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Regulatory Mechanisms and Clinical Value of the Exosome-TAM Signaling Axis in the Tumor Microenvironment

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Abstract. Tumor-associated macrophages (TAMs) are key immune cells within the tumor microenvironment. Their M2-type immunosuppressive phenotype can markedly facilitate tumor progression and metastasis. As vital carriers for cell-to-cell communication in the tumor microenvironment, exosomes carry diverse bioactive substances, mediate macrophage polarization and metabolic reprogramming, and further drive tumor immune escape and therapeutic resistance. This paper systematically reviews the regulatory mechanisms of exosomes on TAMs and the functions of TAM-derived exosomes, so as to clarify the regulatory mechanisms of tumor immunity and provide theoretical evidence for exosome-based tumor diagnosis and targeted immunotherapy.

Keywords: tumor microenvironment, macrophage, exosome, immune regulation

1. Introduction

The tumor microenvironment represents a complex immune ecosystem that governs tumor initiation, progression and therapeutic response. Dynamic interactions between the immune system and tumor cells constitute the core factor influencing disease progression. Tumor-associated macrophages (TAMs) constitute the major immune cell population in this microenvironment. Most TAMs exhibit an M2-type immunosuppressive phenotype and substantially contribute to tumor growth and metastasis via secreting anti-inflammatory cytokines, promoting angiogenesis, and remodelling the extracellular matrix. Given the pivotal role of TAMs in tumor progression, exploring the molecular mechanisms underlying their reprogramming and exploiting their value for targeted therapy have become research hotspots in the field of tumor immunology.

Existing studies have confirmed that exosomes, a subset of extracellular vesicles, serve as core carriers for signal communication between tumor cells and stromal cells such as macrophages [1]. Generated through exocytosis of intracellular multivesicular bodies, exosomes encapsulate multiple bioactive substances including proteins, lipids and nucleic acids within their lipid bilayer structure. They can cross biological barriers and precisely modulate the functions of recipient cells. Various cell types in the tumor microenvironment secrete large quantities of exosomes, forming an extensive cellular signal-transduction network.

Cumulative evidence indicates that exosome-mediated signal transmission acts as a critical mechanism triggering M2-type macrophage polarization, metabolic reprogramming and tumor therapeutic resistance. Tumor-cell-derived exosomes educate macrophages and convert them into

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tumor-promoting cells. In-depth analysis of the molecular mechanisms by which exosomes regulate the origin, phenotype and function of TAMs can not only illuminate the mechanisms of tumor immune escape, but also offer new insights for the clinical translation of exosome-based liquid biopsy and targeted therapy. This paper reviews the functional mechanisms of exosomes, their regulatory effects on TAMs, and the functions of TAM-derived exosomes.

2. Molecular mechanisms of exosomes

Exosomes are a subtype of extracellular vesicles with a diameter of approximately 30-150 nm and a lipid bilayer structure. Distinct from microvesicles that bud directly from the cell membrane, exosomes originate through the endosomal pathway: cell-membrane invagination forms early endosomes. Subsequent inward budding of the endosomal membrane generates intraluminal vesicles (ILVs), which further mature into multivesicular bodies (MVBs). When MVBs fuse with the plasma membrane, internal ILVs are released into the extracellular space as exosomes. Far from being simple membranous vacuoles, exosomes highly selectively enrich diverse bioactive substances derived from parent cells. They are loaded with abundant nucleic acids (e.g., miRNA, mRNA, lncRNA), proteins (including signalling molecules and transcription factors), and specific lipids. Their membrane surface characteristically expresses tetraspanins such as CD9, CD63 and CD81. As critical mediators of intercellular communication, exosomes carry and deliver these functional "cargoes" to profoundly interfere with signalling networks and epigenetic states of recipient cells. They exert essential roles in physiological and pathological processes including immune regulation, tissue repair, and tumour initiation and progression.

Cargo loading, targeted uptake, signal transduction and epigenetic modulation of exosomes are tightly regulated processes rather than random events. For cargo sorting, exosomes exhibit specificity for nucleic acid and protein packaging. RNA sorting relies on RNA-binding proteins. SUMO-modified hnRNPA2B1 recognizes EXOmotif sequences on RNAs and mediates RNA sorting into intraluminal vesicles. The Ago2-miRNA complex is also specifically enriched within exosomes [2]. Protein sorting proceeds via ESCRT-dependent and ESCRT-independent pathways. The ESCRT-dependent pathway employs ESCRT complexes to recognize ubiquitinated proteins and facilitate membrane budding. The ESCRT-independent pathway is mediated by ceramides as well as membrane proteins including CD9 and CD63.

Exosomes achieve precise recognition and uptake by recipient cells via surface molecules. Surface integrins determine organotropism. Integrins α6β1/α6β4 and αvβ5 direct exosomes toward lung and liver tissues respectively. Meanwhile, specific glycosylation modifications on exosome surfaces can be recognized by C-type lectin receptors on immune cells to facilitate cellular uptake.

Upon binding to recipient cells, exosomes trigger multiple signalling cascades. Surface ligands including FasL and TRAIL activate extrinsic apoptotic pathways in target cells and contribute to tumour immune escape [3]. Mutant EGFRvIII carried by glioma-derived exosomes activates proliferative MAPK/ERK and PI3K/AKT pathways [4]. In addition, bioactive molecules such as internalized PKM2 and activated STAT3 delivered by exosomes reprogram recipient-cell metabolism and modulate gene transcription. Exosomes also mediate sustained epigenetic remodelling. Delivered miRNAs degrade target mRNAs and repress gene translation. For instance, miR-21 activates pro-survival pathways by down-regulating PTEN. LncRNAs and circRNAs modulate gene expression and induce tumour drug resistance by competitively sponging miRNAs. Moreover, exosomes deliver epigenetic modifying enzymes such as EZH2 and DNMT1 to alter chromatin modification profiles in recipient cells, silence tumour-suppressor genes, and persistently reshape cellular phenotypes and functions.

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3. Effects of exosomes on macrophages in the tumour microenvironment

To evade immune surveillance and build a microenvironment favourable for growth, tumour cells actively secrete exosomes. These exosomes carry specific cargoes (mainly non-coding RNAs and proteins). After being internalized by macrophages, they remodel macrophage gene-expression profiles by suppressing pro-inflammatory signalling pathways and activating anti-inflammatory cascades, driving macrophage transition from the anti-tumour M1 phenotype to the pro-tumour M2 phenotype.

3.1. Exosome-induced M1 polarization

Exosomes derived from immune cells or tumour-cell exosomes generated after drug or radiotherapy transmit "danger signals" or pro-inflammatory stimuli to macrophages. By activating pattern-recognition receptors (PRRs) or interferon signalling pathways, these exosomes trigger NF-κB or IRF-dependent signal transduction, induce pro-inflammatory cytokine secretion and co-stimulatory-molecule expression in macrophages, and restore their tumour-killing capacity. When the NF-κB pathway is activated, exosomes released by dendritic cells (DCs) or tumour cells undergoing immunogenic cell death (ICD) are enriched with surface HSP70/HSP90 or carry unmethylated CpG DNA (DNA sequences containing unmethylated cytosine-guanine dinucleotides, potent immune stimulants). These molecules bind to surface TLR4 or endosomal TLR9 on macrophages and activate the MyD88/TRAF6 signalling cascade, releasing NF-κB (p65/p50). Nuclear translocation of p65 initiates transcription of canonical M1-associated genes such as *TNF-α*, *IL-1β*, *IL-6* and *iNOS* [5]. Exosomes originating from natural killer (NK) cells may carry interferon-γ (IFN-γ) or nucleic acids that trigger endogenous IFN-β production, leading to activation of interferon regulatory factor (IRF) pathways. IFN-γ binds to IFNGR on macrophages and activates the JAK1/JAK2-STAT1 pathway. Subsequent nuclear translocation of STAT1 dimers cooperates with IRF family factors, constituting one of the core pathways driving M1 polarization. STAT1 directly represses the expression of M2-related genes [6].

Within the native tumour microenvironment, certain miRNAs (e.g., miR-34a, let-7b) reside in the macrophage cytoplasm. They specifically bind to mRNAs of M1-associated genes (e.g., *TNF-α*, *IL-6*, *Notch1*), block pro-inflammatory-factor synthesis, and suppress M1 polarization. Certain therapeutic exosomes are enriched with specific lncRNAs (e.g., lncRNA-COX2) or circRNAs. These lncRNAs or circRNAs possess base sequences highly complementary to miR-34a or let-7b and function as competing endogenous RNAs. They form non-functional RNA-RNA complexes with these miRNAs, de-repressing target genes and permitting normal translation of Notch1 protein. As a key transcriptional regulator, Notch1 translocates into the nucleus and initiates downstream transcription of M1-type genes including *IL-12* and *iNOS*, thereby relieving the inhibition of macrophage M1 polarization [7, 8].

3.2. Exosome-induced M2 polarization

To evade immune surveillance and establish a microenvironment conducive to its growth, tumour cells actively secrete exosomes. Carrying specific cargoes (predominantly non-coding RNAs and proteins), these exosomes are internalized by macrophages. They remodel the gene-expression profile of macrophages by suppressing pro-inflammatory signalling pathways and activating anti-inflammatory pathways, driving macrophage conversion from the anti-tumour M1 phenotype to the pro-tumour M2 phenotype.

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In normal macrophages, the JAK/STAT3 pathway is tightly controlled. Suppressor of cytokine signalling 3 (SOCS3), an intracellular inhibitor of cytokine signal transduction, negatively regulates the JAK/STAT3 pathway and is frequently targeted and suppressed by miRNAs contained within tumour-derived exosomes. Upon JAK/STAT pathway activation, the *SOCS3* gene is induced for expression. The resulting SOCS3 protein binds to JAK kinases or their receptors in a negative-feedback loop and deactivates them. This ensures that inflammatory responses remain transient and controllable [9]. Exosomes secreted by tumour cells (e.g., hepatocellular carcinoma and breast cancer cells) carry abundant specific miRNAs such as miR-21-5p or miR-222-3p. Released miRNAs assemble with the intracellular RNA-induced silencing complex (RISC) to form specialised complexes. These complexes scan the cytoplasm for mRNAs with complementary sequences. MiR-21-5p shares high sequence complementarity with the 3'-UTR region of *SOCS3* mRNA. After binding, the RISC complex directly cleaves and degrades *SOCS3* mRNA. Even without cleavage, RISC sterically blocks ribosomes and prevents SOCS3 protein synthesis. Consequently, intracellular SOCS3 protein levels drop sharply. Freed from negative-feedback restraint, the JAK/STAT3 pathway becomes hyperactivated. JAK2 undergoes extensive autophosphorylation and achieves high activity. Activated JAK2 rapidly phosphorylates STAT3 protein. Phosphorylated STAT3 (p-STAT3) forms dimers and translocates in large quantities into the nucleus. Nuclear p-STAT3 binds to promoter regions of target genes and initiates transcription of a panel of M2 signature genes, yielding mediators including Arg-1 (arginase-1), IL-10 (interleukin-10), TGF-β (transforming growth factor-β), and VEGF (vascular endothelial growth factor) to promote M2 polarization.

Phosphatase and Tensin Homolog (PTEN) is one of the most critical intracellular tumour-suppressor genes. It catalyses the conversion of PIP3 (phosphatidylinositol (3,4,5)-trisphosphate) into PIP2. After tumour-derived exosomes enter macrophages, they release miR-130a or miR-214. These miRNAs precisely recognize and bind specific sites within the 3'-UTR of *PTEN* mRNA. Following complex formation, the miRNAs repress *PTEN* mRNA translation or trigger its degradation, markedly lowering intracellular PTEN protein abundance and causing massive PIP3 accumulation on the plasma membrane. Accumulated PIP3 acts like a magnet and recruits cytosolic Akt (protein kinase B) to the inner leaflet of the cell membrane. At the membrane, Akt is phosphorylated by PDK1 and mTORC2 to produce p-Akt. Activated Akt functions as a multifunctional master regulator. Its activation triggers three outcomes vital for M2 polarization. First, it inhibits the metabolism of pro-apoptotic proteins such as Bad and Caspase-9. This enables M2 macrophages to survive long-term within the hostile tumour microenvironment that would normally kill inflammatory cells, explaining the high TAM density and poor elimination of TAMs in tumours. Second, Akt directly activates downstream mTORC1 (mammalian target of rapamycin complex 1). M1 macrophages rely mainly on glycolysis, a rapid yet low-efficiency energy-producing pathway. Cooperatively, mTORC1 and Akt boost mitochondrial biogenesis and drive fatty-acid oxidation, shifting macrophage metabolism toward oxidative phosphorylation, an efficient metabolic mode suited for sustained tissue repair and pro-tumour functions. Third, the Akt/mTOR pathway stimulates transcription factors such as CREB or represses pro-inflammatory NF-κB subunits. It enhances IL-10 and TGF-β secretion while suppressing IL-12 production, further stabilising the immunosuppressive M2 phenotype [10].

Furthermore, tumour-cell-derived exosomes may carry damage-associated molecular patterns (DAMPs). These DAMPs bind pattern-recognition receptors TLR2 or TLR4 on macrophage surfaces. Macrophages interpret this receptor engagement as severe tissue injury and launch tissue-repair programmes, the core functional programme of M2 macrophages. Under physiological

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conditions, TLR4 activation triggers rapid NF-κB nuclear translocation and robust pro-inflammatory responses. Within the tumour microenvironment, however, signalling is hijacked toward two alternative cascades. The first is MyD88-dependent STAT3 activation. Upon TLR2/TLR4 stimulation, intracellular receptor domains recruit the adaptor protein MyD88. MyD88 further recruits IRAK kinase family members (IRAK1, IRAK4) and TRAF6. Within the tumour microenvironment, typically under persistent IL-6 or IL-10 background stimulation, this molecular complex does not exclusively activate the canonical IKK/NF-κB pathway. Instead, through intermediate steps possibly involving Src-kinase or JAK-family crosstalk, it directly triggers JAK2/STAT3 signalling. As described above, phosphorylated STAT3 dimers translocate into the nucleus, activate target genes, and initiate transcription of multiple M2-signature genes [11]. The second cascade constitutes an IL-6 autocrine loop. TLR activation does induce partial NF-κB activity, which predominantly drives transcription of the *IL-6* gene. Secreted IL-6 binds to IL-6 receptors (IL-6R/gp130) on the macrophage itself. Receptor ligation strongly activates JAK1/JAK2 and induces extensive STAT3 phosphorylation. This establishes a positive-feedback loop: TLR → IL-6 → STAT3 → additional IL-6. Sustained nuclear STAT3 functions as a transcription factor to drive *IL-10* and *TGF-β* transcription. These cytokines in turn suppress NF-κB activity and shut down pro-inflammatory signalling. They also up-regulate anti-apoptotic *Bcl-xL*, pro-angiogenic *VEGF*, and previously mentioned genes such as *Arg-1*. Macrophages cease to behave as aggressive sentinel-like M1 cells and transform into repair-oriented cleaner-like M2 cells. In the tumour context, such "repair" manifests as repairing damaged tumour blood vessels, clearing necrotic tissue to create space for tumour expansion, and suppressing T-cell-mediated anti-tumour responses, collectively exerting pro-tumour effects [12].

Conventional wisdom holds that metabolic enzymes reside exclusively inside cells. Nevertheless, studies demonstrate that tumour-derived exosomes can encapsulate intact, catalytically-active proteins either on their membrane surface or within their lumen. Exosomes rich in ARG1 are secreted by tumour cells including renal-cell carcinoma and hepatocellular carcinoma cells. Upon uptake of these exosomes, TAMs acquire high-activity ARG1 directly without requiring endogenous gene induction. ARG1 rapidly consumes L-arginine within the microenvironment. Arginine depletion down-regulates T-cell receptor (TCR) chain expression and arrests T-cells in the G0 phase, mediating immune escape. Accumulated arginine metabolites (polyamines, putrescine) directly promote macrophage reprogramming toward the tissue-repair M2 phenotype [13, 14]. Moreover, tumour cells predominantly adopt aerobic glycolysis (the Warburg effect), leading to excess lipid biosynthesis and impaired oxidative capacity. Tumour-derived exosomes are enriched with fatty-acid-binding proteins such as FABP4, FABP5, or free fatty acids. Lipids delivered by exosomes enter macrophages via CD36-mediated uptake and are trafficked to mitochondria. Elevated intracellular lipid levels activate nuclear receptors PPARδ and PPARγ. Macrophages, especially M2 macrophages, rely on fatty-acid oxidation (FAO) for energy. These receptors serve as master regulators of M2 polarization: they not only up-regulate FAO-related genes but also directly repress transcription of inflammatory genes [15]. These findings illustrate how tumour cells use exosomes to disrupt intrinsic macrophage metabolic homeostasis and reprogram macrophages into the M2 phenotype adapted to the hypoxic, acidic tumour microenvironment that supplies tumour-supporting metabolites.

Exosome-mediated macrophage regulation is not a unidirectional linear process but a dynamic network involving multiple activated pathways modulated by microenvironmental cues. M1 and M2 polarization represent opposite ends of a continuous spectrum, and exosomal cargo composition determines the phenotypic tilt. M1 polarization is chiefly driven by activation of STAT1, NF-κB

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(p65), IRF5 and AP-1, whereas M2 polarization depends primarily on STAT3, STAT6, PPARγ and KLF4. Exosomes deliver distinct signalling molecules to dictate which set of transcription factors dominates cellular function. For instance, tumour-exosome-borne IL-4/IL-13 signals activate STAT6 and inhibit NF-κB activity. By contrast, immune-cell-derived exosomes deliver IFN-γ to activate STAT1 and antagonise STAT6 function. Furthermore, exosome bioactivity is constrained by the physicochemical properties of the tumour microenvironment (TME). Hypoxia-conditioned tumour-cell-secreted exosomes (hypoxic exosomes) are enriched with miR-210 and HIF-1α protein and exhibit stronger M2-inducing potency than normoxic exosomes. Acidic microenvironments enhance macrophage exosome uptake and favour M2 phenotypic induction. Distinct feedback loops produce divergent cancer-related outcomes for M1- versus M2-associated macrophage programmes. M2-associated signalling establishes a pro-tumour positive-feedback cycle: tumour → M2-inducing exosomes → M2 macrophages → VEGF/EGF secretion → enhanced tumour proliferation → further exosome production. This vicious cycle contributes to therapeutic resistance in tumours. In contrast, anti-cancer responses follow the pathway: immunotherapy → T-cell activation → T-cell-derived exosomes stimulate macrophages → M1 macrophages secrete IL-12 → further T-cell activation.

3.3. Exosomes inhibit macrophage drug sensitivity

Acting as mobile "drug-resistance units", tumour cells can transmit drug-resistant phenotypes outward via exosomes, spreading resistance from drug-resistant tumour cells to stromal cells. Exosomes secreted by chemotherapy-resistant tumour cells (e.g., paclitaxel- or doxorubicin-resistant cells) highly express P-glycoprotein (P-gp/ABCB1) on their membrane. After sensitive macrophages internalize these exosomes, functional P-gp proteins integrate into the macrophage plasma membrane. When macrophages infiltrate peritumoural blood vessels or stroma, these "P-gp-armed" macrophages actively pump diffused chemotherapeutic agents out of the tumour parenchyma, substantially lowering drug exposure of tumour cells [16]. In addition, exosomes derived from drug-resistant cells carry specific miRNAs (e.g., miR-100, miR-222) that target and suppress mTOR or p53 signalling in macrophages. Consequently, macrophages no longer support chemotherapy; instead, they secrete IL-10- and TGF-β-rich exosomes that act back on tumour cells, activate tumour-cell survival pathways STAT3 and ERK, and counteract apoptosis signals triggered by chemotherapeutic agents [17]. This mechanism indicates that tumour cells not only develop intrinsic drug resistance but also "educate" neighbouring cells to acquire stronger defensive capacity. Beyond signal transmission, exosomes serve as a non-canonical secretory pathway and participate in the cellular "waste-disposal" duet. Under chemotherapy-induced cellular stress, macrophages fail to exert cytotoxic functions and instead expel drugs through the exosome pathway [16]. Specifically, macrophages that have phagocytosed nano-drugs or doxorubicin secrete intact drug-loaded exosomes to the extracellular space via Rab27a-mediated exocytosis. This "sponge effect" drastically reduces local drug bioavailability within tumours. Furthermore, when degradative pathways such as autophagy are impaired, cells activate exosome secretion as a compensatory mechanism to expel damaged mitochondria or oncogenic metabolites [18]. Although such "detoxification" supports parental-cell survival, large quantities of damage-associated molecular pattern (DAMP)-containing exosomes are released into the microenvironment, further aggravating the formation of an immunosuppressive niche.

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4. Clinical translation

Traditional tissue biopsy suffers from high invasiveness and limited repeated sampling, and often fails to fully reflect dynamic changes within the tumour immune microenvironment (TME). By contrast, liquid biopsy analyses circulating biomarkers in body fluids and enables real-time, non-invasive disease monitoring. In recent years, TAM-derived exosomes, which carry abundant molecular signatures of their parent cells, have emerged as highly promising diagnostic tools. Studies show that elevated levels of specific membrane proteins (e.g., CD163, CD206) or cargo molecules (e.g., miR-21, PD-L1) in TAM-derived exosomes correlate significantly with tumour burden, malignancy and poor patient prognosis. More importantly, longitudinal monitoring of circulating TAM-exosome concentrations in plasma before and after treatment allows clinicians to evaluate responses to immunotherapy or chemotherapy earlier than imaging examinations, providing precise evidence for individualized subsequent therapeutic regimens. In addition, profound mechanistic understanding of exosome-mediated TAM reprogramming has fuelled the development of engineered-exosome therapeutic strategies. Compared with conventional nanocarriers, exosomes possess intrinsic biocompatibility and the capacity to cross physiological barriers. To overcome TAM-mediated drug resistance and immune suppression, researchers have designed "precision-guided" engineered exosomes. For instance, donor cells can be genetically modified to overexpress macrophage-targeting peptides such as M2pep, or exosomes can be loaded with *SOCS3*-targeting or *PTEN*-targeting siRNA by electroporation. These engineered exosomes preferentially accumulate in tumour tissue and are internalized by TAMs. Once inside recipient cells, their therapeutic cargo blocks the JAK/STAT3 or PI3K/Akt pathways and reprograms pro-tumour M2 macrophages into tumour-killing M1 macrophages. Moreover, exosomes loaded with CSF1R inhibitors or chemotherapeutic agents such as paclitaxel can effectively eliminate TAMs or abrogate their survival signals, thereby markedly suppressing tumour growth and metastasis [19, 20]. Furthermore, exosomes exhibit unique advantages as drug-delivery systems. Their lipid-bilayer shell effectively protects encapsulated nucleic-acid drugs or small-molecule therapeutics from nuclease degradation in body fluids, and surface modification achieves targeted delivery. Particularly for solid-tumour "depolarization" therapy, stem-cell-derived or immune-cell-derived exosomes can evade non-specific clearance by the mononuclear phagocyte system (MPS). This strategy improves target-site drug bioavailability and greatly reduces off-target toxicity toward normal tissues [21].

5. Discussion

Despite abundant achievements of exosomes in basic-science research, their clinical translation still faces severe technical challenges, among which the standardization of isolation and purification techniques ranks first. Ultracentrifugation remains the "gold standard" for exosome isolation. Nevertheless, this method is time-consuming, equipment-demanding, and prone to vesicle-structure damage or contamination by impurities such as lipoproteins and protein aggregates. Residual non-vesicular components may interfere with subsequent proteomic or transcriptomic analyses and even introduce unpredictable immunogenic risks. Furthermore, exosomes derived from distinct cell types or under different physiological-pathological conditions exhibit marked differences in density, size and surface charge. No single isolation technique can simultaneously satisfy the requirements for high purity, high recovery yield and structural integrity. Accordingly, developing efficient, automated isolation platforms based on microfluidics, asymmetric flow field-flow fractionation (AF4) or immunoaffinity capture has become an urgent priority to advance exosome clinical

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translation [22]. Another pressing scientific issue lies in limited understanding of exosome heterogeneity. Conventional nanoparticle-tracking analysis (NTA) or Western blot only provides population-averaged information for samples, which largely masks molecular differences among individual exosome particles. In fact, even exosome populations from identical parental sources can display highly heterogeneous distribution of surface markers and internal cargo. Research conducted from this "population-average" perspective may cause researchers to overlook functionally pathogenic "key subpopulations". With the emergence of single-exosome analysis and single-exosome sequencing, it becomes feasible to resolve the "molecular fingerprints" of TAM-derived exosomes at the single-particle level. This enables precise discrimination between exosomes carrying drug-resistance proteins and those loaded with pro-inflammatory miRNAs, and supplies theoretical foundations for developing targeted intervention strategies against specific exosome subpopulations.

Real-world clinical application of exosomes still demands overcoming dual barriers concerning large-scale production and regulatory supervision. At present, most studies rely on small-scale laboratory preparation. Achieving large-scale, standardized manufacturing of clinical-grade exosomes under good manufacturing practice (GMP) conditions constitutes the core bottleneck restricting industrialization. This procedure covers multiple links including parental-cell screening, culture-condition optimization and scale-up of downstream purification workflows. In addition, as biological products, exosomes require systematic pre-clinical studies and clinical trials to validate their pharmacokinetic profiles, in-vivo distribution patterns and potential immunogenic risks. Notwithstanding these substantial obstacles, deep integration of nanotechnology, bioinformatics and artificial intelligence gives us good reason to anticipate that liquid-biopsy and targeted-therapy strategies based on TAM-derived exosomes will eventually surmount these hurdles and become an indispensable component within precision-oncology frameworks [23].

6. Conclusion

Dynamic crosstalk between tumour cells and immune cells within the tumour microenvironment profoundly modulates tumour progression and therapeutic responses. As central immune cells in the tumour microenvironment, tumour-associated macrophages predominantly adopt the pro-tumour M2 phenotype. They facilitate tumour proliferation, invasion and metastasis via multiple biological pathways and serve as major targets for current tumour-immunology-oriented research. As pivotal mediators of intercellular signal communication in the tumour microenvironment, exosomes deliver diverse bioactive molecules to achieve long-range cellular regulation and play critical roles in remodelling the tumour microenvironment. Existing evidence confirms that tumour-derived exosomes can effectively trigger M2-type polarization and metabolic reprogramming in macrophages, driving tumour immune escape and therapeutic resistance. In summary, elucidating molecular mechanisms whereby exosomes regulate TAM phenotype and function bears important clinical value for unravelling tumour-progression mechanisms and developing novel exosome-based diagnostic tools and targeted immunotherapies. On this basis, this paper systematically reviews functional mechanisms of exosomes, regulatory effects exerted by exosomes on tumour-associated macrophages, and biological functions of TAM-derived exosomes, so as to provide theoretical references for mechanistic research and clinical translation of tumour immunotherapy.

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