor-derived exosomes; ECM, extracellular matrix; BMDC, bone-marrow derived dendritic cells.

underscores the potential of integrin-targeted immunotherapy (Fig. 3C).

Exosomal integrins in angiogenesis, vascular permeability and hematogenous. Tumor metastasis refers to the process by which tumor cells intravasate into blood vessels and lymphatic vessels from the primary tumor site. Tumor angiogenesis is a complex biological process involving several key steps, including local damage to the basement membrane in the tissue, endothelial cell migration activated by angiogenic factors and endothelial cell proliferation and stability. VEGF, fibroblast growth factor (FGF) and other angiogenic signals are key factors regulating the angiogenic process (112). Furthermore, exosomes derived from various human tumor cell lines or plasma are effective inducers of angiogenesis, especially under hypoxic conditions, by modulating endothelial cell properties to promote angiogenesis (113). Exosomes expressing tetraspanins can promote tumor growth by increasing angiogenesis. For instance, TDEs enriched with tetraspanin 8 and integrin α4 enhanced endothelial cell proliferation and angiogenesis in rat pancreatic cancer by upregulating angiogenesis-related genes through endothelial-exosomal interactions (114). With improved understanding of exosome heterogeneity, it is appealing to focus on the role of exosomal integrins in influencing endothelial metabolism and angiogenesis. The effect of exosomal integrins on the angiogenic potential of endothelial cells has also been demonstrated in prostate cancer (PrCa) progression. PrCa exosomes promote angiogenesis by transferring exosomal integrin αvβ6 to endothelial cells that do not typically express epithelial-specific integrin αvβ6. Exosomal integrin αvβ6 uptake is associated with an upregulation of the pro-angiogenic survivin levels and a downregulation of the angiogenic inhibitory phosphorylated STAT1 in endothelial cells (115). The increased expression of integrin αvβ3 during angiogenesis in lung, colon, pancreatic and breast cancer also suggests that integrins are involved in tumor angiogenesis (62).

In the TME, EMT endows endothelial cells and cancer cells with invasive capabilities, allowing cancer cells to traverse the matrix with the assistance of TAM-derived VEGFA. This leads to an abnormal increase in vascular permeability and the simultaneous intravasation of tumor cells (116). β1 integrins can affect vascular permeability, especially during inflammation, as the recruitment of circulating cells to inflamed tissues involves recognition of cell adhesion molecules (117). Specifically, integrin β1 can affect the ability of circulating cells to block, adhere and extravasate at sites of injury and vascular permeability (118). Integrin α4β1 serves a role in the homing of circulating progenitor cells to tumor neovascularization that expresses vascular cell adhesion protein 1 and cellular fibronectin (119). Additionally, integrin αvβ3 is required for angiogenesis induced by basic FGF or TNF-α, while αvβ5 is required for angiogenesis induced by VEGF, TGF-α or phorbol ester (120).

Hematogenous dissemination is often the primary mechanism of distant metastasis, leading to the implantation

of tumor cells into distant organs through extravasation, ultimately forming micro and macro tumor metastases (121). Although primary tumors can shed millions of cells into the blood vessels every day, a very small number of circulating tumor cells (CTCs) eventually reach distant organs (122). The permeability of blood vessels increases the possibility of tumor cells and TDEs entering the blood. Millions of exosomes are secreted by primary tumors into the blood vessels every day, and are then transferred to specific organs via the vascular pathway by exosomal integrins (16) (Fig. 3D).

Exosomal integrins in organotropism and the establishment of PMNs. The combined systemic effects of tumor-secreted factors and tumor-shed extracellular vesicles induces a receptive tissue microenvironment from a distance. The formation of the microenvironment is initiated with local changes such as the induction of vascular permeability, remodeling of stroma and extracellular matrix, followed by systemic effects on the immune system. These microenvironments are termed PMNs. The presence of a PMN means that metastasis to specific organs is not random but predictable (123). Clinical cases have revealed that metastatic organ patterns follow particular rules, with certain tumors preferentially metastasizing and colonizing specific organs. Breast and prostate cancers preferentially metastasize to bone (124). However, colorectal and pancreatic cancers preferentially colonize the liver and lung (125). The mechanisms directing tumor cells to specific distant organs have long puzzled researchers, and the precise mechanisms remain largely unknown. However, Hoshino *et al* (16) confirmed that the key reason lies in exosomal integrins. The role of exosomes and exosomal integrins in tumor growth and metastasis has been emphasized. Exosomal integrins can be localized to specific organs. After target cells at the metastatic site ingest these exosomes, the PMN is established by activating Src phosphorylation and pro-inflammatory S-100 expression.

Studies have shown that PMN formation is a chronological event that precedes the arrival and colonization of tumor cells, effectively initiating the target site of metastasis. Soluble molecules secreted by the primary tumor have a crucial role in the formation of the PMN, promoting metastasis and even determining organ-specific sites of the metastasis (126,127). Hoshino *et al* (16) injected FM1-43 dye-labeled exosome isolated from organotropic human breast and pancreatic cancer cell lines, which predominantly metastasize to the lungs, into naive animals. Tumor FM1-43-labeled exosomes were then detected in pre-metastatic cells by electron microscopy, suggesting that tumor exosome uptake occurs at future metastatic sites. Tumor-derived secreted factors (TDSFs) and soluble molecular components, including EVs, secreted by primary tumors induce the mobilization and recruitment of multiple cell populations to secondary organ sites (123). Primary TDEs can promote the formation of the TME at secondary sites and guide bone marrow-derived dendritic cells (BMDCs) to form a pre-metastatic microenvironment. For instance, bone marrow-derived hematopoietic progenitor cells expressing VEGFR1 are mobilized and recruited to the PMN of the lungs (128). TDEs promote the formation of the PMN by inducing vascular remodeling, preparing for the arrival of CTCs, promoting the development of inflammation and recruiting BMDC (129). Exosomes from metastatic melanoma increase the metastasis of primary tumors by educating bone marrow progenitor cells via upregulation of the mesenchymal to epithelial transition factor receptor. In addition, melanoma-derived exosomes promote vascular leakage at the pre-metastatic site and reprogram bone marrow progenitor cells to adopt pro-angiogenic phenotypes (130). Macrophage inhibitory factor in pancreatic cancer cell exosomes induces the release of TGF-β, which in turn promotes the production of fibronectin. The deposition of fibronectin promotes the colonization of bone marrow-derived macrophages and neutrophils in liver metastasis (131).

Through quantitative mass spectrometry and western blotting analysis, it has been demonstrated that integrin α6, combined with integrins β4 and β1, is abundantly present in lung-tropic exosomes (16). Conversely, integrins β5 and αv are present in liver-derived exosomes and integrin β3 is predominant in brain-derived exosomes. Infrared imaging showed that integrins β4 and β5 are responsible for the specific uptake of exosomes by the liver and lung, respectively (16,132). In another study, integrin αvβ6 was encapsulated in exosomes isolated from PC3 and RWPE PrCa cell lines and was effectively transferred from donor cells to αvβ6-negative recipient cells, colonizing on their surfaces (133). PrCa is prone to distant metastasis, with bone metastasis being particularly significant and a primary cause of death in patients with PrCa (134). Among various integrins, αvβ3 has gained notable attention for its role in promoting bone metastasis through multiple regulatory mechanisms (135). Extracellular or membrane ligands (such as small integrin-binding ligand N-linked glycoproteins, connective tissue growth factor, cellular chemokines and ion channel proteins) combine with or activate αvβ3 to mediate PrCa bone metastasis. Moreover, the FAK, PI3K, ERK and αvβ3/RUNX2/RANKL intercellular signaling pathway is stimulated by αVβ3 and has been reported to be related to PrCa metastasis (136). The circulating exosomal integrin β3 level is associated with the survival rate and intracranial control after whole-brain radiotherapy in patients with brain metastasis from lung cancer, supporting the suggestion that exosomal integrin β3 mediates the pattern of brain metastasis (137). Additionally, integrins α3 and β1 are more abundant in urinary exosomes from patients with metastatic PrCa compared with those from individuals with benign prostatic hyperplasia or non-metastatic PrCa (138). In conclusion, exosomal integrins can be identified as determinants of metastatic organotropism (Fig. 3E).

5. Exosomal integrins in tumor drug resistance

Exosomes have a notable influence on drug resistance, which is induced through a variety of mechanisms. During chemotherapy, cancer cells cannot remove exosomes containing unfavorable biomolecules. However, drug-resistant cancer cells can load chemotherapy drugs into exosomes and expel them from tumor cells directly (139,140). Another mechanism involves exosomes carrying a drug-resistant phenotype from drug-resistant cancer cells to drug-sensitive cancer cells (141). Additionally, exosomes can regulate the transfer of functional proteins and/or miRNAs, contributing to drug resistance (142). The contents of exosomes can also cause

Table I. Role of exosomes and integrins in tumor drug resistance.

First author, year	Exosome/integrin	Drug	Cancer	Function	(Refs.)
Corcoran *et al*, 2012	Exosome	Docetaxel	Prostate	Cells become drug resistant by up taking exosomes derived from drug-resistant cells	(182)
Xiao *et al*, 2014	Exosome	Cisplatin	Lung	miRNAs and mRNAs are exchanged by exosomes	(183)
Safaei *et al*, 2005	Exosome	Cisplatin	Ovarian	Drug efflux	(145)
Martinez *et al*, 2017	Exosome	Trastuzumab	$HER2^+$ breast	Immune evasion	(144)
Luo *et al*, 2018	Integrin αvβ3	Cisplatin	Breast	Inactivates the integrin αvβ3/FAK/PI3K/AKT pathway	(155)
Yu *et al*, 2021	Integrin αv	Temozolomide	Glioblastoma	ECM proteins confer CAM-DR through integrin αv	(176)
Hazlehurst *et al*, 2007	Integrin β1	Imatinib	Leukemia	Integrin β1-mediated adhesion	(184)

CAM-DR, cell adhesion-mediated drug resistance; ECM, extracellular matrix; FAK, focal adhesion kinase; miRNA, microRNA.

immunosuppression, leading to drug resistance in HER2+ breast cancer (143,144). Therefore, the roles of exosomes and integrins in drug resistance across different cancer types are reviewed here (Table I).

In drug-resistant human ovarian cancer, cisplatin (CDDP) is encapsulated in exosomes and released within the secretory pathway (145). The ATP-binding cassette (ABC) transporter superfamily, including ABCB1 [also known as P-glycoprotein (P-gp)], ABCC1 (also known as multidrug resistance protein 1) and ABCG2 (also known as breast cancer resistance protein), function as multidrug resistance efflux transporters. These transporters, located on the exosomal membrane, actively pump anticancer drugs out of cells, resulting in chemoresistance (146). P-gp, a key anticancer pump transporter, plays a notable role in drug resistance by retaining drug concentrations in tumor cells below the therapeutic levels after chemotherapy, rendering the treatment ineffective. This process may be mediated by exosomal integrin, which facilitate the intercellular transfer of P-gp from multidrug-resistant cells to drug-sensitive cells (147). Suppression of αvβ6 downregulated the levels of MDR1 gene mRNA and P-gp. In particular, β6 shRNA-mediated silencing of the αvβ6 gene markedly decreased drug efflux ability (148). In addition, the delivery mechanisms of exosomes carrying nucleic acids and proteins are closely related to tumor drug resistance. For instance, the content of exosomes from paclitaxel-resistant ovarian cancer cells, namely miR-1246, induces chemoresistance by inhibiting 3'UTR caveolin-1, which directly suppresses the increase of p-gp expression (149).

The effect of adhesion crosstalk between tumor cells and stromal cells on the development of tumor drug resistance has been studied in detail. Cancer cells adhere to the ECM or stromal cells and can avoid being killed by radiotherapy and chemotherapy, which is known as cell adhesion-mediated drug resistance (CAM-DR) (150). CAM-DR is determined by the integrin-ECM interaction. For instance, integrin β1 is considered essential for radiotherapy resistance in human head and neck cancer (151) and mediates cell adhesion to the ECM. The role of integrins in tumor drug resistance is primarily related to integrin-mediated signaling pathways (152). For instance, the integrin β1/Src/AKT signaling pathway serves a key role in acquiring resistance to epidermal growth factor receptor-targeted anticancer drugs, such as gefitinib and erlotinib, in lung cancer (153). In human glioblastoma, resistance to temozolomide is mainly due to integrin α5β1 downregulating the p53 pathway (154). In breast cancer cells, integrin αvβ3 and its mediated FAK/PI3K/AKT signaling pathway are involved in CDDP resistance (155). Additionally, integrin α6 serves a key role in cancer drug resistance by regulating the MAPK/ERK and PI3K/AKT signaling pathways (156). Finally, integrin β4 and vinculin in exosomes are associated with taxane resistance in PrCa (157).

6. Exosomal integrins in the treatment and diagnosis of tumors

Exosomes are natural nano-biological delivery systems with properties of stability, biocompatibility (endogenous origin) and the ability to cross various physiological barriers. These features make exosomes promising carriers for delivering several drugs and biomacromolecules for cancer therapy (158). For instance, loading exosomes with paclitaxel has indicated the potential for delivering multiple chemotherapeutics to treat drug-resistant cancer (159). In cancer treatment, exosomes protect the integrity of nucleic acids and shield proteins from various enzymes and the immune system, making them excellent carriers for delivering these macromolecules in therapy. Kobayashi *et al* (160) demonstrated that loading miR-199a-3p into exosomes inhibited c-Met expression and reduced ovarian cancer cell proliferation, invasiveness and dissemination. Similarly, exosomes loaded with signal regulatory protein α (SIRPα) block the CD47 receptor on tumor cells more effectively when compared with ferritin-SIRPα, indicating that these exosomes have antitumor applications (161). In addition, since TDEs carry specific integrins on their surface,

Table II. Application of exosome/integrins in tumor diagnosis and treatment.

A, Diagnosis/prognosis

Exosomes/integrins	Cargo	Target	Function	(Refs.) or clinical trial no.
Exosomal integrin β4	-	Prostate cancer associated with taxane resistance	Biomarker/diagnosis	(157)
Exosomal integrin α2β1	-	Non-cancerous lung fibroblasts or epithelial	Biomarker of lung metastasis	(16)
Integrin αvβ6	-	Epithelial cancer cells	Biomarker of cancer	(171)
Integrins αv, α6 and β1	-	Epithelial cancer cells	Tumor stage	(169)
Integrin β3	-	Lung cancer	Brain metastasis	(137)

B, Treatment

Exosomes/integrins	Cargo	Target	Function	(Refs.) or clinical trial no.
Exosome	Paclitaxel	MDR cancer	Inhibits tumor growth	(159)
Exosome	miR-199a-3p	Ovarian cancer	Inhibits the proliferation, invasiveness and dissemination of tumors	(160)
Exosome	SIRPα	HT29 human colon adenocarcinoma cells	Inhibits tumor growth	(161)
Exosome	Doxorubicin	Osteosarcoma *in vitro*	Antitumor	(185)
Exosome	Curcumin	Colon tumors	Mediated by changes in signal transduction to inhibit tumor growth	NCT01294072
Exosomal integrin αv	Doxorubicin	Human breast cancer cells *in vitro*	A total of three times the uptake efficiency of unmodified exosomes	(186)
Exosomal integrin αvβ3	Doxorubicin-RGD4C conjugate	Mouse MDA-MB-435 breast cancer model	Inhibits tumor growth and lung metastasis, low toxicity to the liver and heart	(187)
Exosomal integrin αvβ3	A15 binds to integrin αvβ3 in an RGD-dependent manner	Tumors with upregulated integrin αvβ3 expression such as melanoma, glioma and breast cancer	Targets specific organs to improve treatment efficiency	(188-190)

MDR, multidrug resistance; miR, microRNA; RGD, Arg-Gly-Asp; SIRPα, signal regulatory protein α.

they ensure targeted delivery to specific organs and tissues. Exosome targeting was also accomplished by genetic modification of exosome donor cells (162). This characteristic enhances the accuracy and efficiency of delivering therapeutic contents through exosomes and exosomal integrins compared with other biological carriers (163). However, to meet the demands of large-scale clinical applications, the loading capacity and methods for exosomes require optimization.

The diagnosis of cancer is often invasive. However, non-invasive diagnostic methods in clinical oncology have emerged as feasible alternatives with the study of exosomes (164,165). Exosomes, which represent their source cells, contain biological information and are steadily secreted into body fluids, making them ideal specimens for liquid biopsy. More specifically, cancer biomarkers can be determined according to the characteristics of TDE contents (such as the proteins and nucleic acids) in blood, ascites or urine, as these exosomes contain information related to cancer progression (166). A study has shown that integrin β4 and vinculin levels in exosomes isolated from PC3 cells can serve as effective biomarkers for diagnosing PrCa associated with

taxane resistance (157). The presence of integrin α2β1 in exosomes from tumor metastatic cells, but not in exosomes from non-cancerous WI-38 lung fibroblasts or epithelial MCF10A cells, indicates that this integrin can be regarded as a biomarker of metastasis (16).

Integrins have are promising, yet challenging, targets for the treatment of cancer. The specific expression of integrins in TDEs allows them to be used for disease monitoring, predicting patient survival and potentially distinguishing between cancer types and stages (167-169). For instance, integrin αvβ6, which is not expressed in normal adult epithelial cells but is present in cancer cells, can be utilized for the diagnosis and treatment of certain cancers such as ovarian, pancreatic, esophageal, bile duct, oral and cervical cancers (170). In mouse models, heavy lead peptides combined with αvβ6 have been used for non-invasive imaging, highlighting the potential of αvβ6 as a promising biomarker (171). Additionally, a patent states that the monoclonal antibody, 10D5, which specifically binds to β6, can be used to treat cancer (172). Invasive diagnostic techniques for multiple brain metastasis are often impractical in clinical settings, making it attractive to evaluate circulating EVs and related integrins as biomarkers. Experts isolated and quantified exosomal integrins of 75 patients with lung cancer with brain metastasis and analyzed the association of exosomal integrins with clinical factors, survival and intracranial or extracranial failure. Accordingly, it was proposed that integrin β3 may serve as a potential biomarker for the development of brain metastasis (137). Furthermore, the differential expression of exosomal integrins α6, αv and β1 is associated with the tumor stage of various epithelial cancers such as colon, lung, ovarian and prostate cancers (169).

Integrins are cell adhesion and signaling proteins present on the surface of various cell subsets, making them potential therapeutic targets. Numerous integrins involved in tumor progression have been studied as attractive therapeutic targets for cancer therapy (173,174). A study has shown that integrin antagonists, which currently include monoclonal antibodies, RGD peptide analogues and non-RGD antagonists, inhibit tumor growth by affecting tumor cells and tumor-associated host cells. For instance, integrin αvβ3 and αvβ5 inhibitors, such as cilengitide, have demonstrated this capability (132). Cilengitide can reduce the expression levels of integrin genes and inhibit the proliferation of tumor cells (175). In addition, cilengitide can activate αvβ3 and αvβ5 integrins of the FAK/Paxillin/AKT signaling pathway to combat chemotherapy resistance in glioblastoma (176). At present and to the best of our knowledge, there are seven drugs targeting integrins on the market: Abciximab, eptifibatide, tirofiban, natalizumab, vidolizumab, lifitegrast and carotegrast. However, drugs specifically targeting exosomal integrins have not yet been officially introduced to the market (52). The application of exosomes and integrins in cancer treatment and diagnosis is summarized in Table II.

7. Challenges and prospectives

The effectiveness of bodily fluid biopsy relies on advanced techniques for the isolation and characterization of exosomal integrins. Despite significant efforts in developing liquid biopsy methods and tumor biomarkers in oncology, only a few have progressed to the clinical stage. This is because clinical studies using liquid biopsy are often reliant on integrin content and heterogeneity, thereby rendering them more expensive and time-consuming compared with other common clinical testing techniques (177). To promote exosomal integrins as biomarkers to a broader population, more portable, efficient and accurate characterization techniques are needed (178). Standardization in the selection, separation, characterization, storage, management and quality control of exosomal integrins is crucial for their clinical application in tumor diagnosis and treatment. Most existing studies use tumor cell integrins as markers, but these are often affected by the complexity of tumors. Using specific integrins from TDEs in the humoral circulation as markers could reduce this interference.

Over the past 30 years, research on exosomal integrins as therapeutic targets has gained significant attention. However, most drugs have failed in phase III clinical trials, highlighting the challenges in translating experimental findings into clinical therapies (179). The pharmacodynamics and complex physiology of integrins contribute to the ongoing problems of toxicity and poor efficacy in drugs that have reached the market (180). Current treatment strategies mainly focus on interfering with integrin-ligand interactions. However, the class-specific nature of integrin-targeted therapy presents another challenge. Since the same integrin subunit can form different integrin heterodimers, the accuracy of targeted therapies is affected. Additionally, other molecules can interfere with targeted drugs. For instance, abciximab binds to both glycoprotein IIb/IIIa and integrin αvβ3 with a similar affinity, suggesting it may act as an antagonist of both GPIIb/IIIa and αvβ3 (181). Such complexities complicate the use of preclinical experimental data in developing effective therapies.

The heterodimeric structure of integrins enables them to specifically recognize amino-acid motifs. The binding of ligands to integrins can affect the allosteric states of integrins, thereby altering the movement of EVs. This suggests that exosomal integrins may act as sensors of the molecular environment. To effectively utilize exosomal integrins in cancer therapy, it is essential to fully understand their mechanisms of action in tumor development. Additionally, combining targeted drugs that act on ligands and integrins or their downstream effectors may offer a promising approach. This direction could lead to the development of new therapeutic strategies.

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Authors' contributions

RX and XZ made significant contributions to the conception and design of the manuscript. YS, LS, and SW were responsible for the acquisition, analysis and interpretation of data. RX and YS undertook the editing, drafting and writing of the manuscript. Data authentication is not applicable. All authors have read and approved the final version of the manuscript.

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Competing interests

The authors declare that they have no competing interests.

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