Cell Communication and Signaling

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Targeting Endocytosis and Cell Communications in the Tumor Immune Microenvironment

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Abstract

The existence of multiple endocytic pathways is well known, and their exact biological effects in tumors have been intensively investigated. Endocytosis can affect the connection between tumor cells and determine the fate of tumor cells. Many relationships between endocytosis and tumor cells have been elucidated, but the mechanism of endocytosis between different types of cells in tumors needs to be explored in greater depth. Endocytic receptors sense the environment and are induced by specific ligands to trigger communication between tumor and immune cells. Crosstalk in the tumor microenvironment can occur through direct contact between cell adhesion molecules or indirectly through exosomes. So a better understanding of the endocytic pathways that control cell adhesion molecules and function is expected to lead to new candidates for cancer treatment. In additional, tumor-derived exosomes may changes immune cell function, which may be a key role for tumors to evade immune detection and response. The overall understanding of exosomes through endocytosis is also expected to bring new candidates for therapeutic regulation of tumor immune microenvironment. In this case, endocytic pathways coordinate cell adhesion molecules and exosomes and can be used as targets in the tumor immune microenvironment for cancer treatment.

Keywords: Endocytosis, Tumor immune microenvironment, Adhesion molecules, Exosome

Background

Endocytosis refers to the formation of 60–120 nm vesicles through invagination of the plasma membrane, which wraps and imports foreign substances into cells to regulate the internalization of substances (liquid and extracellular components, such as proteins, lipids, metabolites, small molecules and ions), signal transduction and composition [1–3]. The endocytic pathway integrates various signals to promote the development of cells. Receptor-mediated signal transduction can be regulated by endosome sorting, which effectively isolates the receptor from cytoplasmic effectors and promotes proteolysis. Receptor-related processes are more closely related to phosphorylation [4] and ubiquitination levels [5].

The well-known effects of endocytosis is necessary for a diverse range of morphogenetic and dynamic tissue events. Endocytosis can cause changes in tissue morphology through various processes, such as signal transduction and effects on the cytoskeleton [6]. Similarly, asymmetric division caused by endocytic transport is an important target for manipulating stem cells that lead to tumor recurrence [7]. In addition, endocytosis and different types of cells intertwine to play a decisive role in the tumor microenvironment (TME). The crosstalk in the tumor microenvironment can occur directly through cell-to-cell contact between cell adhesion molecules or indirectly through extracellular vesicles. Immune cells, including specialized antigen-presenting cells and natural killer cells, rely on endocytosis to quickly gather receptors

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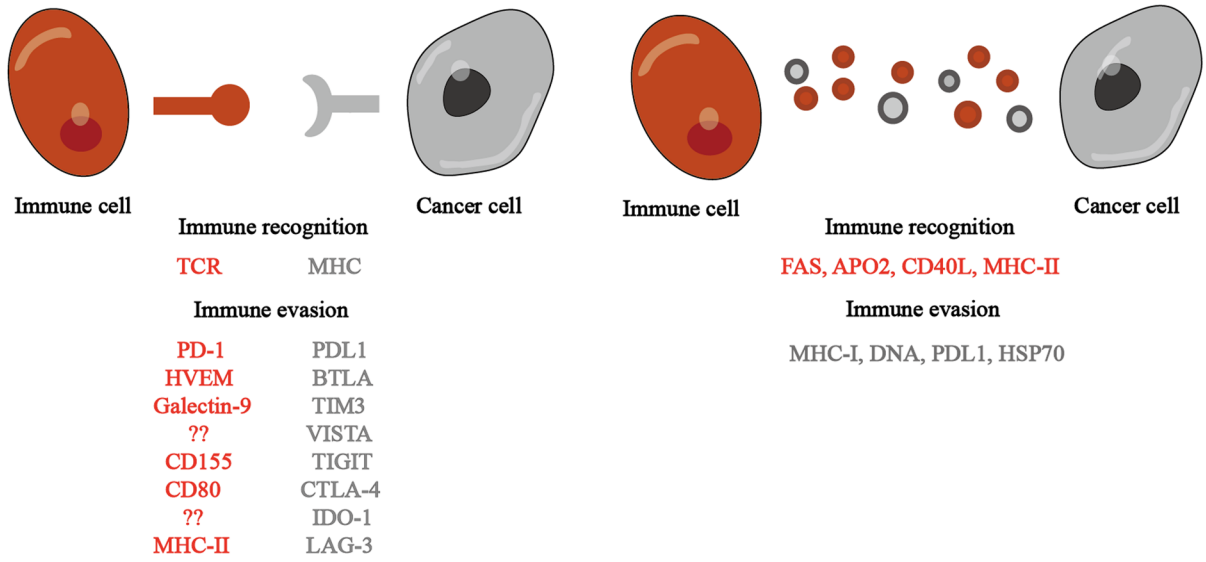


Fig. 1 Cell-to-cell communication through direct and indirect contact. Crosstalk in the tumor microenvironment can be through direct contact between adhesion molecules, or indirectly through secretion signals from extracellular vesicles. Tumor surface antigen regulation and tumor-induced immune suppression involve endocytic pathway in tumor immunity. In addition, immunosuppression may arise through accumulating and secreting exosomes around tumor

to detect targets on tumor cells for antigen presentation [8]. Exosomes target specific types of recipient cells, and the exchange of information between cells also involves endocytosis [9]. Therefore, endocytosis mediates the communication between tumor cells and immune cells and coordinates the interaction between different types of cells to control the tumor immune microenvironment (Fig. 1). We review and clarify the role of endocytosis in tumor cells and the latest developments in communication in the tumor microenvironment.

Progression of endocytosis in tumor cells

Studies in the past decade have shown that the functional interaction between cell signaling and endocytosis is important at all stages of morphogenesis and regulating cell proliferation, metabolism, movement, differentiation and immunity [10]. Cells sense the environment and each other through activation of cell surface signal receptors induced by ligands. Among them, tyrosine kinase receptor (RTK) and G protein-coupled receptor (GPCR) participate in homeostatic regulation to prevent ligand-induced overactivation of downstream effectors. This paradigm has also been extended to other receptors, including transforming growth factor (TGFβ) and cytokines. In addition, Notch and Wnt coordinate the fate of adjacent tumor cells through endocytosis, highlighting the influence of cell morphology on fate [11, 12]. Endocytosis seems to be the simplest way to regulate cell signal transduction by controlling the number of activated receptors. The activation of receptors or downstream effectors usually stimulates endocytosis, but questions remain about endocytosis and signal transduction under in vivo conditions. Endocytosis and signal transduction seem to be two aspects of the same coin, raising the question of whether the same biochemical pathway can achieve different biological results. Similarly, given that the high overlap between pathways is activated by multiple signal receptors, can the detection mechanism on the cell membrane break down many input signals into specific signals?.

The increasing understanding of the link between endocytosis and signal transduction raises the possibility that targeted interference with endocytosis may alter disease-related phenotypes, especially those related to abnormal cell specifications. The endocytosis mechanism in tumor heterogeneity may be the basis of the specific characteristics of tumors and their level of sensitivity to therapeutic drugs targeting signal receptors [13]. The dynamic balance in tissues strongly depends on the interaction between cells and the extracellular matrix [14]. In contrast, integral proteins can regulated the extracellular

matrix (ECM) and transmit signals between the cell and its surroundings [15].

In the past decades of research, the main focus has been on studies related to endocytosis and signaling pathways. With a better understanding of the tumor immune microenvironment, the relationship between tumor cells and immune cells is now recognized, and endocytosis mediates cell-to-cell communication through the regulation of direct or indirectly contact. Therefore, we discuss in depth about endocytosis mediating tumor immune microenvironment through regulation of cell adhesion molecules (including major histocompatibility complex (MHC), immune checkpoints) and exosomes.

Endocytosis mediates tumor immune microenvironment through cell adhesion molecules

Endocytosis and tumor immune microenvironment

The overall complexity of tumors presents challenges to the development of effective anticancer treatments [16–18]. In the process of tumor development, tumor heterogeneity intensifies as tumor cells and noncellular components of the tumor microenvironment (TME) mature [19, 20]. The TME consists of extracellular matrix (ECM), stromal cells (such as fibroblasts, mesenchymal stromal cells, pericytes, occasionally fat cells, blood and lymphatic network) and immune cells (including T and B lymphocytes, natural killer cells, macrophages) [21]. Tumor immune escape refers to the ability of tumor cells to avoid recognition and attack by the immune system. It is an important strategy for tumor survival and development [22]. Tumor surface antigen regulation and tumor-induced immune suppression involve the endocytic pathway in tumor immunity.

The cells of the innate immune system, such as monocytes, macrophages and dendritic cells (DCs)—are specialized antigen-presenting cells. In addition to this natural killer cells (NKs) rely on recognition of receptors and other cell surface molecules to rapidly detect microbial proteins or membrane molecules on tumor cells to orchestrate downstream inflammatory responses [23]. Key to the bridging role between innate and adaptive immunity is the processing and cross-presentation of antigens by APCs to T cells. The ability of APCs to engulf tumor cells through phagocytosis, a process that involves target cell recognition, phagocytosis and lysosomal digestion, is regulated by receptor-ligand interactions. Although healthy normal tissues and cells inherit the ability to avoid self-clearance by phagocytosis by expressing anti-phagocytic molecules, cells are more dependent on similar mechanisms to evade immune eradication [24, 25]. Thus identifying and targeting phagocytic checkpoints in cancer will provide a new avenue to develop cancer immunotherapies to eliminate tumor immune escape.

More and more phagocytic checkpoints are found to play an essential role in innate and adaptive immunity. Phagocytic checkpoint blockade, including anti-CD47 therapy and PD-L1 blockade, stimulates the innate and adaptive immune systems to generate anti-tumor responses, combining them with existing cancer immunotherapy strategies to improve the response rate to tumor treatment [26]. When major signaling pathways are constitutively activated by genetic disorders, such as v-Src or mutated K-Ras, a receptor-independent pattern of macropinocytosis occurs. Macropinocytosis provides tumor cells with an additional means of acquiring nutrients and internalizing adhesions molecules to support their growth and spread. By inhaling and concentrating amino acids and proteins in the extracellular fluid, tumor cells activate the mammalian target of rapamycin 1 (mTORC1) to stimulate transcriptional translation and support growth [27]. Thus, endocytosis inhibitors as well as immune checkpoint blockade therapy offer promise for clinical trials in a wide range of tumors, and can be used in combination with other monoclonal antibodies or immune checkpoint inhibitors (Table 1).

Endocytosis and cell adhesion molecules

The differentiation of initial T cells into effector cells can promote the killing of cancer cells. This effect occurs when the T-cell receptor (TCR) triggered by the signal accumulates, and then specific antigen presenting cells (APCs) are recognized [28]. The imbalance of endocytic events that control TCR circulation and degradation has been considered an important determinant of antigen presentation by immune cells. TCR is a protein complex formed by an antigen recognition module composed of α and β chains and a signal transduction module composed of ζ chain homodimers and CD3 chain clusters [29].

At present, clathrin-dependent and clathrin-independent endocytosis have been identified as the main pathways involved in the internalization of TCR [30]. Postendocytosis receptor movement is coordinated by ubiquitinated Rab GTPases, SNARE and regulators and effectors of endosomal subpopulations [31, 32]. The cargo can be recovered directly from early endosomes (ESEs) via a rapid, microtubule-independent process is achieved by rabenosyn5, which is the Fab 1, YOTB, Vac 1 and EEA1 (FYVE) domain containing Rab5 and Rab4 effectors [33]. Internalized receptors are incorporated into endosomes and can also be delivered to the plasma membrane through a slow, microtubule-dependent pathway [34]. In addition to the universal Rabs, Rab3d, Rab8a, Rab8b, Rab29, Rab35, intraflagellar transport (IFT), and electrohydrodynamic (EHD) family proteins

Table 1 Categorization and features of endocytosis process

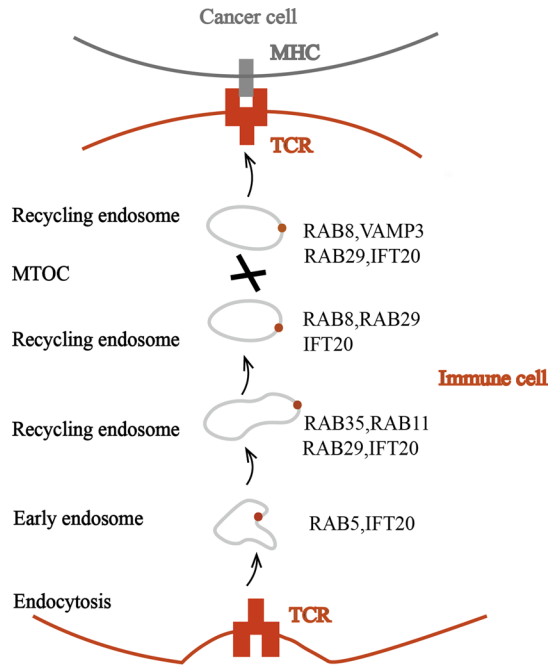
Endocytosis process	Associated protein	Mechanical	Inhibitor	Endocytosis checkpoint
Clathrin-mediated endocytosis	Actin	Membrane tension	Clorpromazine	E-, N-, and VE-cadherin, integrins, Notch, RTKs (EGFR, Her2, and FGFR1), Wnt, GPCR
	Clathrin	Membrane tension		
	ENTH domain	Membrane tension		
	N-BAR	Membrane tension		
Caveolae-mediated endocytosis	Cav-1	Low shear stress	Methyl-cyclodextrin	
	Cavin-1	Membrane stretch		
	Filamin A	Loss of cell adhesion		
Clathrin/caveolae-independent endocytosis	GPI-anchored	Membrane tension		Integrins, Notch, RTKs(EGFR, Her2, and FGFR1), Wnt, GPCR
	Vinculin	Membrane tension		
	TORC2	Membrane tension		
Macropinocytosis	Rac1 and CDC42	Aspect ratio of cargo	EPIA, amiloride	MHCI, MHC-II, mTORC1
	Phosphatidic acid	Membrane stretching		
	PLD2	Membrane tension		
	SCAR/WAVE	Actin-nucleation-promoting factors		
	WASp/N-WASp	Actin-nucleation-promoting factors		
Phagocytosis	Rac1	Substrate stiffness		CD47-Signal-regulatory protein α (SIRPα), PDL1, MHC I-LILRB1
	Cdc42	Substrate stiffness		
	MRTF-A	Area confinement		
	TRPV4	Substrate stiffness		

act sequentially in this pathway based on the ability to recycle TCRs [35–37]. Rab8 has been identified as the terminal pathway. It recruits v-SNARE VAMP3 and t-SNARE SNAP23 synaptic fusion protein to finally allow the recovered TCR to be fused to the cell membrane [36]. T cells can also enhance the release of extracellular vesicles (EVs) through stimulation, such as TCR triggering or T-cell activation [38, 39]. Activated T cells release biologically active Fas ligand and APO2 ligand in EVs, thereby promoting activation and inducing cell death [40]. In addition, the EVs formed by $CD8^+$ CTL MVBs contain granzyme and perforin [41] (Fig. 2).

To achieve complete activation, B cells rely on their ability to capture external antigens and present them to $CD4^+$ T cells as peptide fragments loaded on major histocompatibility complex class II (MHC II) molecules [42]. This interaction differentiates B cells into plasma cells that produce high affinity and develop into memory B-cell populations [43]. Regarding the mechanism by which B cells extract antigens on the cell surface, one view is that local lysosomes secrete and release proteases and acidify the synaptic cleft of related antigens to facilitate their extraction of antigen [44]. Another view is that the tension exerted on the synaptic membrane mediated by myosin II-A triggers internalization of the antigen into coated clathrin [45].

The binding of surface antigens to the B-cell receptor (BCR) triggers the recruitment of PAR3 to the antigen contact site, which leads to polarization of the microtubule network, in which the centrosome transfers to the immune synapse in a Cdc42-dependent manner [44, 46]. Centrosome relocation directs the recruitment of MHC II^+ lysosomes, which can fuse with antigen-containing endosomes to facilitate antigen processing. It is worth noting that the $Lamp1^+$ multivesicular compartment, which contains both antigen and MHC molecules, has been found to be closely related to the immune synapse of activated B lymphocytes [44]. Therefore, determining the specific mechanism used to selectively enhance the extraction of antigens by B cells to enhance the activation of T cells should be the focus of future research.

Immunosuppression involves inducing the expression of immunosuppressive molecules or their receptors, including cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed cell death protein 1 (PD-1), T cell immunoglobulin and mucin domain 3 (TIM-3), Indoleamine 2,3-dioxygenase (IDO), V-domain Ig inhibitor of T-cell activation (VISTA), killer cell immunoglobulin-like receptors (KIR), T cell immunoglobulin and ITIM domain (TIGIT), B and T lymphocyte attenuator (BTLA) and Lymphocyte activation gene-3 (LAG-3), which are called immune checkpoints and can inhibit the activated lymphocytes of effector T cells and ultimately lead to



Direct cell-to-cell communication TCR through endocytosis
Endocytic carrying TCRs internalized at the plasma membrane are incorporated into a network of endosomal systems.
Internalized TCRs can be sorted to early endosomes and recycled to plasma membrane through recycling endosomes, remain associated to signaling endosomes.

Fig. 2 Regulation of immune response by exosomes. Exosomes from distinct cellular sources, including immune cells (B cell, T cell, macrophage, and dendritic cells) and cancer cells, exosomes with cargos that can influence the proliferation and activity of recipient cells of both the innate and adaptive immune system

tumor immune escape [47]. Immune checkpoints are also specifically expressed on protumor immune cells (e.g., Tregs). For example, PD-1 on T effectors reduces activation, while PD-1 on Tregs enhances immunosuppressive effects. In addition, linker for activation of T cells (LAT) [48, 49] and lymphocyte-specific protein tyrosine kinase (LCK) [50, 51], with the assistance of specific vesicle-related proteins, ensure the optimal TCR level required for T-cell activation. Changes in endocytic transport are associated with cancer, so a better understanding of the endocytic pathways that control immune checkpoints and function is expected to lead to new candidates for cancer treatment.

Endocytosis mediates tumor immune microenvironment through exosomes

Endocytosis and exosomes

In addition, immunosuppression may arise through the accumulation and secretion of exosomes around tumors. Exosomes can inactivate cytotoxic T lymphocytes (CTLs) to enhance the immune tolerance of tumor cells [52–55]. The communication between cancer cells and surrounding cells is a bidirectional process that involves multiple mechanisms. Crosstalk in the tumor microenvironment can occur directly through contact between antigen presentation or indirectly through secretion signals from extracellular vesicles. Therefore, the therapeutic method of regulating cell-to-cell communication by endocytosis may be a promising strategy in the fight against tumors.

Liquid and extracellular components (such as proteins, lipids, metabolites, small molecules and ions) can enter cells through endocytosis and plasma membrane invagination, along with cell surface proteins [56]. Tumor-derived exosomes are bound and internalized by organ-specific cells. Heparan sulfate proteoglycans mediate the interaction between cells and exosomes. Exosome transfer to the recipient cell can be competitively blocked by heparinoids because heparin is structurally similar to heparan sulfate [57]. The plasma membrane bud formed on the side of the cell cavity has an orientation from outside to inside, which leads to the formation of the ESE (early endosome) [58]. The ESE can also be fused with the ER (endoplasmic reticulum) and anti-Golgi network (TGN), which may explain why the phagocytic cargo contains components of the ER, TGN and mitochondria, and the ESE may contain membrane and intraluminal components representing different origins [58]. MVBs are formed by the inward invagination of the late endosome restriction membrane (that is, the two invaginations of the plasma membrane). MVBs contain multiple intraluminal vesicles (ILVs), which lead to exosomal cargo in future modifications. As part of the formation of ILVs, proteins (originally located on the cell surface) can be clearly distributed between ILVs [56]. MVBs can be fused with autophagosomes, and the final content will be degraded in the lysosome, allowing the degradation products to be recovered by the cell. MVB that does not follow this trajectory is transported to the plasma membrane through the cell cytoskeleton and microtubule network and is docked on the lumen side of the plasma membrane with the help of MVB docking protein to cause exocytosis [59]. Rabs, endosomal sorting complex required for transport (ESCRT) and other related proteins (CD9, CD81, CD63, TSG101, Alix, and putative universal biomarker of syntenin-1) are used as exosomal markers or are related to the biogenesis of exosomes [58, 60] (Fig. 3).

Exosomes can also contain different types of cell surface proteins, intracellular proteins, RNA, DNA, amino acids and metabolites [56]. The questions surrounding the function of exosomes focus mainly on understanding the fate of their components and their induction of

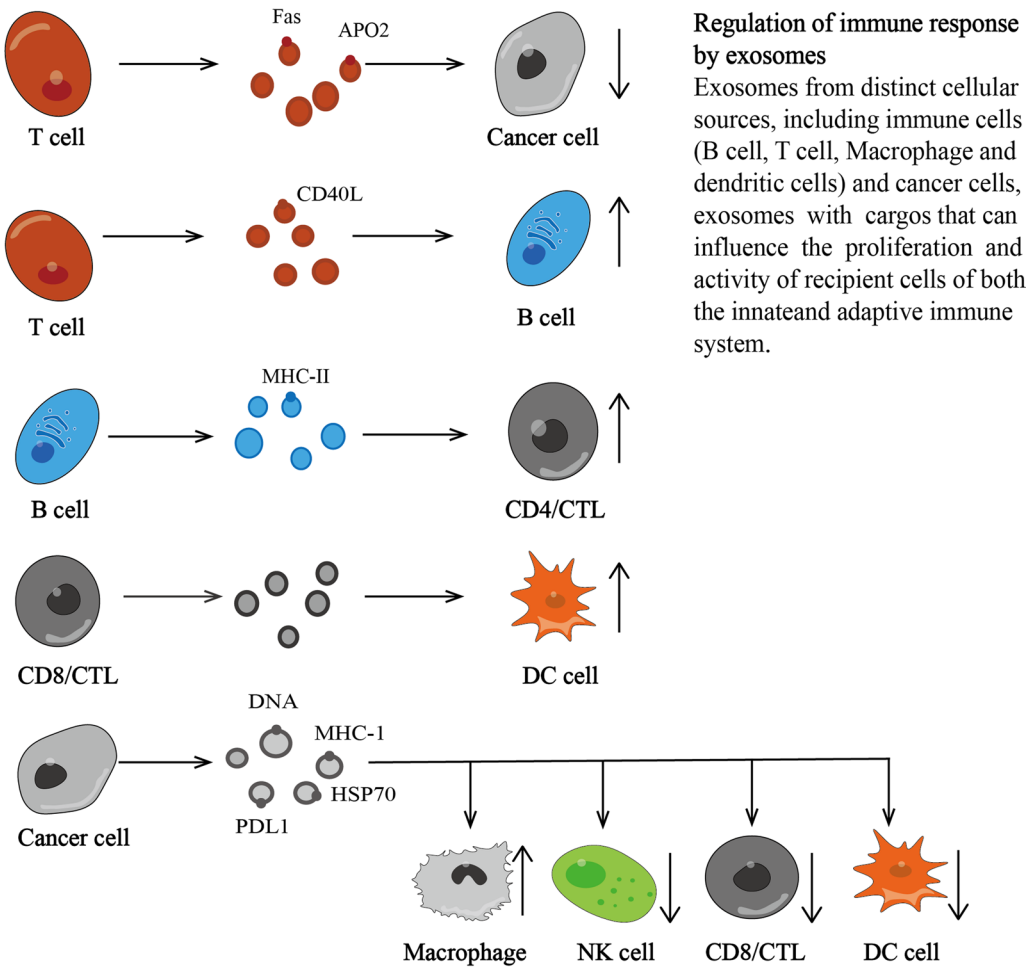


Fig. 3 Regulation of immune response by exosomes. Exosomes from distinct cellular souurces, including immune cells (B cell, T cell, Macrophage and Dendritic cells) and cancer cells, exosomes with cargos than can influence the proliferation and activity of recipient cells of both the innateand adaptive immune system

phenotypic and molecular changes in recipient cells. The uptake and secretion pathways of exosomes may intersect, resulting in a mixed population of endogenously produced and circulating exosomes produced over time. The unique mechanisms and pathways related to the uptake of exosomes [58, 61], as well as the specificity of exosomes for certain cell types, increase the functional complexity of exosomes in cell-to-cell communication.

Exosomes are vesicles with membrane structures between 40 and 160 nm (both 100 nm) in diameter [9, 62, 63] containing RNA, proteins and lipids that play a role in tumor proliferation, metastasis, immunosuppression and drug tolerance [58, 61]. These processes seem to be similar to leukocyte transendothelial migration, in which integrins are involved in the adhesion/attachment of exosomes to receptor cells, followed by the enrichment of four transmembrane microstructural domains facilitating exosome fusion [64–67]. The endocytosis of exosomes is the most important way they deliver content. It can be divided into micropinocytosis [68, 69], phagocytosis [70], clathrin-mediated endocytosis [71], caveolin-mediated endocytosis [72] and clathrin/caveolin-independent endocytosis [73]. The endocytosis of exosomes depends on the actin cytoskeleton, phosphatidylinositol 3-kinase (PI3K) and dynamin2 [70]. Studies have shown that the pharmacological inhibitors EIPA and LY294002 inhibit Na^{+}-H^{+} ion exchange and PI3K activity, which can inhibit the effect of macropinocytosis and reduce the uptake of exosomes [74]. Clathrin-dependent endocytosis uses clathrin and AP2 to cover the membrane and induce exosomes to invade vesicles; clathrin/cavolin-independent endocytosis is caused by RhoA, Cdc42 and Arf6 [75].

Exosomes targeting recipient cells by endocytosis have been confirmed in tumors. For example, oncogenic signals induced by KRAS mutation expression promote

exosomal uptake in human pancreatic cancer cells through micropinocytosis [2, 76] and promote the uptake of exosomal cargo by human melanoma cells by fusion with the plasma membrane [77]. Exosomes derived from rat adrenal medulloma PC12 cells are more likely to rely on clathrin-dependent endocytic uptake [74]. It is possible that internalized exosomal cargo varies depending on the endocytosis and the recipient cell status that regulates uptake of extracellular molecules and vesicles.

Exosomes in tumor progression and metastasis

The discovery of exosomes, especially their role in mediating the transportation or "trafficking" of biological materials, has explained various pathological and physiological phenomena that involve the transmission of information between cells [78]. As a new model for mediating information exchange between cells, exosomes transport oncogene message during the occurrence and development of tumors. Recent studies have elaborated on the important role of exosomes in tumor carcinogenesis [76]. Tumor-derived exosomes can promote tumor formation by regulating the synthesis of cell-independent ncRNA [79]. During the development of cancer, there is competition between cancer cells and neighboring normal cells [80]. As a homeostatic mechanism, abundant noncancer cells can release tumor suppressor miRNAs, thereby suppressing the malignant phenotype of adjacent cancer cells [81–86]. In addition, it has been reported that differences in exosome content can distinguish several types of cancer cells (such as prostate cancer, gastric cancer, and laryngeal squamous cell carcinoma) from normal cells [87].

Exosomal RNA derived from tumor cells can enhance the proliferation, migration and tube formation of endothelial cells, thereby promoting tumors and lymphatic vasculature [88–93]. Proteomic analysis of exosomes showed that the integrin expression pattern of cancer cells contributes to the tendency of metastasis [94]. For example, integrin α6β4 and α6β1 are related to lung metastasis, and integrin αvβ5 is related to liver metastasis [95]. Depletion of integrins α6β4 and αvβ5 reduced exosomal uptake and resulted in the inhibition of lung and liver metastasis, respectively. Therefore, the integrins found on specific tumor-derived exosomes can be used to predict organ-specific cancer metastasis and are a new target for the development of cancer metastasis treatment strategies [96–99].

Exosomes regulate cancer immunology

In most studies, the recipient cells of tumor derived exosomes are cancer-related immune cells and other stromal cells, which dynamically regulate each other in the tumor microenvironment [100]. Compared with studying the role of exosomes in other types of cells, research on tumor related exosomes is progressing rapidly. More and more evidence supports the complex intercellular communication mediated by exosomes in tumor immune microenvironment. Tumor-derived exosomes content HSP72 can trigger myeloid-derived inhibitory cell activation through STAT3 [101]. Tumor exosomes block the maturation and migration of dendritic cells in a PD-L1 dependent manner [102]. The tumor-derived exosomal DNA by circulating neutrophils can enhance the production of tissue factor and IL-8, thereby promoting tumor inflammation and thrombosis [103]. Therefore, tumor-derived exosomes may changes immune cell function, which may be a key role for tumors to evade immune detection and response.

Similarly, exosomes released by immune cells affect tumor development by regulating immune response [104]. Exosomes released by NK cells show FasL membrane expression, and produce strong cytotoxicity to cancer by eliminating Fas + tumor cells [105]. In addition, in patients with acute myeloid leukemia (AML), plasma exosomes carrying leukemia-related antigens and a variety of inhibitory molecules can inhibit tumor activity by interfering with NK-92 cells [106]. NK-92 cell-derived exosomes TNF-α have cytotoxic effects on melanoma cells and block cell proliferation signaling pathways [107]. In a phase II trial, IFN-γ mature DC-derived exosomes loaded with MHC class peptides can enhance NK cell activity in patients with non-small cell lung cancer (NSCLC) [108]. T cells can also transfer CD40L to B cells through helper T cells [109]. The binding of antigen-loaded B cells to specific $CD4^+$ T cells stimulates the release of EVs with peptide MHC-II complexes, which directly stimulate naive $CD4^+$ T cells [110] (Fig. 3). In addition, ovalbumin (OVA)-stimulated dendritic cell exosomes are more effective than microvesicles to trigger antigen (OVA)-specific $CD8^+$ T cell activation [111].

Conclusion

The field of communication in the tumor microenvironment is a relatively new concept in tumor biology and rapidly evolving. Cancer-stromal crosstalk is an extremely complex phenomenon, and different forms of cellular communication are highly expressed in cancer and clearly involved in cancer development. Different forms of cell communication are highly expressed in cancer and obviously participate in the occurrence of cancer. With our in-depth exploration and understanding of the connection of endocytosis, we believe that the communication between cells is essential for the creation of tumor niches. Therefore, a novel medical method focuses on inhibiting cell-to-cell communication in cancer, or using these communication methods as a vehicle for

delivering drugs to tumor cells. Immune cells can rely on endocytosis to mediates cell adhesion molecules quickly detect targets on tumor cells. The overall understanding of exosomes through endocytosis is also expected to bring new candidates for therapeutic regulation of tumor immune microenvironment. Therefore, further research is needed to fully understand endocytosis and clarify possible specific targets to inhibit tumors.

Abbreviations

TME: Tumor microenvironment; ILVs: Intraluminal vesicles; RTK: Tyrosine kinase receptor; GPCR: G protein-coupled receptor; TGFβ: Transforming growth factor; ECM: Extracellular matrix; TCR: T cell receptor; BCR: B cell receptor; MHC: Major histocompatibility complex; CTLA-4: Cytotoxic T-lymphocyte-associated protein 4; PD-1: Programmed cell death protein 1; TIM-3: T cell immunoglobulin and mucin domain 3; IDO: Indoleamine 2,3-dioxygenase; VISTA: V-domain Ig inhibitor of T-cell activation; KIR: Killer cell immunoglobulin-like receptors; TIGIT: T cell immunoglobulin and ITIM domain; BTLA: B and T lymphocyte attenuator; LAG-3: Lymphocyte activation gene-3; CTL: Cytotoxic T lymphocytes; Treg cells: Regulatory T cells; MDSC: Marrow-derived suppressor cells; DC: Dendritic cells; NK: Natural killer; mTORC1: Mammalian target of rapamycin 1; APC: Antigen presenting cells; ESE: Early endosome; FYVE: Fab 1, YOTB, Vac 1 and EEA1; IFT: Intraflagellar transport; EHD: Electrohydrodynamic; LCK: Lymphocyte-specific protein tyrosine kinase; LAT: Linker for activation of T cells; EVs: Extracellular vesicles; MVBs: Multivesicular bodies; ER: Endoplasmic reticulum; TGN: Anti-Golgi network; ESCRT: Endosomal sorting complex required for transport; PI3K: Phosphatidylinositol 3-kinase; PS: Phosphatidylserine; FasL: Fas ligand; AML: Acute myeloid leukemia; NSCLC: Non-small cell lung cancer; OVA: Ovalbumin; SC: Stem cell; IC: Immune checkpoint; MSI-H: Microsatellite instability; dmmR: DNA mismatch repair defect; HLA-B: Human leukocyte antigen B; CEACAM-1: Carcinoembryonic antigen cell adhesion molecule 1; PVR: Poliovirus receptor.

Supplementary Information

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Author contributions

BW and QW offered direction and guidance of the manuscript. BW and XS drafted the initial manuscript. QW and MX-J revised the manuscript. BW and MX-J illustrated the figures for the manuscript. All authors approved the final manuscript.

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Availability of data and materials

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Declarations

Consent for publication

All authors agree to submit the article for publication.

Competing interests

This manuscript has been read and approved by all authors and all declare that they have no competing interests.

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References

1. Conner SD, Schmid SL. Regulated portals of entry into the cell. Nature. 2003;422:37–44.
2. Commisso C, Davidson SM, Soydaner-Azeloglu RG, Parker SJ, Kamphorst JJ, Hackett S, Grabocka E, Nofal M, Drebin JA, Thompson CB, et al. Macropinocytosis of protein is an amino acid supply route in Ras-transformed cells. Nature. 2013;497:633–7.
3. Germain RN. An innately interesting decade of research in immunology. Nat Med. 2004;10:1307–20.
4. Wallroth A, Haucke V. Phosphoinositide conversion in endocytosis and the endolysosomal system. J Biol Chem. 2018;293:1526–35.
5. Piper RC, Dikic I, Lukacs GL. Ubiquitin-dependent sorting in endocytosis. Cold Spring Harb Perspect Biol. 2014;6:a016808.
6. Nino CA, Sala S, Polo S. When ubiquitin meets E-cadherin: plasticity of the epithelial cellular barrier. Semin Cell Dev Biol. 2019;93:136–44.
7. Polo S, Di Fiore PP. Endocytosis conducts the cell signaling orchestra. Cell. 2006;124:897–900.
8. Chao MP, Weissman IL, Majeti R. The CD47-SIRPalpha pathway in cancer immune evasion and potential therapeutic implications. Curr Opin Immunol. 2012;24:225–32.
9. Kalluri R, LeBleu VS. The biology, function, and biomedical applications of exosomes. Science. 2020. https://doi.org/10.1126/science.aau6977.
10. Sorkin A, von Zastrow M. Endocytosis and signalling: intertwining molecular networks. Nat Rev Mol Cell Biol. 2009;10:609–22.
11. Lloyd-Lewis B, Mourikis P, Fre S. Notch signalling: sensor and instructor of the microenvironment to coordinate cell fate and organ morphogenesis. Curr Opin Cell Biol. 2019;61:16–23.
12. Clara JA, Monge C, Yang Y, Takebe N. Targeting signalling pathways and the immune microenvironment of cancer stem cells–a clinical update. Nat Rev Clin Oncol. 2020;17:204–32.
13. Mosesson Y, Mills GB, Yarden Y. Derailed endocytosis: an emerging feature of cancer. Nat Rev Cancer. 2008;8:835–50.
14. Shapiro L, Weis WI. Structure and biochemistry of cadherins and catenins. Cold Spring Harb Perspect Biol. 2009;1:a003053.
15. Hamidi H, Ivaska J. Every step of the way: integrins in cancer progression and metastasis. Nat Rev Cancer. 2018;18:533–48.
16. Liu J, Dang H, Wang XW. The significance of intertumor and intratumor heterogeneity in liver cancer. Exp Mol Med. 2018;50:e416.
17. Grzywa TM, Paskal W, Wlodarski PK. Intratumor and intertumor heterogeneity in melanoma. Transl Oncol. 2017;10:956–75.
18. Mroz EA, Rocco JW. Intra-tumor heterogeneity in head and neck cancer and its clinical implications. World J Otorhinolaryngol Head Neck Surg. 2016;2:60–7.
19. Stanta G, Bonin S. Overview on clinical relevance of intra-tumor heterogeneity. Front Med (Lausanne). 2018;5:85.
20. Wang M, Zhao J, Zhang L, Wei F, Lian Y, Wu Y, Gong Z, Zhang S, Zhou J, Cao K, et al. Role of tumor microenvironment in tumorigenesis. J Cancer. 2017;8:761–73.
21. Chen F, Zhuang X, Lin L, Yu P, Wang Y, Shi Y, Hu G, Sun Y. New horizons in tumor microenvironment biology challenges and opportunities. BMC Med. 2015;13:45.
22. He X, Xu C. Immune checkpoint signaling and cancer immunotherapy. Cell Res. 2020;30:660–9.
23. Morvan MG, Lanier LL. NK cells and cancer: you can teach innate cells new tricks. Nat Rev Cancer. 2016;16:7–19.
24. Iwasaki A, Medzhitov R. Regulation of adaptive immunity by the innate immune system. Science. 2010;327:291–5.

25. Dranoff G. Cytokines in cancer pathogenesis and cancer therapy. Nat Rev Cancer. 2004;4:11–22.
26. Jutras I, Desjardins M. Phagocytosis: at the crossroads of innate and adaptive immunity. Annu Rev Cell Dev Biol. 2005;21:511–27.
27. Florey O, Overholtzer M. Macropinocytosis and autophagy cross-talk in nutrient scavenging. Philos Trans Royal Soc B Biol Sci. 2019;374(1765):20180154.
28. Sasmal DK, Feng W, Roy S, Leung P, He Y, Cai C, Cao G, Lian H, Qin J, Hui E, Schreiber H, Adams EJ, Huang J. TCR-pMHC bond conformation controls TCR ligand discrimination. Cell Mol Immunol. 2020;17(3):203–17.
29. Alcover A, Alarcon B, Di Bartolo V. Cell biology of T cell receptor expression and regulation. Annu Rev Immunol. 2018;36:103–25.
30. Compeer EB, Kraus F, Ecker M, Redpath G, Amiezer M, Rother N, Nicovich PR, Kapoor-Kaushik N, Deng Q, Samson GPB, et al. A mobile endocytic network connects clathrin-independent receptor endocytosis to recycling and promotes T cell activation. Nat Commun. 2018;9:1597.
31. Pfeffer SR. Rab GTPase regulation of membrane identity. Curr Opin Cell Biol. 2013;25:414–9.
32. Zhen Y, Stenmark H. Cellular functions of Rab GTPases at a glance. J Cell Sci. 2015;128:3171–6.
33. de Renzis S, Sonnichsen B, Zerial M. Divalent Rab effectors regulate the sub-compartmental organization and sorting of early endosomes. Nat Cell Biol. 2002;4:124–33.
34. Patino-Lopez G, Dong X, Ben-Aissa K, Bernot KM, Itoh T, Fukuda M, Kruhlak MJ, Samelson LE, Shaw S. Rab35 and its GAP EPI64C in T cells regulate receptor recycling and immunological synapse formation. J Biol Chem. 2008;283:18323–30.
35. Soares H, Lasserre R, Alcover A. Orchestrating cytoskeleton and intracellular vesicle traffic to build functional immunological synapses. Immunol Rev. 2013;256:118–32.
36. Finetti F, Patrussi L, Masi G, Onnis A, Galgano D, Lucherini OM, Pazour GJ, Baldari CT. Specific recycling receptors are targeted to the immune synapse by the intraflagellar transport system. J Cell Sci. 2014;127:1924–37.
37. Onnis A, Finetti F, Patrussi L, Gottardo M, Cassioli C, Spano S, Baldari CT. The small GTPase Rab29 is a common regulator of immune synapse assembly and ciliogenesis. Cell Death Differ. 2015;22:1687–99.
38. Blanchard N, Lankar D, Faure F, Regnault A, Dumont C, Raposo G, Hivroz C. TCR activation of human T cells induces the production of exosomes bearing the TCR/CD3/zeta complex. J Immunol. 2002;168:3235–41.
39. van der Vlist EJ, Arkesteijn GJ, van de Lest CH, Stoorvogel W, Nolte-'t Hoen EN, Wauben MH. CD4(+) T cell activation promotes the differential release of distinct populations of nanosized vesicles. J Extracell Vesicles. 2012;1:18364.
40. Monleon I, Martinez-Lorenzo MJ, Monteagudo L, Lasierra P, Taules M, Iturralde M, Pineiro A, Larrad L, Alava MA, Naval J, Anel A. Differential secretion of Fas ligand- or APO2 ligand/TNF-related apoptosis-inducing ligand-carrying microvesicles during activation-induced death of human T cells. J Immunol. 2001;167:6736–44.
41. Peters PJ, Borst J, Oorschot V, Fukuda M, Krahenbuhl O, Tschopp J, Slot JW, Geuze HJ. Cytotoxic T lymphocyte granules are secretory lysosomes, containing both perforin and granzymes. J Exp Med. 1991;173:1099–109.
42. Welsh RA, Song N, Sadegh-Nasseri S. How does B cell antigen presentation affect memory CD4 T cell differentiation and longevity? Front Immunol. 2021;12:677036.
43. Mitchison NA. T-cell-B-cell cooperation. Nat Rev Immunol. 2004;4:308–12.
44. Yuseff MI, Reversat A, Lankar D, Diaz J, Fanget I, Pierobon P, Randrian V, Larochette N, Vascotto F, Desdouets C, et al. Polarized secretion of lysosomes at the B cell synapse couples antigen extraction to processing and presentation. Immunity. 2011;35:361–74.
45. Natkanski E, Lee WY, Mistry B, Casal A, Molloy JE, Tolar P. B cells use mechanical energy to discriminate antigen affinities. Science. 2013;340:1587–90.
46. Goldstein B, Macara IG. The PAR proteins: fundamental players in animal cell polarization. Dev Cell. 2007;13:609–22.
47. Toor SM, Sasidharan Nair V, Decock J, Elkord E. Immune checkpoints in the tumor microenvironment. Semin Cancer Biol. 2020;65:1–12.
48. Mingueneau M, Roncagalli R, Gregoire C, Kissenpfennig A, Miazek A, Archambaud C, Wang Y, Perrin P, Bertosio E, Sansoni A, et al. Loss of the LAT adaptor converts antigen-responsive T cells into pathogenic effectors that function independently of the T cell receptor. Immunity. 2009;31:197–208.
49. Zhang W, Sommers CL, Burshtyn DN, Stebbins CC, DeJarnette JB, Trible RP, Grinberg A, Tsay HC, Jacobs HM, Kessler CM, et al. Essential role of LAT in T cell development. Immunity. 1999;10:323–32.
50. Ventimiglia LN, Alonso MA. The role of membrane rafts in Lck transport, regulation and signalling in T-cells. Biochem J. 2013;454:169–79.
51. Nika K, Soldani C, Salek M, Paster W, Gray A, Etzensperger R, Fugger L, Polzella P, Cerundolo V, Dushek O, et al. Constitutively active Lck kinase in T cells drives antigen receptor signal transduction. Immunity. 2010;32:766–77.
52. Wang YA, Li XL, Mo YZ, Fan CM, Tang L, Xiong F, Guo C, Xiang B, Zhou M, Ma J, et al. Effects of tumor metabolic microenvironment on regulatory T cells. Mol Cancer. 2018;17:168.
53. Yu J, Du W, Yan F, Wang Y, Li H, Cao S, Yu W, Shen C, Liu J, Ren X. Myeloid-derived suppressor cells suppress antitumor immune responses through IDO expression and correlate with lymph node metastasis in patients with breast cancer. J Immunol. 2013;190:3783–97.
54. Benencia F, Muccioli M, Alnaeeli M. Perspectives on reprograming cancer-associated dendritic cells for anti-tumor therapies. Front Oncol. 2014;4:72.
55. Chanmee T, Ontong P, Konno K, Itano N. Tumor-associated macrophages as major players in the tumor microenvironment. Cancers (Basel). 2014;6:1670–90.
56. Van Niel G, D'Angelo G, Raposo G. Shedding light on the cell biology of extracellular vesicles. Nat Rev Mol Cell Biol. 2018;19:213–28.
57. Cerezo-Magaña M, Bång-Rudenstam A, Belting M. The pleiotropic role of proteoglycans in extracellular vesicle mediated communication in the tumor microenvironment. Semin Cancer Biol. 2020;62:99–107.
58. Mathieu M, Martin-Jaular L, Lavieu G, Thery C. Specificities of secretion and uptake of exosomes and other extracellular vesicles for cell-to-cell communication. Nat Cell Biol. 2019;21:9–17.
59. Kahlert C, Kalluri R. Exosomes in tumor microenvironment influence cancer progression and metastasis. J Mol Med (Berl). 2013;91:431–7.
60. Kugeratski FG, Hodge K, Lilla S, McAndrews KM, Zhou X, Hwang RF, Zanivan S, Kalluri R. Quantitative proteomics identifies the core proteome of exosomes with syntenin-1 as the highest abundant protein and a putative universal biomarker. Nat Cell Biol. 2021;23:631–41.
61. McKelvey KJ, Powell KL, Ashton AW, Morris JM, McCracken SA. Exosomes: mechanisms of uptake. J Circ Biomark. 2015;4:7.
62. Khan S, Jutzy JM, Aspe JR, McGregor DW, Neidigh JW, Wall NR. Survivin is released from cancer cells via exosomes. Apoptosis. 2011;16:1–12.
63. Valadi H, Ekstrom K, Bossios A, Sjostrand M, Lee JJ, Lotvall JO. Exosome-mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells. Nat Cell Biol. 2007;9:654–9.
64. Hemler ME. Tetraspanin proteins mediate cellular penetration, invasion, and fusion events and define a novel type of membrane microdomain. Annu Rev Cell Dev Biol. 2003;19:397–422.
65. Rana S, Zoller M. Exosome target cell selection and the importance of exosomal tetraspanins: a hypothesis. Biochem Soc Trans. 2011;39:559–62.
66. Mulcahy LA, Pink RC, Carter DR. Routes and mechanisms of extracellular vesicle uptake. J Extracell Vesicles. 2014;3:24641.
67. Chivet M, Javalet C, Laulagnier K, Blot B, Hemming FJ, Sadoul R. Exosomes secreted by cortical neurons upon glutamatergic synapse activation specifically interact with neurons. J Extracell Vesicles. 2014;3:24722.
68. Nakase I, Kobayashi NB, Takatani-Nakase T, Yoshida T. Active macropinocytosis induction by stimulation of epidermal growth factor receptor and oncogenic Ras expression potentiates cellular uptake efficacy of exosomes. Sci Rep. 2015;5:10300.
69. Fitzner D, Schnaars M, van Rossum D, Krishnamoorthy G, Dibaj P, Bakhti M, Regen T, Hanisch UK, Simons M. Selective transfer of exosomes from oligodendrocytes to microglia by macropinocytosis. J Cell Sci. 2011;124:447–58.
70. Feng D, Zhao WL, Ye YY, Bai XC, Liu RQ, Chang LF, Zhou Q, Sui SF. Cellular internalization of exosomes occurs through phagocytosis. Traffic. 2010;11:675–87.
71. Barres C, Blanc L, Bette-Bobillo P, Andre S, Mamoun R, Gabius HJ, Vidal M. Galectin-5 is bound onto the surface of rat reticulocyte

exosomes and modulates vesicle uptake by macrophages. Blood. 2010;115:696–705.
72. Nanbo A, Kawanishi E, Yoshida R, Yoshiyama H. Exosomes derived from Epstein-Barr virus-infected cells are internalized via caveola-dependent endocytosis and promote phenotypic modulation in target cells. J Virol. 2013;87:10334–47.
73. Hazan-Halevy I, Rosenblum D, Weinstein S, Bairey O, Raanani P, Peer D. Cell-specific uptake of mantle cell lymphoma-derived exosomes by malignant and non-malignant B-lymphocytes. Cancer Lett. 2015;364:59–69.
74. Tian T, Zhu YL, Zhou YY, Liang GF, Wang YY, Hu FH, Xiao ZD. Exosome uptake through clathrin-mediated endocytosis and macropinocytosis and mediating miR-21 delivery. J Biol Chem. 2014;289:22258–67.
75. Mayor S, Pagano RE. Pathways of clathrin-independent endocytosis. Nat Rev Mol Cell Biol. 2007;8:603–12.
76. Kamerkar S, LeBleu VS, Sugimoto H, Yang S, Ruivo CF, Melo SA, Lee JJ, Kalluri R. Exosomes facilitate therapeutic targeting of oncogenic KRAS in pancreatic cancer. Nature. 2017;546:498–503.
77. Parolini I, Federici C, Raggi C, Lugini L, Palleschi S, De Milito A, Coscia C, Iessi E, Logozzi M, Molinari A, et al. Microenvironmental pH is a key factor for exosome traffic in tumor cells. J Biol Chem. 2009;284:34211–22.
78. Dilsiz N. Hallmarks of exosomes. Future Sci OA. 2021;8(1):FSO764.
79. Melo SA, Sugimoto H, O'Connell JT, Kato N, Villanueva A, Vidal A, Qiu L, Vitkin E, Perelman LT, Melo CA, et al. Cancer exosomes perform cell-independent microRNA biogenesis and promote tumorigenesis. Cancer Cell. 2014;26:707–21.
80. Kanada M, Bachmann MH, Contag CH. Signaling by extracellular vesicles advances cancer hallmarks. Trends Cancer. 2016;2:84–94.
81. Kosaka N, Yoshioka Y, Fujita Y, Ochiya T. Versatile roles of extracellular vesicles in cancer. J Clin Invest. 2016;126:1163–72.
82. Kosaka N, Iguchi H, Yoshioka Y, Hagiwara K, Takeshita F, Ochiya T. Competitive interactions of cancer cells and normal cells via secretory microRNAs. J Biol Chem. 2012;287:1397–405.
83. Han S, Gonzalo DH, Feely M, Rinaldi C, Belsare S, Zhai H, Kalra K, Gerber MH, Forsmark CE, Hughes SJ. Stroma-derived extracellular vesicles deliver tumor-suppressive miRNAs to pancreatic cancer cells. Oncotarget. 2018;9:5764–77.
84. Fonsato V, Collino F, Herrera MB, Cavallari C, Deregibus MC, Cisterna B, Bruno S, Romagnoli R, Salizzoni M, Tetta C, Camussi G. Human liver stem cell-derived microvesicles inhibit hepatoma growth in SCID mice by delivering antitumor microRNAs. Stem Cells. 2012;30:1985–98.
85. Zheng R, Du M, Wang X, Xu W, Liang J, Wang W, Lv Q, Qin C, Chu H, Wang M, et al. Exosome-transmitted long non-coding RNA PTENP1 suppresses bladder cancer progression. Mol Cancer. 2018;17:143.
86. Zhang H, Deng T, Ge S, Liu Y, Bai M, Zhu K, Fan Q, Li J, Ning T, Tian F, et al. Exosome circRNA secreted from adipocytes promotes the growth of hepatocellular carcinoma by targeting deubiquitination-related USP7. Oncogene. 2019;38:2844–59.
87. Silva A, Bullock M, Calin G. The clinical relevance of long non-coding RNAs in cancer. Cancers (Basel). 2015;7:2169–82.
88. Lin XJ, Fang JH, Yang XJ, Zhang C, Yuan Y, Zheng L, Zhuang SM. Hepatocellular carcinoma cell-secreted exosomal microRNA-210 promotes angiogenesis in vitro and in vivo. Mol Ther Nucleic Acids. 2018;11:243–52.
89. Li B, Hong J, Hong M, Wang Y, Yu T, Zang S, Wu Q. piRNA-823 delivered by multiple myeloma-derived extracellular vesicles promoted tumorigenesis through re-educating endothelial cells in the tumor environment. Oncogene. 2019;38:5227–38.
90. Bao L, You B, Shi S, Shan Y, Zhang Q, Yue H, Zhang J, Zhang W, Shi Y, Liu Y, et al. Metastasis-associated miR-23a from nasopharyngeal carcinoma-derived exosomes mediates angiogenesis by repressing a novel target gene TSGA10. Oncogene. 2018;37:2873–89.
91. Conigliaro A, Costa V, Lo Dico A, Saieva L, Buccheri S, Dieli F, Manno M, Raccosta S, Mancone C, Tripodi M, et al. CD90+ liver cancer cells modulate endothelial cell phenotype through the release of exosomes containing H19 lncRNA. Mol Cancer. 2015;14:155.
92. He M, Qin H, Poon TC, Sze SC, Ding X, Co NN, Ngai SM, Chan TF, Wong N. Hepatocellular carcinoma-derived exosomes promote motility of immortalized hepatocyte through transfer of oncogenic proteins and RNAs. Carcinogenesis. 2015;36:1008–18.
93. Mao L, Li J, Chen WX, Cai YQ, Yu DD, Zhong SL, Zhao JH, Zhou JW, Tang JH. Exosomes decrease sensitivity of breast cancer cells to adriamycin by delivering microRNAs. Tumour Biol. 2016;37:5247–56.
94. Hoshino A, Costa-Silva B, Shen TL, Rodrigues G, Hashimoto A, Tesic Mark M, Molina H, Kohsaka S, et al. Tumour exosome integrins determine organotropic metastasis. Nature. 2015;527(7578):329–35.
95. Jiang K, Dong C, Yin Z, Li R, Mao J, Wang C, Zhang J, Gao Z, Liang R, Wang Q, Wang L. Exosome-derived ENO1 regulates integrin α6β4 expression and promotes hepatocellular carcinoma growth and metastasis. Cell Death Dis. 2020;11(11):972.
96. Li T, Wan Y, Su Z, Li J, Han M, Zhou C. Mesenchymal stem cell-derived exosomal microRNA-3940-5p inhibits colorectal cancer metastasis by targeting integrin α6. Dig Dis Sci. 2021;66(6):1916–27.
97. Grigoryeva ES, Savelieva OE, Popova NO, Cherdyntseva NV, Perelmuter VM. Do tumor exosome integrins alone determine organotropic metastasis? Mol Biol Rep. 2020;47(10):8145–57.
98. Li K, Chen Y, Li A, Tan C, Liu X. Exosomes play roles in sequential processes of tumor metastasis. Int J Cancer. 2019;144(7):1486–95.
99. Hoshino A, Costa-Silva B, Shen TL, Rodrigues G, Hashimoto A, Tesic Mark M, Molina H, Kohsaka S, Di Giannatale A, Ceder S, et al. Tumour exosome integrins determine organotropic metastasis. Nature. 2015;527:329–35.
100. Fong MY, Zhou W, Liu L, Alontaga AY, Chandra M, Ashby J, Chow A, O'Connor ST, Li S, Chin AR, et al. Breast-cancer-secreted miR-122 reprograms glucose metabolism in premetastatic niche to promote metastasis. Nat Cell Biol. 2015;17(2):183–94.
101. Chalmin F, Ladoire S, Mignot G, Vincent J, Bruchard M, Remy-Martin JP, Boireau W, Rouleau A, Simon B, Lanneau D, et al. Membrane-associated Hsp72 from tumor-derived exosomes mediates STAT3-dependent immunosuppressive function of mouse and human myeloid-derived suppressor cells. J Clin Invest. 2010;120(2):457–71.
102. Ning Y, Shen K, Wu Q, Sun X, Bai Y, Xie Y, Pan J, Qi C. Tumor exosomes block dendritic cells maturation to decrease the T cell immune response. Immunol Lett. 2018;199:36–43.
103. Chennakrishnaiah S, Meehan B, D'Asti E, Montermini L, Lee TH, Karatzas N, Buchanan M, Tawil N, Choi D, Divangahi M, et al. Leukocytes as a reservoir of circulating oncogenic DNA and regulatory targets of tumor-derived extracellular vesicles. J Thromb Haemost. 2018;16(9):1800–13.
104. Subramanian A, Gupta V, Sarkar S, Maity G, Banerjee S, Ghosh A, Harris L, Christenson LK, Hung W, Bansal A, et al. Exosomes in carcinogenesis: molecular palkis carry signals for the regulation of cancer progression and metastasis. J Cell Commun Signal. 2016;10(3):241–9.
105. Lugini L, Cecchetti S, Huber V, Luciani F, Macchia G, Spadaro F, Paris L, Abalsamo L, Colone M, Molinari A, et al. Immune surveillance properties of human NK cell-derived exosomes. J Immunol. 2012;189(6):2833–42.
106. Hong CS, Sharma P, Yerneni SS, Simms P, Jackson EK, Whiteside TL, Boyiadzis M. Circulating exosomes carrying an immunosuppressive cargo interfere with cellular immunotherapy in acute myeloid leukemia. Sci Rep. 2017;7(1):14684.
107. Zhu L, Kalimuthu S, Gangadaran P, Oh JM, Lee HW, Baek SH, Jeong SY, Lee SW, Lee J, Ahn BC. Exosomes derived from natural killer cells exert therapeutic effect in melanoma. Theranostics. 2017;7(10):2732–45.
108. Kibria G, Ramos EK, Wan Y, Gius DR, Liu H. Exosomes as a drug delivery system in cancer therapy: potential and challenges. Mol Pharm. 2018;15(9):3625–33.
109. Gardell JL, Parker DC. CD40L is transferred to antigen-presenting B cells during delivery of T-cell fhelp. Eur J Immunol. 2017;47(1):41–50.
110. Muntasell A, Berger AC, Roche PA. T cell-induced secretion of MHC class II-peptide complexes on B cell exosomes. EMBO J. 2007;26(19):4263–72.
111. Xie Y, Zhang H, Li W, Deng Y, Munegowda MA, Chibbar R, Qureshi M, Xiang J. Dendritic cells recruit T cell exosomes via exosomal LFA-1 leading to inhibition of CD8+ CTL responses through downregulation of peptide/MHC class I and Fas ligand-mediated cytotoxicity. J Immunol. 2010;185(9):5268–78.

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