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Tumor microenvironment information transfer mechanism and diagnosis and treatment applications based on extracellular vesicles (EVs)

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Abstract. Extracellular vesicles (EVs) serve as key mediators of cell-to-cell communication in the tumor microenvironment (TME), regulating tumor progression, immune evasion, and metastasis by delivering bioactive molecules such as nucleic acids, proteins, and metabolites. In this paper, we systematically analyze the biogenesis mechanism, microenvironment regulatory network, and clinical transformation prospect of EVs, and lay a theoretical foundation for the development of new cancer diagnosis and treatment strategies.

Keywords: Extracellular vesicles;tumor microenvironment; immune evasion; liquid biopsy; engineered EVs.

1. Introduction

The tumor microenvironment is a dynamic ecosystem composed of tumor cells, stromal cells, immune cells, and extracellular matrix, and its information transmission network determines the occurrence and development of tumors. Extracellular vesicles (EVs) play a central role in tumorigenesis, metastasis, and treatment resistance through the delivery of bioactive molecules (such as nucleic acids, proteins, and metabolites) through the delivery of bioactive molecules(Urabe et al., 2020) Its functional diversity stems from the highly heterogeneous biogenesis mechanism: EVs are mainly divided into three subtypes: exosomes, microvesicles, and apoptotic bodies, according to their origin and size differences(Gupta et al., 2021). Exosomes (30-150 nm) are released by ESCRT complexes or ceramide pathways after multivesicular body (MVB) maturation, carrying markers such as CD63/TSG101 and pro-metastasis miRNA. Microvesicles (100-1000 nm) are formed through plasma membrane budding, relying on RhoA/ROCK signaling to remodel the cytoskeleton and deliver integrin αvβ3 and other pro-cancer proteins. Apoptotic bodies (500-5000 nm) encapsulate nuclear debris and have the dual functions of immune activation and inhibition(Akers et al., 2013). However, the overlap between EV isoform separation technology and markers is still a bottleneck in current research, and new technologies such as nanoflow detection provide a new perspective for analyzing their heterogeneity.

The selective loading of EV contents is regulated by precision molecular switches: hnRNPA2B1 enables nucleic acid sorting by recognizing the GGAG motif of miRNAs, while SUMOylated hnRNPA1 mediates mRNA target loading. Four transmembrane proteins (e.g., CD63/CD81) form membrane microdomains to enrich transmembrane proteins, while ESCRT-III complexes capture ubiquitinated substrates(Colombo et al., 2013). Metabolites such as lactate are specifically enriched in the acidic microenvironment via the MCT1 transporter. These mechanisms form a cross-regulatory network that gives EVs the ability to manipulate the microenvironment. In the tumor microenvironment (TME), EVs reshape the immunosuppressive ecology through multidimensional signaling: delivery of PD-L1 to induce T cell exhaustion, synergistic TGF-β/miR-21-5p polarization of M2 macrophages, and amplification of MDSCs through the HMGB1-TLR2/4 axis to form a positive feedback loop for immune escape(Yuan et al., 2022). At the same time, EVs drive the formation of abnormal blood vessels (such as glioma VEGF/IL-8 pro-vascular leakage) and the formation of premetastatic niches (breast cancer integrin α6β4-S100A4 axis), providing "soil" for metastasis. More critically, EVs mediate chemoresistance through mechanisms such as the delivery

of P-gp pumps and anti-apoptotic miRNAs (such as miR-208b), forming a multi-level drug resistance barrier(Ren et al., 2019).

Integrin-based organ tropism provides markers for metastasis prediction, inhibition of nSMase2 to reduce exosome secretion can enhance chemosensitivity, and targeting PD-L1+ EVs or lock nucleic acid antagonistic miRNAs show therapeutic potential(Ye et al., 2023). In this paper, we systematically analyze the biogenesis mechanism, microenvironment regulatory network, and clinical transformation prospect of EVs, aiming to provide new ideas for breaking through the bottleneck of cancer treatment.

2. Biogenesis and content sorting mechanisms of EVs

2.1 Subtypes and Generation pathways of EVs

Extracellular vesicles (EVs) can be divided into three main subtypes according to their biogenesis and functional properties: exosomes, microvesicles, and apoptotic bodies, and their generation pathways and content loading mechanisms are significantly different(Marar et al., 2021). Exosomes (30-150 nm) originate from the endocytic pathway, and after the early endosomes mature through the multivesicular body (MVB) stage, endosomes form endoluminal vesicles through ESCRT complex-dependent or ceramide-mediated independent pathways and are finally released by Rab GTPase regulation and plasma membrane fusion, typical markers include CD63 and TSG101, which carry nucleic acid molecules such as miR-105 that can destroy the vascular barrier and promote tumor metastasis(Toh et al., 2018). Microvesicles (100-1000 nm) are directly budded through the plasma membrane, the RhoA/ROCK signaling pathway drives cytoskeletal remodeling, and the TMEM16F-mediated asymmetric destruction of phospholipids triggers membrane budding, and its surface integrin αvβ3 and other proteins can transmit EGFRvIII mutants to induce malignant transformation of microenvironment cells(An et al., 2018). Apoptotic bodies (500-5000 nm) are formed at the end of programmed cell death, and caspase-3-activated actomyosin contraction leads to membrane blistering, encapsulating nuclear debris and the mitochondrial debris, both by releasing tumor DNA to activate anti-immune responses and by delivering immunosuppressive factors to promote treatment resistance(Penter et al., 2023). In addition, migraines coordinate collective invasion through cell migration trajectory remnants, and mitochondria-derived vesicles may activate metastasis signals through mtDNA. At present, EVs subtype research still faces the challenges of isolation technology limitations (such as ultracentrifugation cannot distinguish exosomes from microvesicles) and marker overlap, while new technologies such as nanoflow cytometry have provided breakthroughs for the analysis of EVs heterogeneity, and therapeutic strategies targeting key nodes of secretion regulation (such as inhibiting nSMase2 and reducing exosome release) have shown anti-tumor potential(Tallon et al., 2021).

2.2 Molecular switches for selective loading of contents

The selective loading of the contents of extracellular vesicles (EVs) is a central mechanism for the precise regulation of information transfer by cells, a process that is synergistically controlled by multi-level molecular switches(Wu et al., 2022). When it comes to nucleic acid sorting, the heterogeneous ribonucleoprotein (hnRNP) family plays a key role: hnRNPA2B1 recognizes miRNAs The 3'-end conserved GGAG motif and its enrichment into EVs in a methylation-dependent manner plays a key role in the delivery of metastatic miR-1228a by breast cancer EVs, while the SUMO-modified hnRNPA1 mediates the directed loading of specific mRNAs (e.g., MET proto-oncogene mRNA) by binding to uridate-rich regions of mRNA (e.g., ARE elements), and this post-translational modification enhances the binding ability of hnRNPA1 to the multivesicular body membrane and promotes the transport of mRNA to EVs(Li et al., 2024). At the protein sorting level, tetraspanins such as CD63/CD81 recruit transmembrane proteins (such as EGFR, PD-L1) to the membrane surface of EVs by forming dynamic membrane microdomains (TEMs), for example, the colocalization of CD63 and LAMP1 in melanoma EVs can promote the targeted loading of lysosomal proteins(Shapiro

et al., 2007); The ESCRT-III complex, on the other hand, recognizes ubiquitinated-modified substrates (e.g., Syntenin) through the Bro1 domain of the ALIX protein, drives intraluminal vesicle formation and captures cytoplasmic proteins (e.g., Wnt3a), a mechanism that is critical in colon cancer EVs-mediated Wnt signaling(Su et al., 2020). For example, in acidic TME, the lactate transporter MCT1 actively pumps lactate into EVs through proton gradients, so that the concentration of lactate in EVs reaches more than 5 times that of the cytoplasm, and these lactates can be taken up by recipient tumor-associated macrophages and promote angiogenesis by inhibiting HIF-1α degradation(Sato & Takeda, 2023). It is worth noting that these sorting mechanisms often have cross-regulation, such as the SUMO of hnRNPA2B1 can enhance its interaction with the ESCRT component STAM1 to form a nucleic acid-protein loading complex, and this multi-level regulatory network ensures the functional synergy of EVs contents, making it a sophisticated molecular tool for tumor cells to manipulate the microenvironment(Lim et al., 2011).

3. EVs-mediated tumor microenvironment regulation network

3.1 Establishment of immunosuppressive TME

Tumor-derived extracellular vesicles (TDEs) regulate immune cell function through multi-dimensional regulation, driving the formation of an immunosuppressive tumor microenvironment (TME)(Morrissey et al., 2021). First, the PD-L1 molecules carried on the surface of TDEs can be captured by tumor-infiltrated antigen-presenting cells (APCs), cross-presented to the surface of CD8+ T cells through MHC-I, and continuously activate their PD-1 receptors, resulting in upregulation of T cell depletion markers (such as TIM-3, LAG-3) and reduced secretion of effector factors (IFN-γ, Granzyme B). This mechanism has been confirmed to inhibit anti-PD-1 therapeutic effect in serum EVs in patients with metastatic breast cancer(Cela et al., 2025). Secondly, TDEs reshape the macrophage phenotype through content synergistic action: the TGF-β it carries induces STAT6 activation through Smad3 phosphorylation, while miR-21-5p enhances arginase-1 (Arg1) expression by targeting the PTEN/Akt pathway, and dual signaling promotes macrophages to polarize to M2 type, promoting IL-10 and VEGF secretion in liver cancer tissues(Zhang et al., 2024). In addition, as a damage-related molecular model (DAMP), the high-mobility group protein B1 (HMGB1) in pancreatic cancer EVs activates myeloid inhibitory cells (MDSCs) through the TLR2/4-MyD88-NF-κB signaling axis, inducing their large amplification and secreting ROS and ARG1, resulting in inhibition of T cell proliferation. Preclinical studies have shown that knocking out HMGB1 can increase the sensitivity of gemcitabine chemotherapy by 3.1 times(Zhang et al., 2017). These mechanisms form a cascade network: IL-6 secreted by MDSCs further promotes the release of PD-L1+ EVs in tumor cells, while CCL22 produced by M2 macrophages recruits Treg cells to jointly build a positive feedback loop for immunosuppression(Cho et al., 2019).

3.2 Angiogenesis

Tumor-derived extracellular vesicles (EVs) synergistically promote angiogenesis and metastasis formation through space-time differentiated regulatory mechanisms, creating a favorable microenvironment for tumor progression. During the local invasion stage, glioblastoma EVs deliver vascular endothelial growth factor (VEGF) and interleukin-8 (IL-8) to brain microvascular endothelial cells through the paracrine pathway: VEGF activates the VEGFR2-PI3K/Akt pathway, induces endothelial cells to proliferate and form immature blood vessels; while IL-8 enhances MMP-9 secretion through CXCR1/2 receptors, degrades the basement membrane and promotes vascular leakage(Zhao et al., 2010). This abnormal vascularization not only accelerates tumor growth but also creates conditions for extravasation of circulating tumor cells. During the systematic metastasis stage, breast cancer EVs surface integrin α6β4, as the "molecular postal code", specifically recognizes laminin in the extracellular matrix of lung tissue, prompting selective uptake of EVs by lung fibroblasts. TGF-β and Wnt5a carried in EVs upregulate S100A4 expression through the Smad2/3 and JNK signaling pathways, which induced the release of proinflammatory factors (such as IL-6,

TNF-α) by activating the NF-κB pathway, remodeling lung tissues to form a pre-metastatic niche rich in fibronectin and osteopontin(Peng et al., 2020). It is worth noting that this organ tropism is integrin specific: EVs expressing integrin αvβ5 tend to target the liver, while the α6β4/α6β1 combination determines the tendency of lung metastasis, which provides a biomarker for predicting metastasis sites(Hoshino et al., 2015). Preclinical models show that knocking down EVs integrin α6 can reduce lung metastasis in breast cancer by 73% while inhibiting S100A4 can block the formation of vascular leakage points in metastatic niches. These findings reveal the central role of EVs-mediated bioinformatic transmission in tumor metastasis cascades(Kanniyappan et al., 2024).

3.3 The delivery of chemotherapy resistance

Tumor-derived extracellular vesicles (EVs) deliver chemotherapy resistance properties through multiple mechanisms, significantly weakening the anti-tumor treatment effect. At the level of drug efflux mechanism, ovarian cancer EVs directly transfer P-glycoprotein (P-gp) to the surface of the membrane membrane of sensitive tumors through membrane fusion(De Rubis & Bebawy, 2021). The transmembrane pump uses ATP hydrolysis energy to actively expel paclitaxel and other drugs from the cell. Experiments show that the intracellular paclitaxel concentration of cells receiving drug-resistant EVs has decreased by 62%, and the IC50 value has increased by 8.3 times. At the apoptosis regulation level, miR-208b enriched in colorectal cancer EVs inhibits its translation and blocks mitochondrial apoptosis pathway by targeting the 3'UTR region of apoptotic protease activator 1 (APAF1) mRNA, resulting in a 75% reduction in the activation rate of caspase-9 induced by oxaliplatin(Luo et al., 2020). It is worth noting that there is a synergistic effect between these two mechanisms: breast cancer EVs simultaneously transmit ABCB1 mRNA (encoding P-gp) and anti-apoptotic miR-221, reducing drug accumulation through efflux pumps while inhibiting Bim protein expression, forming a dual drug resistance barrier(Zaki et al., 2022). Clinical cohort analysis showed that the elevated miR-208b level in serum EVs before chemotherapy in colorectal cancer patients was significantly correlated with low APAF1 expression ($r=-0.81$, $p<0.001$) and shortened progression-free survival (HR=3.2), suggesting its potential as a predictive marker of drug resistance(Yong et al., 2014). Targeted intervention strategies such as GW4869 inhibition of EVs secretion can restore the sensitivity of ovarian cancer PDX models to paclitaxel by 4.1 times while locking nucleic acid (LNA) antagonism of miR-208b can reverse oxaliplatin resistance in colorectal cancer organoids(Ning et al., 2021).

3.4 Coordination of metabolic reprogramming

The latest research shows that tumor EVs reshape the energy metabolism network of microenvironment cells by transmitting metabolic enzymes and metabolic intermediates(Covarrubias et al., 2021). For example, pancreatic ductal adenocarcinoma (PDAC) EVs carry glutamine synthase (GLS), which activates the mTORC1 pathway of receptor astrocytes, prompting them to secrete alanine to supplement the TCA cycle of tumor cells, forming a "metabolic symbiosis". In addition, succinic acid enriched in EVs stabilizes hypoxia signaling pathways by inhibiting the PHD enzyme activity of HIF-1α, promoting glycolytic conversion of endothelial cells in the renal cancer microenvironment, leading to abnormal vascular hyperplasia(Vetrovoy & Rybnikova, 2019). This metabolic regulation is intersected with epigenetic modification: α-ketoglutarate (α-KG) delivered by EVs enhances TET-mediated DNA demethylation, activates profibrotic genes (such as COL1A1) in mesenchymal stem cells, and provides matrix support for transfer(Aoki et al., 2024).

4. Application of EVs in cancer diagnosis and treatment

4.1 Liquid biopsy and early diagnosis

Extracellular vesicles (EVs) have become a promising non-invasive diagnostic tool in the field of liquid biopsy due to their ability to carry tumor-specific molecular fingerprints. Compared with the traditional single marker detection, the multi-component combined analysis of EV significantly

improves the diagnostic performance: in prostate cancer, the combined detection of PCA3 long non-coding RNA, PSA protein and transmembrane protein TMEM256 in EV can increase the diagnostic AUC value to 0.93, effectively distinguishing high-risk patients with Gleason score ≥7(Sandúa et al., 2023); Stage II patients are distinguished from chronic pancreatitis with a sensitivity of 100% and a specificity of 80% (Melo et al., 2015), and the mechanism is related to the abnormal glycosylation modification of tumor cells. In terms of technological innovation, microfluidic chip technologies (such as ExoSIC) can capture > from 100 μL of plasma in less than 30 minutes through size exclusion and immunoaffinity bimodal enrichment 90% of EVs while removing 99.7% of plasma protein interferences(Yin et al., 2023); The aptamer-EV catch uses the three-dimensional structure of aptamers to specifically identify targets such as PD-L1/EGFR on the surface of EVs membranes, and combines with the CRISPR-Cas12a signal amplification system to achieve a detection sensitivity of 10 EV/μL, which is 1000 times higher than that of traditional ELISA(Hu et al., 2022). These technological breakthroughs not only enable the accurate analysis of the molecular characteristics of EV subsets but also promote the transformation of circulating tumor EV detection from scientific research to clinical practice

4.2 Targeted therapies for engineered EVs

Extracellular vesicles (EVs) have become a new generation of smart drug delivery vehicles due to their natural biocompatibility, low immunogenicity, and ability to cross biological barriers. In terms of chemotherapy drug loading, electroporation can increase the paclitaxel encapsulation efficiency to 68% by changing the membrane permeability of EVs by instantaneous electric field, and the EV delivery system can increase the intratumoral drug concentration of TCM in the triple negative breast cancer model by 4.2 times compared with the free drug, and significantly reduce the cytotoxicity to normal tissues(Luo et al., 2021). For gene therapy, engineered iExosomes can specifically silence the KRAS mutant gene in pancreatic cancer by loading siKRASG12D, and its surface CD47 protein evades immune clearance by binding to SIRPα, and preclinical studies have shown that a single injection can reduce tumor KRAS protein levels by 82% and prolong survival by 2.3 times(Drosten & Barbacid, 2020). In order to improve targeting, EVs surface engineering modification technology has developed rapidly: GE11 peptide is targeted on the EV membrane through plasma membrane anchoring technology (such as Lactadherin C1C2 domain), which increases the EVs accumulation rate of EGFR-high expressing tumors by 7.5 times, while pH-sensitive liposomal membrane (such as DOPE/CHEMS)-modified EV can trigger membrane fusion in the acidic tumor microenvironment (pH 6.5) and achieve controlled spatiotemporal release of doxorubicin (91% release rate within 72 hours), combined with photothermal therapy, increased the tumor inhibition rate of melanoma to 89%(Moreira et al., 2023).

4.3 Immunotherapy synergistic strategies

The engineering of EVs provides a new idea for breaking through the resistance of immune checkpoint inhibitors: bispecific antibody modification of EVs: anchoring anti-CD3/PD-L1 bispecific antibodies to the surface of the EVs membrane can simultaneously activate T cells and block the PD-1/PD-L1 axis(Graham et al., 2023). In melanoma models, this strategy resulted in a 5-fold increase in the number of tumor-infiltrating lymphocytes (TILs) and a complete response rate of 40%. STING agonist delivery, such as EVs encapsulating cGAMP and modifying the tumor-targeting peptide iRGD, can specifically activate the STING pathway in antigen-presenting cells and induce the release of type I interferon(Li & Chen, 2018). The combination of anti-CTLA-4 therapy increased the immune response rate from 12% to 65% in cold tumor models such as pancreatic cancer. The oncolytic virus-EVs hybrid system encapsulates the oncolytic virus in EVs and uses the EVs membrane to protect the virus from serum-neutralizing antibody clearance(Lukacher et al., 2025). Preclinical data showed that EVs-OV therapy increased viral replication efficiency by 8-fold in glioma and significantly reduced systemic inflammatory response(Tan et al., 2023).

5. Conclusion

As the core medium of tumor microenvironment information transmission, the dual role of EVs (disease drivers versus treatment carriers) provides a new perspective for cancer diagnosis and treatment. EVs play a key role in tumor immune evasion, angiogenesis, premetastatic niche formation, and chemoresistance through their heterogeneous biogenesis and content sorting networks. EVs-based liquid biopsy technologies (e.g., multi-marker co-detection, microfluidic chip enrichment) and engineered drug delivery systems (e.g., siRNA loading, pH-sensitive modifications) have shown significant clinical translation potential, providing a new strategy for early diagnosis and precision treatment of tumors. EVs-based diagnosis and treatment strategies are accelerating clinical translation: in the field of diagnosis, multi-marker combination detection (such as Glypican-1+CD63+EVs for early diagnosis of pancreatic cancer) combined with microfluidic chip/nanoflow cytometry technology has made the detection sensitivity reach the level of single EVs; In terms of treatment, engineered EVs are enhanced by surface modification (e.g., GE11 peptide-targeted EGFR) and intelligent drug delivery (pH-sensitive liposomal controlled-release doxorubicin), while bispecific antibody-modified EVs (anti-CD3/PD-L1) and oncolytic virus-EVs hybrid systems significantly enhance the immunotherapy effect. Future research needs to break through the bottlenecks of multi-omics analysis of single EVs and metabolic-epigenetic cross-regulation analysis, and promote AI-driven EVs fingerprint prediction and drug delivery system optimization. The dual role of EVs (disease drivers and treatment vectors) provides a new paradigm for precision medicine in oncology, and its clinical translation is expected to reshape the cancer diagnosis and treatment landscape in the next 5-10 years.

However, there are still many challenges in EVs research: the limitations of EVs isoform isolation technology, such as the inability of ultracentrifugation to distinguish exosomes from microvesicles and marker overlap, which restricts the accurate analysis of their functional heterogeneity; The spatiotemporal dynamic regulatory network of the sorting mechanism of EVs content has not been fully elucidated, for example, the synergistic mechanism between the post-translational modification of the hnRNP family and the ESCRT complex still needs to be further explored. The large-scale production, targeting efficiency, and in vivo safety of engineered EVs still need to be optimized, for example, the controlled release kinetics of pH-sensitive drug delivery systems may be affected by TME heterogeneity. Future research needs to focus on the following directions: 1) the development of multi-omics analysis techniques at the level of single EVs (such as nano-flow cytometry combined with Raman spectroscopy) to achieve precise correlation between the molecular characteristics of EVs subsets and functional phenotypes; 2) to analyze the interaction mechanism between tumor metabolic reprogramming (e.g., lactate enrichment) and EVs content loading, and reveal the metabolic-epigenetic cross-regulatory network.

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