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REVIEW

Migrasomes: A New Role in Disease Diagnosis and Treatment

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Abstract: Migrasomes, vesicle-like organelles observed during cell migration, have emerged as a significant focus in cell biology. These organelles play a pivotal role in intercellular communication, signal transduction, and tissue development through the release of signalling molecules. Evidence indicates that the pathogenesis and progression of various diseases are closely associated with aberrant cell migration, impaired intercellular communication, and disrupted signalling pathways. Notably, migrasomes can facilitate the invasion and metastasis of tumor cells: they carry metastasis-promoting signals and help form an immunosuppressive microenvironment. Additionally, migrasomes mediate viral spread. Migrasomes derived from macrophages can accelerate the progression of cardiovascular and cerebrovascular diseases by promoting neuroinflammation and neuronal damage. Meanwhile, migrasomes derived from podocytes serve as biomarkers for early kidney injury. Thus, elucidating the role of migrasomes in pathological processes and defining their specific functions holds great promise for developing novel therapeutic strategies for diseases. This review synthesizes current advances in migrasome biology, highlighting their potential as diagnostic biomarkers and therapeutic targets for conditions such as cancer, viral infections, and renal disorders.

Keywords: migrasomes, diseases, diagnosis and therapy, cell migration

Introduction

Migrasomes are a newly discovered organelle, first identified and named by Yu Li's team.[1] Their formation occurs at the ends or branching nodes of contractile fibres in the tails of migrating cells and is facilitated by cellular migration activities, which result in the release of migrasomes from the mother cell. These organelles are membrane-enclosed structures, enriched with a variety of bioactive molecules, including proteins, RNAs, and lipids,[2] and play a pivotal role in intercellular communication by releasing extracellular cargo or directly delivering it to recipient cells. Recent researches have revealed that migrasomes are involved in the development and progression of several diseases, including tumour metastasis, cardiovascular and cerebrovascular diseases, and renal disorders.[3–5] This review systematically explores the biological characteristics and regulatory mechanisms of migrasomes, elaborates on their multifaceted roles in intercellular communication, homeostasis maintenance, and immunomodulation, and synthesizes emerging evidence linking them to the pathogenesis of various diseases. By integrating these insights, this work seeks to provide novel perspectives for understanding disease progression and highlight the translational potential of migrasomes in driving innovations in diagnosis and therapy.

Biological Characterisation of Migrasomes

Structure and Formation of Migrasomes

Migrasomes are vesicle-like structures that form during cell migration, originating from the junctions or tips of contractile fibres. Typically elliptical, their diameters range from 0.5 to 3 μm.[1] The formation of migrasomes depends on cytoskeletal reorganisation and interactions with the extracellular matrix (ECM). These organelles are rich in cholesterol, tetraspanins

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(TSPANs), and integrins, which are essential for their biogenesis and function.[6,7] Integrins play a crucial role in migrasome formation. They are highly enriched on migrasomes in an activated ligand-bound state, enabling specific pairing with ECM proteins.[6] Examples include integrin α5 binding to fibronectin in rat kidney cells and integrin α1 interacting with type IV collagen in hamster ovary cells.[6] These interactions not only provide structural support for the initial formation of migrasomes but also lead to subsequent activation of the downstream RhoA–ROCK1 signaling pathway. The RhoA-ROCK1 signaling pathway regulates the reorganization of the actin cytoskeleton and enhances the persistence and speed of cell migration, thereby driving the cascade of migrasome formation.[6]

Sphingomyelin Synthase 2 (SMS2), which forms a fixed focus at the leading edge of migrating cells and enters contractile fibres, as a key player in migrasome formation.[8] SMS2 catalyzes the conversion of ceramides into sphingomyelin (SM), facilitating the assembly of tetraspanin-enriched microdomains (TEMs) through SM-cholesterol interactions, thus promoting migrasome growth. TSPANs, which aggregate at the ends of contractile fibres and migrasome membranes, also play a pivotal role in migrasome formation, increasing in concentration over time.[9] In the contractile fibre membrane, TSPANs form TEMs with molecules such as cholesterol, integrins, and other four-transmembrane proteins, further assembling into larger macrodomains known as tetraspanin-enriched microdomain assemblies (TEMA).[7] These structures stabilize migrasome morphology by modulating the biophysical properties of the membrane. Furthermore, the phosphatidylinositol (4,5)-bisphosphate (PI(4,5)P2)-Rab35 axis is a key signalling pathway involved in migrasome formation through the regulation of cytoskeleton rearrangement.[10] The PI(4,5)P2-Rab35 axis orchestrates cytoskeletal reorganisation of retraction fibres (RFs) via hierarchical signalling. PI(4,5)P2, generated by phosphoinositide 5-kinase 1a (PIP5K1A), marks the site of migrasome formation, recruiting and activating Rab35. This process mediates the aggregation of integrin α5β1, transmits mechanical tension through the focal adhesion-actin network, and ultimately drives membrane expansion and migrasome release. Han et al also demonstrated the involvement of calcium ions and their receptor, Synaptotagmin-1 (Syt1), in the early stages of migrasome formation,[11] although the exact mechanism by which these ion channels regulate the formation of migrasomal structures requires further investigation. The process of migrasome formation is illustrated in Figure 1.

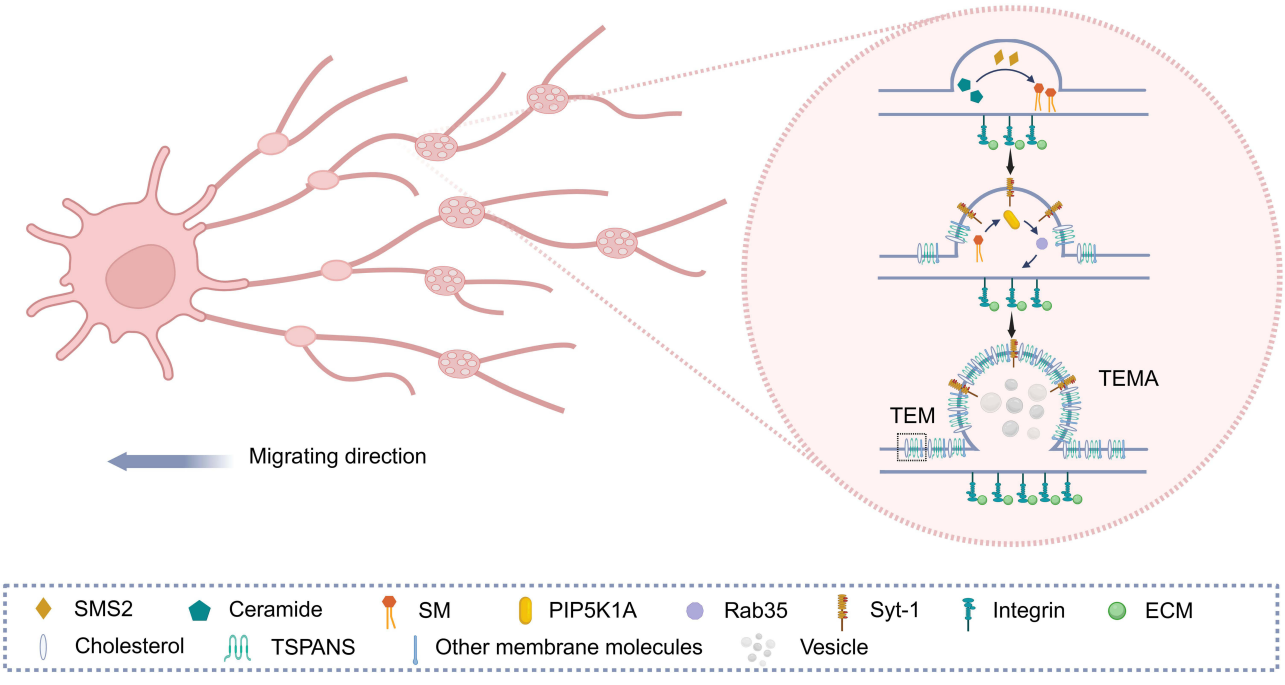

Figure 1 Biological formation of migrasomes. During cell migration, integrins bind specifically to the ECM, and SMS2 anchors the formation sites of migrasomes. The PI(4,5)P2-Rab35 signalling axis promotes the maturation and expansion of these initiation sites. TEM, rich in transmembrane proteins and cholesterol, gradually assemble into TEMA on retracting fibres. These TEMA transition into the typical vesicular structure of migrasomes, facilitating the final expansion of migrasomes.
Abbreviations: SMS2, sphingomyelin synthase 2; SM, sphingomyelin; PIP5K1A, phosphatidylinositol 4-monophosphate 5-kinase 1 alpha; Rab35, Ras-related protein Rab-35; Syt1, Synaptotagmin-1; ECM, extracellular matrix; TSPANs, tetraspanins; TEM, Tetraspanin-enriched microdomain; TEMA, Tetraspanin-enriched microdomain assemblies.

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Regulatory Factors of Migrasome Genesis

The duration and rate of cell migration are critical kinetic parameters in migrasome formation.[12] Specifically, studies have demonstrated that cells undergoing directional turns form significantly fewer migrasomes compared to those migrating in a straight line. Additionally, a positive correlation exists between cell migration speed and migrasome formation: faster-migrating cells generate a greater number of migrasomes. This phenomenon is primarily attributed to the fact that rapidly migrating cells produce longer RFs, which provide more sites for migrasome biogenesis. Furthermore, cytoskeletal components such as vimentin (an intermediate filament protein) influence migrasome formation by modulating cell migration patterns. Vimentin controls actin stress fibers through RhoA and promotes cell migration.[13,14] Loss of vimentin (vimentin-KO) in L929 cells results in defects in both persistence and speed of cell migration, producing fewer migrasomes than wild-type cells.[12] Certain speculative physical factors may influence migrasome formation, such as temperature, which is closely linked to cell migration, may potentially impact migrasome formation. Elevated temperature activates the NF-κB pathway, which significantly upregulates the expression of genes related to the extracellular matrix ECM and adhesion molecules.[15] This upregulation enhances integrin-mediated adhesion between cells and the ECM, leading to excessive cell adhesion and a subsequent reduction in cell migration speed.[15,16] Additionally, alterations in pH may disrupt the stability of the intracellular environment, thereby affecting the cytoskeleton and the function of proteins associated with migrasomes. Integrin-mediated adhesion to the ECM serves as a critical anchoring mechanism during cell migration, a process that is finely regulated by local acidic pH. Under acidic microenvironments (pH 6.8), integrin $\alpha_2\beta_1$ undergoes a conformational change, shifting from a bent inactive state to an extended active state.[16] This transition exposes high-affinity binding sites for ECM components such as collagen, thereby enhancing cellular adhesion to the matrix and facilitating cell migration.

External factors such as cytokines can modulate migrasome formation by regulating relevant molecules. The cytokine TNF-α activates endothelial cells, leading to the rearrangement of their F-actin from a stellate structure to parallel stress fibres.[17] This rearrangement enhances the directional migration capacity of the cells, with migrasomes forming at the ends of RFs. However, the universality of these regulatory factors in migrasome biogenesis remains unclear, and several unresolved questions persist regarding the precise mechanisms that govern the formation and regulation of migrasomes.

Biological Functions of the Migrasomes

As membrane-enclosed organelles generated during cell migration, migrasomes play pivotal roles in intercellular communication, maintenance of tissue homeostasis, and regulation of immune microenvironments by carrying and releasing bioactive molecules (eg, proteins, RNAs, lipids). Recent studies have gradually unraveled the molecular mechanisms underlying their functions and their physiological and pathological significance.

Cell Communication and Material Transfer

Migrasomes mediate localized, efficient cell-to-cell communication by delivering signaling molecules with high precision. They also facilitate the lateral transfer of biomaterials, thereby playing a key role in embryonic development, angiogenesis, and intercellular crosstalk.[18]

During zebrafish embryonic development, migrasomes can regulate the establishment of the dorsoventral axis by enriching the chemokine CXCL12. Jiang et al demonstrated that migrasomes mediate the chemotactic aggregation of Dorsal Forerunner Cells (DFCs). This process relies on the binding of CXCL12, specifically carried by migrasomes, to the CXCR4b receptor on the surface of DFCs, thereby regulating the formation of Kupffer's vesicles (an essential step in dorsoventral axis establishment).[19] This mode of signalling, distinct from diffuse secretion, ensures spatiotemporal precision in developmental patterning. In chicken embryos, migrasomes released by migrating monocytes are enriched with vascular endothelial growth factor VEGFA and CXCL12.[20] VEGFA can activate the VEGFR2-AKT signaling pathway in endothelial cells, promoting the tube formation of vascular endothelial cells; CXCL12, on the other hand, recruits more monocytes through chemotaxis, forming a positive feedback loop of "monocyte-migrasome-angiogenesis".[20] Knockdown of the migrasome marker TSPAN4 in monocytes of the chick embryo chorioallantoic membrane significantly reduces migrasome formation and impairs angiogenesis, which can be rescued by exogenous migrasome supplementation, highlighting migrasomes as "signal carriers" in embryonic vascular development.

Migrasomes also mediate the lateral transfer of proteins, RNAs, and organelles through the release of their contents or uptake by neighbouring cells. Intravital imaging of blood vessels in the mouse liver demonstrated that neutrophils, during rapid migration, adhere to the vascular wall, produce RFs, and consequently form migrasomes.[21] A portion of these migrasomes detaches from the vascular wall and enters the bloodstream. Serving as "mobile signal carriers", these circulating migrasomes are capable of interacting with distant immune cells for signal transmission, thereby reinforcing the immune surveillance system within the body. Additionally, Migrasomes derived from mouse fibroblasts also exhibit the function of lateral substance transfer.[22] Pten, which is considered a tumor suppressor protein.[23] When migrasomes carrying Pten were added to Pten-deficient mutant cells, Pten protein expression became detectable in these mutant cells, accompanied by a corresponding decrease in AKT phosphorylation levels. This result directly demonstrates that Pten protein delivered by migrasomes can be translated into functionally active proteins within recipient cells.[22] Thus, migrasomes can act as carriers for the lateral transfer of mRNA and proteins. However, the role of molecules carried by migrasomes in vivo and in pathophysiological processes remains to be further verified.

Furthermore, migrasomes play a role in antigen transport and immune signal transmission. Jing et al utilized fluorescent artificial antigens (FAA) and super-resolution imaging to demonstrate the presence of migrasomes within the extensive membrane fiber networks formed by dendritic cells (DCs). These migrasomes encapsulate FAAs and mediate intercellular signal transmission either by transporting antigens through membrane fibers or by being released as free carriers.[24] Similarly, after traumatic brain injury, neutrophils directly transfer antigens, chemokines, and other regulatory factors to microglia via migrasomes.[25] This mode of communication, distinct from traditional cell bridges or gap junctions, is migration-dependent.[26] Building on the well-established role of migrasomes in cellular communication, a recent study by Ma et al further demonstrates that these organelles are capable of releasing migrasome-derived nanoparticles (MDNPs) via three distinct mechanisms: self-rupture to release internal vesicles, budding from the migrasome membrane, and direct formation from fragmented contractile fibers (Shown in Figure 2).[27] While morphologically similar to conventional extracellular vesicles (EVs), MDNPs exhibit a distinct biomarker profile—defined by high expression of the migrasome marker PIGK and lack of the canonical EV markers TSG101 and ALIX—and harbor a unique repertoire of miRNAs. This cargo differs substantially from that of both their parent migrasomes and classical EVs, suggesting that migrasomes may amplify and diversify their signaling potential through MDNP release, thereby supporting complex, multi-tiered intercellular communication. Collectively, these studies underscore how migrasomes,

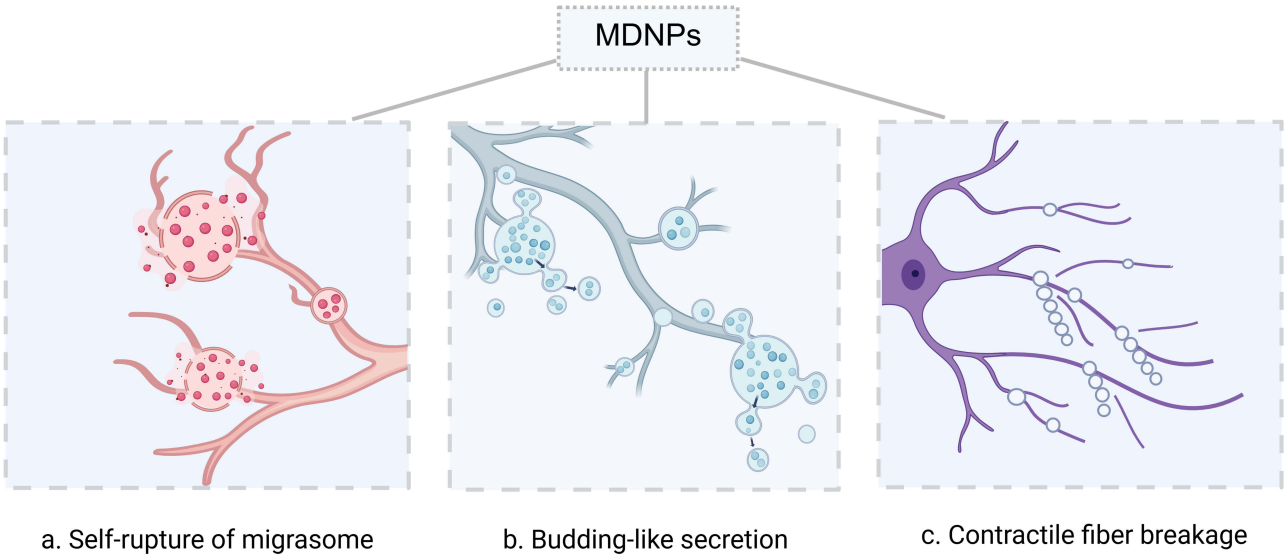

Figure 2 Three generation mechanisms of MDNPs. (**a**) Self-rupture of migrasome: The membrane of a mature migrasome ruptures, releasing its enclosed MDNPs directly into the extracellular space. (**b**) Budding-like secretion: MDNPs are generated and released through a membrane budding process from the migrasome surface. (**c**) Contractile fiber breakage: During cell migration, broken contractile fibers directly form chains of bead-like vesicles termed "Retractosomes", which occur along the fibers rather than on pre-formed migrasomes.
Abbreviation: MDNPs, migrasome-derived nanoparticles.

by transporting signaling molecules and cellular contents, enable efficient cell-cell communication and provide a mechanistically diverse platform for the spatiotemporal regulation of cellular behaviors.

Homeostasis Maintenance

Migrasomes contribute to maintaining tissue and intracellular homeostasis by regulating substance balance, clearing damaged organelles, and supporting system stability (eg, cardiovascular and nervous systems).

TSPANs, key structural molecules of migrasomes, are widely expressed in the cardiovascular system and participate in thrombosis, hemostasis, and vascular injury repair.[28,29] In the central nervous system, studies have identified DNA-binding proteins within migrasomes in the brain tissue of mice following cerebral infarction, suggesting a potential role of migrasomes in maintaining homeostasis in the central nervous system.[30] Neural crest cells (NCCs), which play an essential role in nervous system development, have been shown to actively release two types of extracellular vesicles—exosomes and migrasomes—during their migration.[31] These cells form contractile fibers enriched in tetraspanin proteins, and migrasomes are generated on these fibers. Migrasomes can be taken up by neighboring cells and are thought to be involved in transferring signaling molecules—such as mRNAs—thereby regulating neural homeostasis.

At the cellular level, the migrasome-mediated "mitocytosis" serves as a crucial quality control mechanism. Migratory cells expel damaged mitochondria through migrasomes—membrane-bound structures localized on the contractile fibers left behind by the cells. This process enables cells to selectively eliminate dysfunctional organelles and maintain metabolic homeostasis.[4,32] Specifically, when cultured mammalian cells are subjected to mild mitochondrial stress, damaged mitochondria form tubular outward protrusions, which undergo fission near the plasma membrane. The resulting mitochondrial fragments adhere to the plasma membrane under the mediation of Myosin 19, are transported toward the plasma membrane by the kinesin KIF5B, and are subsequently trapped by contractile fibers before finally entering migrasomes.[33] Notably, compared with healthy mitochondria, damaged mitochondria exhibit weaker binding ability to dynein (an inward-transporting motor protein). This characteristic allows damaged mitochondria to be selectively enriched at the cell periphery, thereby facilitating their clearance. Impaired mitocytosis leads to reduced mitochondrial membrane potential in macrophages and neutrophils, accompanied by a decrease in neutrophil count.[32] These findings highlight the role of this process in maintaining mitochondrial homeostasis and ensuring cell survival. Furthermore, low-intensity pulsed ultrasound facilitates the efflux of damaged mitochondria through migrasome-mediated mitochondrial transfer, thereby reducing the accumulation of dysfunctional mitochondria and protecting the heart against myocardial ischemia-reperfusion injury.[34] Migrating cells consume more energy than stationary cells, likely due to heightened respiration, increased reactive oxygen species (ROS) production, and elevated mitochondrial stress. To mitigate this stress, migrating cells eliminate damaged organelles. For example, Poole et al observed that migrating tumor cells depend on mitophagy—specifically, the BNIP3-dependent pathway during matrix detachment—to balance energy and ROS levels, thus sustaining migration.[35] Notably, the focus of Poole et al on canonical mitophagy provides a foundation for exploring migrasomes as a complementary "clearance system" during cell migration—though this regulatory mechanism requires further explicit investigation. Additionally, migrasomes support intracellular cholesterol homeostasis by facilitating cholesterol efflux, a process mediated by the release of cholesterol-rich vesicles.[36] Under high cholesterol conditions, migrasomes help mitigate intracellular accumulation by secreting microparticles, preventing toxicity and maintaining cellular lipid homeostasis. These findings emphasize that migrasomes are integral for managing tissue repair and maintaining cellular functions.

Immunomodulation

Migrasomes regulate immune microenvironment by carrying immune-related molecules, participating in inflammatory responses, influencing immune cell activity, and facilitating tumor immune evasion.

Migrasomes exhibit dual functions in bacteria-related immune responses: they can act as "pathogen clearance mediators" in the host defense system, and also serve as "signal amplifiers" for bacterial toxin-induced inflammation exacerbation. For instance, BM-MSCs can load antimicrobial peptides into migrasomes upon bacterial stimulation. After BM-MSC transplantation, the released migrasomes enhance the LC3-associated phagocytosis (LAP) of pulmonary macrophages.[37] The activation of LAP relies on NADPH oxidase. This enzyme can generate ROS, which exert a killing effect on intracellular pathogens,

thereby enhancing bacterial clearance efficiency.[38] However, when migrasomes are induced by bacterial toxins that target small GTPases—such as Clostridium difficile toxin TcdB3—their function shifts toward amplifying inflammatory responses. This toxin drives the formation of non-classical migrasomes, which can trigger the release of vesicles containing inflammatory factors in both stationary and motile cell types, thereby exacerbating acute inflammatory responses.[39] The transformation of these two functions of migrasomes provides a "scenario-dependent" research perspective to elucidate the role of migrasomes in bacteria-associated diseases. Furthermore, monocytes stimulated by lipopolysaccharide (LPS) can release migrasomes enriched with proinflammatory cytokines such as TNF-α and IL-6.[40] Endowed with surface adhesion molecules, these migrasomes are capable of rapidly accumulating at local inflammatory sites and thereby serve as a major source of cytokine secretion. In a murine model of sepsis induced by LPS, circulating neutrophils release migrasomes containing superoxide dismutase 2 (SOD2).[41] SOD2 within these migrasomes reduces the accumulation of ROS in endothelial cells, alleviates oxidative stress-induced damage. Circulating migrasomes adsorb and enrich coagulation factors through a cholesterol ester-dependent mechanism.[42] Relying on high-affinity adhesion molecules such as integrin α_2 on their surface, these migrasomes rapidly accumulate at injury sites, activate platelets to form larger aggregates, inhibit the excessive activation of the coagulation system, and ultimately alleviate sepsis-induced multiple organ dysfunction. Unlike systemic antioxidants, these vesicles concentrate protection at the site where it is most needed—the vascular barrier—balancing inflammation and coagulation without exerting excessive effects.

Migrasomes also intervene in inflammation by regulating immune cell activity.[43] For example, DCs utilize migrasomes to transfer antigens and chemokines to other DCs, thereby influencing immune signaling and function.[24] Gu et al found that migrasomes derived from human umbilical cord mesenchymal stem cells (MSCs) exert immunomodulatory effects by regulating the function of DCs in an ovalbumin-induced asthmatic mouse model.[44] Migrasomes specifically taken up by pulmonary DCs can inhibit the RAGE-NF-κB inflammatory signaling pathway, downregulate the expression of pro-inflammatory factors (eg, IL-6), and reduce DC-mediated Th2 cell activation, leading to a decrease in the levels of Th2-type cytokines (eg, IL-4, IL-5, and IL-13) in lung tissues. This represents a novel mechanism by which MSCs exert anti-inflammatory mechanisms through migrasomes, demonstrating that DCs are key target cells for migrasome-mediated regulation of immune responses. In the context of bone repair, Li et al observed that migrasomes derived from M2 macrophages are adsorbed onto the surface of titania nanotubes.[45] The migrasomes can activate the PI3K-AKT signaling pathway, enhancing the osteogenic differentiation capacity of bone marrow mesenchymal stem cells (BM-MSCs).[46] Additionally, M2 macrophage-derived migrasomes are capable of transmitting the anti-inflammatory signals of M2 macrophages to osteoblasts.[45] This process prevents excessive local inflammation from interfering with osteogenic differentiation. Furthermore, Migrasomes carry immune checkpoint molecules such as PD-L1 to modulate the tumor microenvironment.[47] Tumour cells release PD-L1 through migrasomes, inducing apoptosis in effector T cells, inhibiting the proliferation of natural killer cells, and promoting monocyte differentiation into immunosuppressive macrophages—facilitating cancer cell escape from immune surveillance. Thus, migrasomes play a crucial role in disease pathogenesis by exerting their biological functions via cellular communication, homeostasis maintenance, and immune regulation (illustrated in Figure 3).

Involvement of Migrasomes in Disease Development

Growing evidence indicates that migrasomes are deeply involved in the pathological processes of various diseases, acting through mechanisms such as mediating intercellular communication, regulating microenvironments, and participating in signaling pathways. As such, migrasomes hold promise as biomarkers or potential therapeutic targets for diseases (including tumors, viral infections, cardiovascular diseases, renal diseases, etc).

Migrasomes as a Driver of Tumor Metastasis and Progression

Tumor cells exhibit high aggressiveness and enhanced migratory capacity, rendering them a major source of migrasomes.[48,49] Consequently, migrasomes have been implicated in cancer metastasis and progression, establishing them as potential targets for therapeutic intervention.

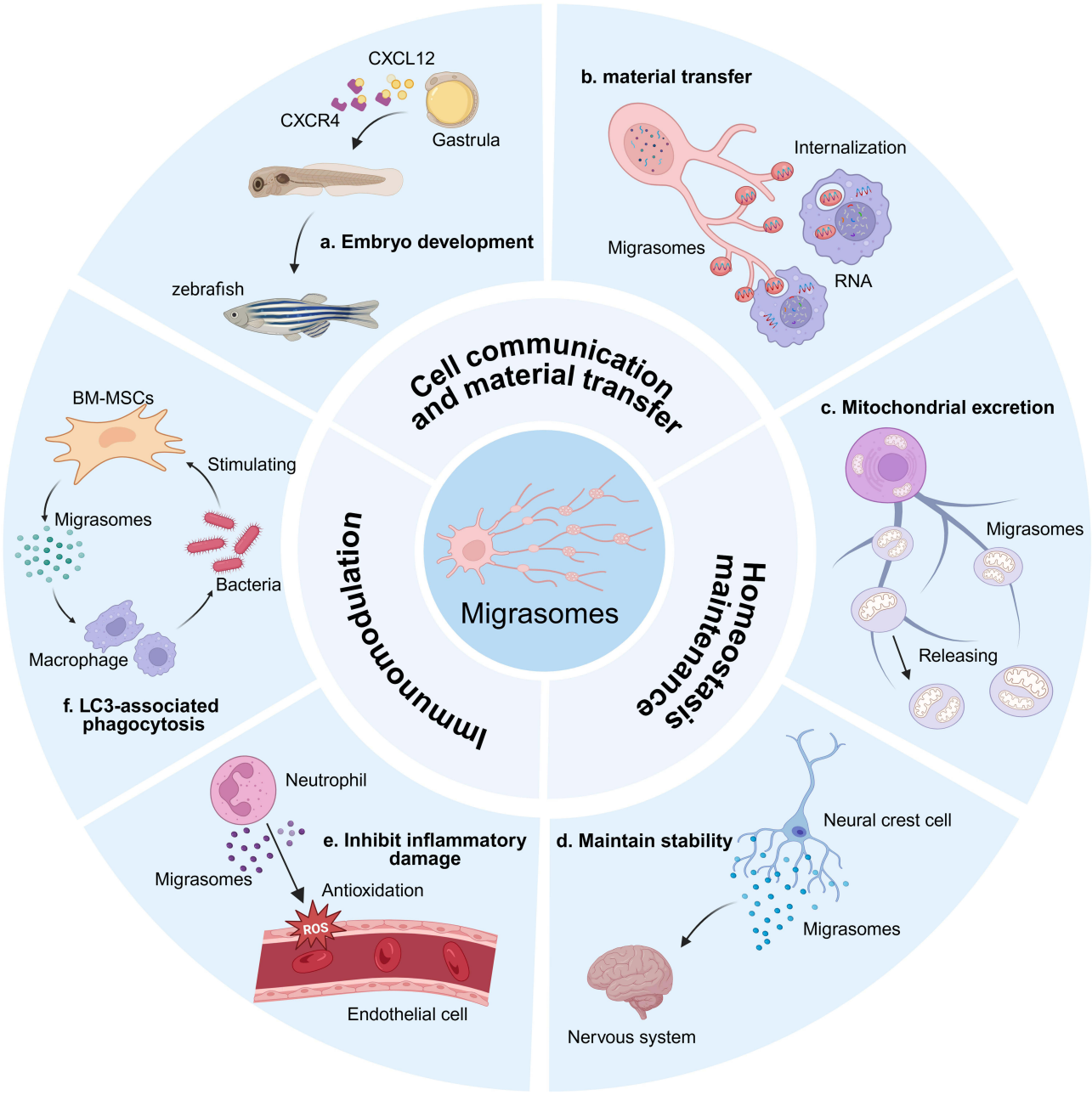

Figure 3 Functions of migrasomes. 1. Cell communication and material transfer. (**a**) Migrasomes enriched with chemokine CXCL12 influence the establishment of the dorsoventral axis in zebrafish by interacting with the receptor CXCR4. (**b**) Migrasomes are internalised by adjacent cells to mediate the horizontal transfer of RNA. 2. Homeostasis maintenance. (**c**) Migrasomes mediate "mitochondrial extracellular efflux" removing damaged mitochondria from cells. (**d**) Neural crest cells secrete migrasomes to support normal nervous system development. 3. Immunomodulation. (**e**) Bone marrow mesenchymal stem cells release migrasomes loaded with antimicrobial peptides under bacterial stimulation to enhance macrophage phagocytosis of bacteria. (**f**) Neutrophils in septic mice produce migrasomes containing SOD2 to reduce ROS accumulation in endothelial cells and preserve vascular barrier function.

Abbreviations: CXCL12, c-x-c motif chemokine ligand 12; CXCR4, c-x-c chemokine receptor type 4; ROS, reactive oxygen species; BM-MSCs, bone marrow-derived mesenchymal stem cells; LC3, microtubule-associated protein 1A/1B-light chain 3.

Hepatocellular Carcinoma (HCC)

The complex tumor microenvironment of HCC contributes to its poor therapeutic response and clinical prognosis. Recent studies on migrasomes have provided novel insights into potential therapeutic strategies for HCC.[50] Zhang et al revealed that CD151 promotes HCC invasion and metastasis through a dual mechanism mediated by migrasome formation. The migrasomes act as "intercellular invasion signal amplifiers" to enhance the collective invasive capacity of tumor cells,

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and VEGF-rich migrasomes can provide nutrients for the growth of tumor cells by inducing angiogenesis.[51] Analysis of tumor tissues from clinical HCC patients confirmed the co-localization of CD151 with migrasome markers TSPAN4, with high expression significantly correlating with metastatic risk.[52,53] In parallel, knockdown of ITGA5 inhibits the proliferation, migration, and invasion of HCC cells, while its overexpression exacerbates malignant phenotypes. This indicates that ITGA5 is a key migrasome-related gene involved in the proliferation and metastasis of HCC. ITGA5 is involved in tumorigenesis through PI3K/AKT signaling.[54] Moreover, the PI3K-AKT signaling pathway enhances the malignant proliferation capacity of HCC cells, promotes tumor metastasis, and induces an immunosuppressive microenvironment, potentially synergizing with immune checkpoints such as PD-L1.[47] High ITGA5 expression is associated with shorter survival in patients with HCC and increases the sensitivity of HCC cells to the PI3Kβ inhibitor TGX221.[54] Collectively, these findings indicate that the CD151-migrasome axis and ITGA5 mediate HCC metastasis, offering valuable insights into the function of migrasomes and the mechanisms underlying hepatocellular carcinoma metastasis.

Osteosarcoma

The aggressive nature of osteosarcoma is closely linked to its complex tumor microenvironment. A study by Liu et al revealed that osteosarcoma cell-derived migrasomes (OCDMs) play a key role in promoting tumor proliferation and metastasis.[55] Inhibiting the formation of OCDMs was shown to suppress malignant progression. Mechanistically, OCDMs release migrasome-associated nanoparticles (MANPs) loaded with MFGE8. After uptake by macrophages, MANPs enhance the phagocytosis of apoptotic tumor cells, which in turn polarizes macrophages toward an M2-like immunosuppressive phenotype. This reshaping of the tumor microenvironment facilitates osteosarcoma progression. Targeting the MFGE8-MANP-macrophage axis may offer a promising therapeutic strategy for inhibiting migrasome-mediated immune suppression and metastasis in osteosarcoma.

Pancreatic Cancer

Research on pancreatic cancer has shown that both murine and human pancreatic cancer cells generate pancreatic cancer cell-derived migrasomes (PCDMs)—a population detectable within tumor tissues.[56] These PCDMs are subsequently phagocytosed by macrophages and, through the release of CXCL5 and TGF-β1, drive the polarization of macrophages toward an M2 phenotype.[57] M2 macrophages highly express ARG1, which depletes arginine in the microenvironment, thereby inhibiting the activation and function of $CD4^+$ and $CD8^+$ T cells and establishing an immunosuppressive niche conducive to tumor proliferation and invasion.[58] Concurrently, a distinct population of $TSPAN4^+$ fibroblasts has been identified as key contributors to migrasome-mediated metastatic niche formation in pancreatic adenocarcinoma.[59] Through migrasome-driven metabolic reprogramming and stromal-immune crosstalk, these fibroblasts enhance extracellular matrix remodeling, facilitate immune evasion, and promote angiogenesis. Multi-omics analyses of fibroblasts in pancreatic cancer tissues reveal that $TSPAN4^+$ fibroblasts act as communication hubs, engaging with macrophages, endothelial cells, and tumor cells via pathways such as PERIOSTIN-PI3K/Akt, non-canonical WNT, and TGF-β, further reinforcing an immunosuppressive microenvironment.[59] Together, these findings underscore the dual origin—both tumor cells and stromal fibroblasts—of migrasomes in pancreatic cancer and highlight their role in orchestrating immune suppression and metastatic progression. Targeting migrasome formation or associated signaling molecules such as TSPAN4 and ARG1 may offer promising therapeutic strategies to disrupt this pro-tumor communication network.

Gastric Cancer (GC)

Migrasomes have been increasingly implicated in the progression and metastasis of GC, with recent studies highlighting their role in mediating intercellular communication and remodeling the tumor microenvironment. In GC tissues, TSPAN4 expression is significantly elevated compared to adjacent non-tumor regions.[60] Inhibition of TSPAN4 in gastric cancer cells can effectively prevent their tumorigenesis and progression, underscoring its pivotal role in disease progression. At the molecular regulatory level, lysine-specific demethylase 1 (LSD1) forms a complex with estrogen receptor α (ERα). Upon estrogen stimulation, the association of complex is enhanced, leading to the upregulation of fibronectin (FN1) expression through transcriptional regulatory mechanisms.[61] As a key structural protein in the formation of migrasomes, FN1 promotes migrasome generation, which further facilitates the migration and invasion capabilities of GC cells. Clinically, patients with high LSD1 expression exhibit a lymph node metastasis rate of 78%, significantly higher than that

in patients with low LSD1 expression.[61] Additionally, a positive correlation is observed between LSD1 expression levels and the number of migrasomes. Moreover, TSPAN4, along with other migrasome-related genes such as BMP1, CPQ, TGFB2, and WNT11, contributes to an immunosuppressive microenvironment by modulating immune cell infiltration and checkpoint molecule expression.[62] The coordinated actions of TSPAN4, LSD1/ERα, FN1, and other migrasome-associated components underscore their critical roles in gastric cancer metastasis and immune suppression. Targeting migrasome biogenesis or key regulatory nodes—such as TSPAN4—could provide novel therapeutic strategies to inhibit GC progression and improve the efficacy of current treatments.

Migrasomes Mediate Viral Transmission and Pathogenesis

In the context of viral infection and pathogenesis, intercellular viral transmission represents a key step—one that was traditionally thought to rely on free viral particles or direct cell-to-cell contact. However, recent studies have revealed that migrasomes, as a novel member of the extracellular vesicle (EV) family, facilitate viral spread by encapsulating viral particles and shielding them from immune clearance.[63,64]

Chikungunya Virus (CHIKV)

In the investigation of viral transmission mechanisms, the transmission route of CHIKV has garnered considerable attention. Zhang et al have identified a strong association between CHIKV and migrasomes, thereby opening a new avenue for elucidating the virus's transmission mechanism.[65] They found that the non-structural protein nsP1 of CHIKV interacts with the phosphatidylinositol kinase PIP5K1A in host cells, promoting the production of $PI(4,5)P_2$ and thereby inducing migrasome biogenesis. The resulting migrasomes encapsulate virus-associated components, acting as novel carriers for CHIKV dissemination. This allows the virus to evade host immune defenses and achieve intercellular transmission. This finding not only advances our understanding of CHIKV transmission routes but also identifies potential intervention targets for chikungunya fever prevention and control—holding substantial significance for the management of related diseases.

Vaccinia Virus

Poxvirus infection induces migrasome formation during the later stages of infection.[66] It is well known that poxvirus transmission is mediated by extracellular enveloped virus (EEV) and intracellular mature virus (IMV). Lv et al found that both EEV and IMV are present in migrasomes, suggesting that migrasomes may play a role in the transmission of poxviruses.[66] Since the impact of nanoparticles on viral transmission dynamics remains unclear, Tang et al further explored the impact of polystyrene nanoparticles (PS-NPs) on the transmission of vaccinia virus via migrasomes,[67] and found that PS-NP treatment increased migrasome formation, and the number of migrasomes released by vaccinia virus-infected cells also rose. This suggests that PS-NPs facilitate migrasome production and release, creating additional carriers for viral transmission, and that PS-NPs may act as regulatory factors, enhancing the tendency of the vaccinia virus to transmit via migrasomes.

Herpes Simplex Virus Type 2 (HSV-2)

Cells infected with HSV-2 release migrasomes containing HSV-2 virus particles,[68] and similar migrasome-virus complexes are present in tissues from HSV-2-infected mice. Co-culturing these migrasomes with uninfected cells revealed that the HSV-2 particles within the migrasomes can infect new cells, leading to successful viral replication. This study revealed that HSV-2 utilizes a "cell-migrasome-cell" model for broader transmission, expanding upon the classical HSV-2 transmission model. These findings furnish theoretical support for the development of novel targeted interventions against HSV-2 infections, while the migrasome-virus transmission model yields valuable insights into the transmission mechanisms of other viruses.

Migrasomes Contribute to the Development of Cardiovascular and Cerebrovascular Diseases

Emerging research indicates that migrasomes contribute to maintaining vascular homeostasis and support myocardial repair by modulating macrophage polarization and inflammatory responses. These mechanisms underscore the significant role of migrasomes in cardiovascular and cerebrovascular pathophysiology, while offering promising targets for the development of novel therapeutic strategies.

Atherosclerosis

Atherosclerosis represents a prevalent cardiovascular disease, with macrophages playing a critical role in its progression.[69–71] Under physiological conditions, macrophages maintain lipid homeostasis; however, in pathological states, the balance of lipid uptake is disrupted—leading to the formation of foam cells that drive atherosclerotic plaque progression.[70] Notably, migrasomes derived from macrophages further accelerate this disease process. Studies have demonstrated that within the atherosclerotic microenvironment, factors such as oxidized low-density lipoprotein (ox-LDL) stimulate macrophages to generate migrasomes. These migrasomes carry pro-inflammatory factors (eg, CCL2), which bind to CCR2 receptors on the macrophage surface and induce polarization toward the M1 phenotype.[72] M1-polarized macrophages then secrete pro-inflammatory cytokines, which exacerbate inflammation and lipid deposition. Additionally, macrophage-derived migrasomes activate matrix metalloproteinases (MMPs), which degrade the fibrous cap of atherosclerotic plaques and thereby increase the risk of plaque rupture.[73] In carotid plaques from patients with atherosclerosis, a correlation exists between migrasome markers and M1 phenotype markers. Furthermore, studies using an induced myocardial infarction mouse model have confirmed that upregulation of TSPAN4 is associated with atherosclerosis and its severe sequelae, such as myocardial infarction.[72] Thus, targeting macrophage-derived migrasomes may present a novel opportunity for the treatment of atherosclerosis.

Ischemic Stroke

Ischemic neuronal injury and death are the core of disability in stroke.[74] Subsequent neuroinflammatory responses, particularly peripheral immune cell infiltration and microglial activation and migration, significantly exacerbate secondary damage.[75] Schmidt-Pogoda et al demonstrated that a high-salt diet exacerbates ischemic stroke injury by inducing the formation of migrasomes derived from microglia/macrophages, and such migrasomes are also present in the infarcted brain tissues of human stroke patients.[30] These migrasomes can integrate cytoplasmic components of neurons and exhibit a positive correlation with neuronal damage. Compared with the normal mice, mice in the high-salt group had increased neurological deficit scores and a 17.4% increase in infarct volume in ischemic stroke mice. Meanwhile, high salt also promotes microglia to secrete pro-inflammatory factors such as TNF-α and IL-6, which amplify inflammatory damage,[76] these two effects together exacerbate the progression of stroke. Thus, Targeting migrasome formation might reduce neuroinflammation and neuronal injury caused by ischemic strokes.

Acute Myocardial Infarction (AMI)

To explore the diagnostic significance and biological mechanisms of migrasomes in AMI, Zhu et al developed migrasome-related signatures (MS) for AMI diagnosis and analyzed cardiac CD45+ cells from AMI-induced mice using single-cell RNA sequencing. They found high expression of ITGB1 (a migrasome-associated gene) in cardiac macrophages.[77] ITGB1 plays a critical role in the transition between anti-inflammatory and pro-inflammatory macrophage states.[78] ITGB1 forms a receptor complex with ITGB5, transducing signals via the RGD motif to promote macrophage adhesion and migration, activating the FAK and PI3K/AKT signalling pathways to release inflammatory factors and amplify the inflammatory response.[79] During the inflammation resolution and tissue repair stage following the onset of AMI, ITGB1 regulates the secretion of growth factors and cytokines by immune cells, supporting myocardial regeneration and scar tissue formation, thus exerting an anti-inflammatory effect. ITGB1 is positively correlated with AMI risk, and inhibition of ITGB1 with ginsenoside Rh1 may be a new treatment for AMI. Thus, migrasome-associated genes have important implications in predicting and treating AMI, informing future AMI diagnosis and treatment strategies.

Cerebral Amyloid Angiopathy (CAA)

Researchers revealed that macrophage-derived migrasomes drive the progression of CAA through the "migrasome-CD5L-complement activation" pathway.[5] CAA is characterized by the core pathology of β-amyloid protein 1–40 (Aβ40) deposition in cerebral vessel walls.[80,81] After phagocytosing Aβ40, macrophage lineages such as brain-resident microglia and perivascular macrophages abnormally produce migrasomes containing CD5L.[82] The number of migrasomes in the peripheral blood of CAA patients is positively correlated with disease severity, and the deposition of such migrasomes is also observed in the cerebral vessel walls of mice. However, migrasomes do not directly damage blood vessels, but instead adopt an "adhesion-enrichment" strategy—relying on their own adhesive properties to accumulate CD5L on vessel walls, break through the endothelial anti-complement protective barrier,[82] and indirectly trigger cytotoxic effects to damage the blood-brain barrier.[5]

This "local concentration amplification" mechanism not only accounts for the positive correlation between migrasomes and the membrane attack complex (MAC) but also identifies an intervention strategy for targeting migrasomes or CD5L to inhibit CAA progression.

Migrasomes as Early Biomarkers of Podocyte Injury in Nephropathy

In kidney disease research, podocytes function as core components of the glomerular filtration barrier. Podocyte injury represents a key driver of proteinuria and disease progression.[83] Emerging studies further confirm that migrasomes released by podocytes—given their high sensitivity and specificity for early injury—have emerged as reliable biomarkers for detecting podocyte dysfunction.[84–86]

Diabetic Nephropathy (DN)

Podocyte-derived migrasomes are sensitive indicators of early kidney damage, appearing earlier than proteinuria. As key glomerular cells, podocytes can release migrasomes with specific markers such as PIGK when damaged. This release process relies on the Rac-1 signaling pathway: injurious factors like LPS and high glucose can activate the Rac-1 signaling pathway to promote migrasome production, while Rac-1 inhibitors can block the migrasome-generating effect induced by injurious factors like LPS in a dose-dependent manner.[86] The concentration of podocyte-derived migrasomes in the urine of DN patients is significantly higher than that in healthy individuals. These migrasomes specifically express podocin (a podocyte marker) rather than SGLT2 (a renal tubular marker). Notably, in a puromycin amino nucleoside (PAN)-induced nephropathy mouse model, Liu et al observed that high level of podocyte-derived migrasomes was detected in the urine of mice with PAN-induced nephropathy. Additionally, the increase in the number of urinary migrasomes preceded the elevation of proteinuria.[86] Furthermore, the detection of urinary migrasomes in patients with DN demonstrates greater sensitivity compared to conventional biomarkers. This finding not only highlights the potential of migrasomes as an early warning signal in the initial phases of DN development but also implies that they could function as crucial mediators bridging podocyte damage to the progression of the disease. Similarly, Ardalan et al noted increased levels of podocyte-derived EVs in the urine of patients during the early stages of kidney disease. Notably, among these EVs, migrasomes stood out as more sensitive and reliable markers of podocyte stress or injury than proteinuria.[84] Collectively, these observations suggest that migrasomes may represent a novel target for the early intervention of kidney diseases associated with podocyte injury.

Membranous Nephropathy

Multidimensional experiments have elucidated the association between migrasomes and the pathogenesis of membranous nephropathy.[85] Damaged podocytes exhibit enhanced motility and release migrasomes containing TSPAN4 and ITGA5, which are excreted in urine with release levels positively correlated to podocyte injury severity. In animal experiments, urinary migrasome levels in puromycin aminonucleoside-induced nephropathy mice increased on day 2 post-modeling, earlier than traditional indicators like serum creatinine and urinary albumin.[85] Clinically, kidney disease patients showed higher urinary podocyte-derived migrasome concentrations; even early-stage patients (with normal eGFR and 24-hour urinary protein) had elevated migrasome signals, with better diagnostic efficacy than traditional markers such as eGFR and 24-hour urinary protein. Additionally, urinary migrasomes from membranous nephropathy patients highly express PLA2R, which can serve as an antigen to detect relevant serum autoantibodies,[87] showing better diagnostic sensitivity and specificity than the traditional ELISA method, thus providing a new marker option for non-invasive kidney disease diagnosis. However, the specificity of migrasomes remains debated: Ardalan et al found that podocyte-derived migrasomes coexist with exosomes, which gives rise to the risk of cross-contamination among different extracellular vesicle subtypes (exosomes, microparticles) in urine.[84] To distinguish these subtypes as independent biomarkers, additional efforts are needed to develop standardized detection techniques and validate data from large-scale clinical cohorts.

Migrasomes in Other Diseases

Proliferative Vitreoretinopathy (PVR)

PVR is a blinding disease caused primarily by the activation of the retinal pigment epithelium (RPE). Wu et al found that RPE cells can produce TSPAN4-positive migrasomes within the PVR microenvironment. These migrasomes can be

internalized by recipient RPE cells and significantly promote their migration and proliferation, thereby accelerating the progression of PVR.[88] TSPAN4-positive migrasomes were detected in clinical samples from PVR patients, including vitreous humor, subretinal fluid, and PVR membranes. Meanwhile, in a rabbit PVR model, knockdown of TSPAN4 expression reduced PVR grading and alleviated retinal detachment. The underlying mechanism involves TGF-β1 in the PVR microenvironment, which activates the Smad2/3 signaling pathway and upregulates TSPAN4 expression to induce migrasome formation. Time-lapse imaging revealed that migrasome formation is accompanied by the migration process of RPE cells. Targeting TSPAN4 or blocking migrasome formation may prevent or treat PVR.

Nanoplastics Induce Abortion via Migrasomes

Wan et al found that exposure to PS-NPs induces miscarriage in pregnant mice, and this process is associated with the inhibition of ROCK1-mediated migrasome formation by PS-NPs.[89] ROCK1 plays an indispensable role in regulating the migration, invasion, and migrasome formation of trophoblast cells; SOX2 has been identified as a transcription factor for ROCK1. Specifically, PS-NPs trigger autophagy in trophoblast cells, and this activated autophagic process specifically promotes the degradation of SOX2, thereby suppressing SOX2-mediated ROCK1 transcription. ROCK1 downregulation significantly impairs the above processes of trophoblast cell and reduces the number of migrasomes. The combined consequences of diminished migrasome levels and compromised trophoblast cell functionality ultimately contribute to the induction of miscarriage.[89] This research innovatively establishes the link between environmental pollutants, cellular autophagy machinery, and migrasome biological functions, elucidating the mechanisms by which naoplastics cause miscarriage through migrasomes.

The studies outlined above demonstrate that migrasomes can carry metastasis-promoting signals, establish an immunosuppressive microenvironment, and facilitate tumor cell invasion and metastasis by transferring tumor suppressor genes.[22] They can act as vectors to mediate the covert transmission of viruses such as chikungunya and poxvirus;[65,66] In cardiovascular and cerebrovascular diseases, migrasomes contribute to the regulation of vascular and endothelial cell stability.[20] Additionally, migrasomes derived from podocytes serve as biomarkers of early kidney injury. Table 1 summarizes the roles and mechanisms of migrasomes in various diseases. However, research into the role of migrasomes in disease pathological processes is still in its infancy, and numerous unknowns remain to be explored.

The Transformational Application Potential of Migrasomes

As the role of migrasomes in disease pathological mechanisms becomes increasingly clear, their potential for clinical translation has emerged as a research focus. Migrasomes possess unique molecular characteristics, inherent cell-targeting

Table 1 Summary of the Molecular Markers and Functions of Migrasomes in Diseases

Disease Type	Key Molecules	Functional Mechanism	Clinical Significance	Reference
Hepatocellular Carcinoma	ITGA5, CD151, TSPAN4	CD151 promotes migrasome formation to enhance tumor invasion and angiogenesis; ITGA5 activates the PI3K/AKT pathway to facilitate metastasis	ITGA5 expression correlates with drug sensitivity; CD151 serves as a therapeutic target	[51,54]
Osteosarcoma	OCDMs, MANPs	OCDMs release MANPs, which induce M2 polarization of macrophages to promote tumor progression	Inhibiting OCDM biogenesis alleviates the malignant progression of osteosarcoma	[55]
Pancreatic Cancer	PCDMs, CXCL5, TGF-β1	PCDMs are phagocytosed by macrophages, releasing CXCL5/TGF-β1 to induce M2 polarization and T-cell inhibition	Increased tumour burden; targeting PCDMs may suppress pancreatic cancer progression	[56]
Gastric Cancer	TSPAN4	TSPAN4 overexpression promotes cancer cell proliferation and migration	TSPAN4 levels correlate with tumour stage and prognosis; potential diagnostic biomarker	[60]

(*Continued*)

Table 1 (Continued).

Disease Type	Key Molecules	Functional Mechanism	Clinical Significance	Reference
Chikungunya Virus	nsP1, PIP5K1A, PI(4,5)P2	nsP1 promotes PI(4,5)P2 production to induce migrasomes, which encapsulate viruses to facilitate transmission	Blocking the nsP1-PIP5K1A axis could inhibit non-classical viral transmission.	[65]
Vaccinia Virus Infection	EEV, IMV, PS-NPs	Migrasomes carry viruses for transmission; PS-NPs promote migrasome formation to increase transmission	Environmental pollutants (eg, PS-NPs) may exacerbate viral transmission risks	[66,67]
HSV-2 Viral Infection	HSV-2 Viral Particles	Migrasomes encapsulate viral particles and mediate virus transmission via a "cell-migrasome-cell" pathway	Blocking migrasome formation or viral packaging may pave the way for the development of novel antiviral strategies	[68]
Atherosclerosis	TSPAN4, CCL2	Migrasomes carry CCL2 to promote M1 polarization of macrophages, exacerbating inflammation and plaque rupture	Regulating macrophage-derived migrasomes is a new therapeutic direction	[72]
Ischemic Stroke	High-Salt-Induced Migrasomes, Neuronal Debris	High salt promotes migrasome formation, exacerbating nerve injury and inflammation	High-salt diet correlates with stroke prognosis; dynamic migrasome monitoring may guide therapy	[30]
Acute Myocardial Infarction	ITGB1	ITGB1 regulates macrophage inflammation and repair, participating in myocardial injury and regeneration	ITGB1 forms a "migrasome-related signature" for AMI diagnosis and monitoring.	[77]
Cerebral Amyloid Angiopathy	CD5L, Aβ40	Aβ40 stimulates macrophages to release CD5L-containing migrasomes, inducing complement-dependent blood-brain barrier damage	CD5L levels correlate with the severity of vascular injury; potential therapeutic target	[5]
Diabetic Nephropathy	PIGK, Rac-1	Injured podocytes release migrasomes (containing PIGK/podocin) into urine via Rac-1 signaling pathway activation	Urinary podocyte migrasomes are a highly sensitive early biomarker, appearing before proteinuria.	[86]
Membranous Nephropathy	TSPAN4, ITGA5, PLA2R	Injured podocytes release migrasomes; urinary migrasomes highly express the PLA2R antigen.	Migrasomes can be used as non-invasive diagnostic biomarkers	[85,87]
Proliferative Vitreoretinopathy	TSPAN4, TGF-β1	TGF-β1 promotes TSPAN4-positive migrasome formation to accelerate PVR	TSPAN4 levels correlate with PVR severity; targeting migrasomes may inhibit disease progression	[88]
Pregnancy Complications	PS-NPs, ROCK1	PS-NPs inhibit ROCK1, reducing migrasomes and damaging trophoblasts to cause miscarriage	Reveals a new pathway for miscarriage, aiding analysis of environmental-induced pregnancy abnormalities	[89]

Abbreviations: ITGA5, integrin subunit alpha 5; CD151, cluster of differentiation 151; TSPAN4, tetraspanin 4; PI3K/AKT, phosphoinositide 3-kinase/protein kinase b; OCDMs, osteosarcoma cell-derived migrasomes; MANPs, migrasome-associated nanoparticles; PCDMs, pancreatic cancer cell-derived migrasomes; CXCL, c-x-c motif chemokine ligand; TGF-β1, transforming growth factor beta 1; nsP1, non-structural protein 1; PIP5K1A, phosphatidylinositol 4-phosphate 5-kinase type 1 alpha; PI(4,5)P2, phosphatidylinositol (4,5)-bisphosphate; EEV, extracellular enveloped virus; IMV, intracellular mature virus; PS-NPs, polystyrene nanoparticles; HSV-2, herpes simplex virus type 2; CCL2, c-c motif chemokine ligand 2; ITGB1, integrin subunit beta 1; CD5L, cd5 antigen-like; Aβ40, amyloid-β protein 1–40; PIGK, phosphatidylinositol glycan anchor biosynthesis class k; Rac-1, ras-related c3 botulinum toxin substrate 1; PLA2R, phospholipase a2 receptor; PVR, proliferative vitreoretinopathy; ROCK1, rho associated coiled-coil containing protein kinase 1.

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properties, and pathological regulatory functions—traits that enable them to serve not only as specific biomarkers for early disease diagnosis but also as therapeutic targets or drug delivery vectors.

Diagnostic Biomarkers

Migrasomes exhibit significant potential as diagnostic biomarkers across a range of diseases, owing to core advantages including source specificity, early detectability, and correlation with disease severity or progression. In tumor diagnosis, migrasome markers enable the dual function of "early screening and prognostic stratification". For gastric cancer, the migrasome marker TSPAN4 is abnormally elevated as early as the precancerous lesion stage; detecting TSPAN4-positive migrasomes in blood or bodily fluids thus serves as a non-invasive supplementary tool for early screening.[60] In HCC, the migrasome-associated gene ITGA5 not only acts as a core indicator in prognostic models but also guides treatment: HCC cells with high ITGA5 expression display increased sensitivity to the PI3Kβ inhibitor TGX221.[54] In pancreatic cancer, PCDMs can be detected in tissues and body fluids; the CXCL5 and TGF-β1 carried by PCDMs promote the polarization of macrophages toward the M2 phenotype. These polarization-related changes reflect tumor burden and immunosuppressive status, supporting effective disease monitoring.[57] Viruses such as poxviruses and HSV-2 rely on migrasomes for transmission; detecting migrasomes containing viral particles can indicate active viral spread and distinguish between latent and active infections.[67,68] In AMI, the high expression of ITGB1 in cardiac macrophages forms a "migrasome-related signature". This signature not only enables rapid diagnosis of AMI but also reflects the progression of myocardial inflammation through dynamic changes in ITGB1 expression, aiding in disease monitoring.[77] For kidney disease diagnosis, podocyte-derived migrasomes—containing PIGK and podocin—appear in urine much earlier than proteinuria.[85] The concentration of these migrasomes is significantly elevated in the urine of patients with diabetic kidney disease, exhibiting higher detection sensitivity.[86] In patients with membranous nephropathy, urinary migrasomes highly express the PLA2R antigen; using these migrasomes as carriers to detect serum autoantibodies achieves a diagnostic accuracy (AUC=0.9696) that outperforms the traditional ELISA method, while avoiding the invasiveness of renal biopsy.[87]

In summary, with their characteristics of "early detectability, high accuracy, and easy accessibility", migrasomes overcome the limitations of traditional markers in diagnosing tumors, kidney diseases, viral infections, and cardiovascular and cerebrovascular diseases. They provide new tools for early disease screening and ongoing disease monitoring.

Therapeutic Targets

Migrasomes can act as therapeutic targets via their pathological regulatory functions—such as mediating signal transmission and modulating the microenvironment. In cancer therapy, vascularized metastasis of HCC depends on the CD151–migrasome axis; targeting CD151 or TSPAN4 thus inhibits both tumor invasion and angiogenesis.[53] In osteosarcoma, suppressing the formation of OCDMs—for instance, by interfering with MFGE8 expression—can block OCDM-induced M2 polarization of macrophages, thereby reducing tumor proliferation and metastasis.[55] In colorectal cancer, migration-associated genes (eg, TIMP1, CXCL8, and MGP) have been identified as prognostic markers. A risk model based on these genes (AUC > 0.6) has shown greater efficacy in predicting patient survival and response to immunotherapy compared to traditional TNM staging, providing a novel strategy for colorectal cancer prognosis.[90] In 2022, Qin et al utilized pan-cancer analysis techniques and single-cell sequencing methods to investigate the potential of migrasome-associated genes as targets for cancer immunotherapy.[91] They hypothesized that high expression of genes such as PIGK, ITGB1, and NDST1 is frequently associated with poorer prognosis in tumor treatment. As a result, intervening in migrasome-associated genes may hold the potential to improve patient outcomes and survival—particularly for critically ill individuals.

Nanoparticles show substantial promise in cancer therapy. One key mechanism involves their ability to interfere with the recognition, uptake, and clearance of migrasomes by neighboring tumor cells. This effect is mediated through interactions between nanoparticles and lipid raft/caveolae domains, which leads to the coating of migrasomes and contractile fibers, as well as the disruption of cell–ECM interactions.[92] Targeting the intrinsic migration-promoting activity of migrasomes through nanoparticle-based inhibition may represent a novel therapeutic strategy for anti-metastatic nanotherapy.

In the treatment of viral infections, blocking migrasome-mediated "covert transmission" is the core focus. Disrupting the nsP1-PIP5K1A-PI(4,5)P2 pathway of CHIKV or inhibiting the encapsulation of viral particles within migrasomes can interfere with the non-classical transmission routes of viruses such as CHIKV and HSV-2.[65,68] In the treatment of

cardiovascular and cerebrovascular diseases, as well as kidney diseases, targeting the "local effects" of migrasomes can minimize systemic side effects. In cerebral amyloid angiopathy, clearing CD5L-positive migrasomes can block vascular damage while avoiding systemic immunosuppression.[82] In DN, Rac-1 inhibitors reduce the release of podocyte-derived migrasomes in a dose-dependent manner, delaying disease progression with minimal impact on normal renal tissue.[86] Thus, targeted suppression of disease-specific migrasomes opens a novel therapeutic avenue for cancer, viral infections, cardiovascular and cerebrovascular diseases, kidney disorders, and other conditions.

Drug Delivery System

As endogenous organelles, migrasomes outperform traditional artificial carriers due to their low immunogenicity, inherent cell-targeting ability, and capacity to load multiple bioactive molecules. The use of migrasomes for drug delivery has shown promising preliminary results in basic research. In bone regeneration, migrasomes derived from M2 macrophages (induced by titanium nanotube arrays) naturally activate the PI3K-AKT pathway in BM-MSCs to promote osteogenic differentiation.[45] Loading osteogenic factors into these migrasomes is expected to enhance drug accumulation in target cells and avoid inflammation induced by exogenous carriers, providing a potential strategy for improving bone regeneration outcomes. In anti-infective therapy, migrasomes can act as "targeted antibacterial carriers". BM-MSCs stimulated by bacteria load antimicrobial peptides into migrasomes; these migrasomes then target pulmonary macrophages and enhance LAP to facilitate bacterial clearance.[37] Encapsulating broad-spectrum drugs (eg, vancomycin) in BM-MSC-derived migrasomes may increase drug concentrations at pulmonary infection sites while reducing systemic nephrotoxicity—representing a viable direction for optimizing anti-infective treatment regimens. In ocular therapy, regulating the cellular source of migrasomes enhances the specificity of drug delivery. For instance, migrasomes derived from RPE cells naturally accumulate in retinal tissues.[88] Encapsulating antiproliferative drugs (eg, rapamycin) in these migrasomes for the treatment of PVR may inhibit RPE cell proliferation and mitigate retinal toxicity associated with traditional intravitreal injections—opening a new avenue for safer ocular therapeutic strategies. Given their unique advantages, migrasomes have demonstrated cross-disciplinary drug delivery efficacy in basic research. This not only lays a foundation for the development of precise, low-toxicity drug delivery systems but also holds substantial promise for future clinical translation.

Future Prospects

While the application potential of migrasomes in disease diagnosis and therapy has been initially validated, ongoing research still faces limitations that impede translation from basic research to clinical practice. In terms of technical standardization, the detection and isolation of migrasomes remain unstandardized. Currently, migrasome isolation relies on conventional methods such as ultracentrifugation and density gradient centrifugation—approaches that cannot fully distinguish migrasomes from other extracellular vesicles (eg, exosomes).[93,94] Moreover, preprocessing protocols vary across laboratories, leading to poor reproducibility of results. Regarding specificity and clinical evidence, migrasomes lack exclusive molecular markers (eg, TSPAN4 is also expressed in some exosomes), making accurate quantification challenging. Existing evidence primarily stems from small-sample animal studies or single-center research, which fail to encompass diverse patient populations—leaving the generalizability of findings unvalidated. Furthermore, the therapeutic translation of migrasomes is hindered. Current therapeutic targets largely focus on broad-spectrum inhibition of migrasome formation, with a lack of disease-specific intervention strategies. Additionally, migrasome-based drug delivery systems face challenges including difficulty regulating release kinetics and high costs of large-scale production—barriers that prevent them from meeting clinical requirements.

The continuous advancement of emerging technologies provides critical tools to address the aforementioned research bottlenecks, offering hope for advancing migrasome research into an era of in-depth exploration. For example, single-cell RNA sequencing holds substantial potential for deciphering the heterogeneity of migrasome-associated gene expression. In studies of skin aging, this technology has clearly revealed a negative correlation between the extent of fibroblast senescence and the expression of migrasome markers (eg, TSPAN4 and TSPAN9)—thereby yielding valuable insights into the relationship between migrasomes and cellular senescence.[95] Moreover, high-resolution live-cell imaging techniques—such as iterative tomography and structured illumination microscopy—enable dynamic observation of 3D subcellular structures in living cells over several hours, with spatial resolution sufficient to capture subtle structures like migrasomes and contractile fibers.[21,96] These

technologies may further clarify the regulatory role of calcium ions in migrasome formation. Additionally, microfluidic chips can simulate the in vivo microenvironment to modulate cell migration.[97] Theoretically, they also hold promise for providing a controllable experimental system to study migrasome biogenesis. The development of fluorescent protein fusion labeling is critical for tracking migrasome dynamics. This technique involves fusing migrasome markers—such as TSPAN4 and ITGA5—with fluorescent proteins (eg, GFP or mCherry) and introducing the fused plasmids into cells via chemical transfection or electroporation.[96] This technique enables real-time observation of migrasome formation and distribution in living cells. Concurrently, in vitro reconstitution technology provides a controllable system for studying migrasome biogenesis. This method involves purifying key proteins (eg, TSPAN4) and embedding them into artificial proteoliposomes.[96] Giant unilamellar vesicles are generated via electroformation or gel-assisted hydration, followed by migrasome reconstitution using microfluidic channels or tether-pulling approaches.[96] Collectively, these advanced technologies enhance our understanding of migrasomes from multiple perspectives—genetic, structural, dynamic, and mechanistic—laying the groundwork for more precise and comprehensive research in this field.

Conclusion

As a newly discovered organelle formed during cell migration, migrasomes are deeply involved in the development of various diseases by mediating the transmission of signaling molecules, maintaining tissue homeostasis, and regulating the immune microenvironment. This review systematically summarizes the core roles of migrasomes in areas including tumor metastasis, viral infections, cardiovascular and cerebrovascular diseases, and renal pathologies: their specific molecular components can serve as biomarkers for early diagnosis, while their biogenesis mechanisms offer novel insights for the development of targeted therapies.

Despite persistent challenges in standardized detection, subtype sorting, and large-scale clinical validation, migrasome research has opened a new paradigm for understanding intercellular communication and disease progression. Looking ahead, the integration of cutting-edge technologies—such as single-cell techniques and high-resolution imaging—is expected to accelerate the translation of migrasomes into clinical applications, encompassing precision diagnosis, targeted drug delivery, and immunomodulation. This progress holds promise for delivering breakthrough strategies in the prevention and treatment of human diseases.

Disclosure

The author(s) report no conflicts of interest in this work.

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