Migrasomes: Emerging players in intercellular communication and disease pathogenesis (Review)

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Abstract. Migrasomes are novel extracellular organelles that were first reported in 2015. The present review summarizes the discovery, structural characteristics, biological functions and relationships of this new cellular organelle with diseases. Migrasomes are annular organelles that extend from the trailing edge of cells during cell migration and are rich in proteins, lipids, nucleic acids and other biomolecules. They serve important roles at multiple levels, including roles in cell-cell communication, tissue remodeling and immune regulation. The formation and function of migrasomes are associated with the regulation of various molecules and signaling pathways, including nucleation, expansion and maturation. Migrasomes also have important roles in organ morphogenesis, angiogenesis, mitochondrial quality control and immune regulation. In addition, migrasomes are closely associated with the development of various diseases, including kidney diseases, pneumonia after stroke, neurodegenerative diseases and cancer, providing new perspectives and potential targets for disease diagnosis and treatment. For example, in cancer, migrasomes can act as positioning signals, regulating the invasion of liver cancer cells. In neurodegenerative diseases, migrasomes may have a role in clearing damaged mitochondria, thereby helping to alleviate inflammatory responses and cellular dysfunction. Collectively, these findings suggest that migrasomes have notable potential for use in clinical disease diagnosis and treatment.

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Abbreviations: EV, extracellular vesicle; RF, retraction fiber; PLS, pomegranate-like structure; TSPAN, tetraspanin; SM, sphingomyelin; WGA, wheat germ agglutinin; SMS, sphingomyelin synthase; TEM, tetraspanin-enriched microdomain; FA, focal adhesion; NRK, normal rat kidney; ECM, extracellular matrix; PIP2, phosphatidylinositol 4,5-bisphosphate; GFP, green fluorescent protein; PIP5K1A, phosphatidylinositol-4-phosphate 5-kinase type-1α; PD-L1, programmed death-ligand 1; ROCK, Rho-associated protein kinase; RhoA, Ras homolog family member A; PTEN, phosphatase and tensin homolog; CXCL, C-X-C motif chemokine ligand; CXCR4, C-X-C chemokine receptor type 4; DFC, dorsal precursor cell; MSC, mesenchymal stem cell; KIF5B, kinesin-5B; MYO19, myosin head domain-containing protein 1; BM-MSCs, bone marrow mesenchymal stem cells; Syt1, synaptotagmin-1; CAA, cerebral amyloid angiopathy; GBM, glioblastoma

Key words: migrasomes, cell migration, cell-cell communication, mitochondrial quality control, biomarkers

Contents

1. Introduction

Cell migration is a fundamental process in cell biology and refers to the movement of cells from one location to another. During cell migration, a series of elongated tubular structures are produced at the trailing edge of the cell. Notably, cell migration serves a key role in various biological processes, including embryonic development, wound healing, immune response, tissue regeneration and tumor metastasis (1). Extracellular vesicles (EVs) are important mediators of intercellular communication, having notable roles in various physiological and pathological processes; for example, cancer cell-derived EVs can modulate the tumor microenvironment, and EVs from endothelial progenitor cells can induce a proangiogenic phenotype in terminally differentiated endothelial cells and promote angiogenesis. Therefore, EVs exhibit potential as novel biomarkers for diseases, therapeutic agents and drug delivery vehicles (2,3). Previous studies have revealed that EVs, including exosomes, microvesicles and apoptotic bodies,

serve important roles in a number of biological processes, including intercellular communication, tissue homeostasis, cell differentiation, organ development and remodeling (2-5). In 2015, a study by Ma *et al* (6) discovered a new type EV-like structure and proposed the concept of migrasomes as novel cellular organelles. Compared with other EVs, migrasomes exhibit distinct structural, compositional and functional characteristics. With diameters typically >1 μm, migrasomes are substantially larger than exosomes, which have diameters of 30-150 nm. Unlike the biogenesis of conventional EVs, such as exosomes derived from the endosomal pathway or microvesicles generated via plasma membrane budding, migrasome biogenesis is closely associated with cellular migration (6). This unique biogenesis mechanism suggests that migrasomes may serve as migration trail markers, whereas exosomes predominantly facilitate long-range intercellular communication (Table I). The discovery of migrasomes provides a new perspective on how cells transport materials and transmit information through extracellular structures (Fig. 1) (6-14).

2. Discovery of migrasomes

The concept of migrasomes was first introduced through observations of elongated tubular structures located at the rear of migrating cells. In early studies of migrating cells, Taylor and Robbins (7) discovered and documented that elongated tubular structures formed when migrating cells retracted from a substrate. They designated these structures 'retraction fibrils', which were later named 'retraction fibers' (RFs). Despite the initial lack of interest in these structures from researchers, in 2012, a study at Tsinghua University (Beijing, China) led by Yu (15) used transmission electron microscopy to reveal the migration process of rat kidney cells. The study revealed that cells leave behind RFs, which, upon further study, are associated with vesicular structures ranging in diameter from 0.5 to 3 μm (6,15). These structures, situated behind migrating cells that attach to the RFs left behind during cell migration (6), were termed pomegranate-like structures (PLSs) due to their resemblance to pomegranate seeds. By purifying these structures, tetraspanin (TSPAN)4, a distinct marker protein for PLS, was identified via mass spectrometry, which served as a robust reference for future migrasome research. Through knockdown of the negative regulator Shank-associated RH domain interacting protein and treatment with cell migration inhibitors, it was demonstrated that the formation of PLSs is dependent on cell migration (6). Consequently, PLSs were renamed 'migrasomes', being defined as annular organelles formed at the tips or intersections of RFs, or at the rear edge of migrating cells (6).

3. Biological characteristics of migrasomes

Structural features and main components. The process of migrasome production can be visualized dynamically via time-lapse imaging techniques (6,16). Subsequent studies have confirmed the widespread presence of migrasomes across a variety of species, tissues, organs and cell types, including rat eyes, lungs, intestines, zebrafish embryos, chick chorioallantoic membranes and human coronary artery endothelial cells (6,11,17-20) (Fig. 2). As a novel type of organelle, migrasomes are characterized as membrane-bound vesicles with an ellipsoidal shape that harbor numerous smaller vesicles. Their composition primarily comprises proteins, lipids and nucleic acids (6,21). Notably, migrasomes exhibit a distinctive protein profile, which includes membrane proteins, contractile proteins, cytoskeletal proteins, chaperones, vesicular trafficking proteins and cell adhesion proteins, >50% of which are membrane-related (6,21,22). These proteins are engaged predominantly in biological processes, including cell migration, cell matrix adhesion, lipid degradation, protein glycosylation and glycoprotein metabolism (21).

In comparison with the cell membrane and overall lipid composition of the cell, migrasomes are notably enriched in sphingolipids, such as sphingomyelin (SM), ceramide, monosialodihexosylgangliosides and glycosphingolipids, including monoglycosylceramide, diglycosylceramide and triglycosylceramide. In a study by Liang *et al* (23), it was demonstrated that ceramide and SM are essential for the formation and maintenance of migrasomes. Furthermore, filipin III staining and quantitative analysis revealed that migrasomes are enriched in cholesterol, an important component for the physical properties and structural integrity of the migrasome membrane; notably, TSPAN4, TSPAN7 and cholesterol assemble into TSPAN-enriched microdomain (TEMs), the enrichment of which stiffens the plasma membrane, facilitating migrasome initiation (9). Ongoing lipidomics analysis of migrasomes anticipates the discovery of additional lipid components, thereby verifying the growing profile of known biological characteristics and functions of migrasomes.

Migrasomes are rich in nucleic acids. A study by Zhu *et al* (24) employed SYTO™ 14 fluorescence staining to demonstrate the presence of RNA within migrasomes. Sequencing analyses revealed that migrasomes predominantly contain long-chain mRNAs associated with cell metabolism, intracellular membrane transport, cell adhesion, vesicle fusion and the assembly of subcellular membrane structures. These mRNAs can be translated into proteins within recipient cells, participating in the biological responses of recipient cells and regulating their life processes. For example, the phosphatase and tensin homolog (PTEN) mRNA delivered from migrasomes to recipient cells is translated into the PTEN protein, which inhibits the proliferation of the recipient cells (24). Nonetheless, the mechanisms of migrasome RNA sorting and transport have yet to be elucidated, as does the presence of DNA within migrasomes, necessitating further investigation.

Markers of migrasomes. TSPAN4/7, and integrins α1, α3, α5 and β1, which are expressed on the migrasome membrane, serve as important structural markers of migrasomes, with TSPAN4 being the most distinguishing marker, which exhibits the clearest expression when examined by confocal microscopy (6). Nonetheless, the detection of migrasomes using fluorescently labeled marker proteins presents limitations, including complex procedures, extended experimental duration and difficulty (25). Consequently, Chen *et al* (25) investigated fluorescently-labelled wheat germ agglutinin (WGA), which is a more rapid, straightforward and less invasive marker than TSPAN4. However, WGA may non-specifically bind to structures containing sialic acid and *N*-acetyl-D-glucosamine, and its fluorescence intensity can be influenced by various factors; for example, it may also enter the cell and bind to intracellular

Table I. Comparison of migrasomes with other extracellular vesicles.

Feature	Migrasomes	Exosomes	Microvesicles	Apoptotic bodies	Oncosomes
Structure	Pomegranate-like with intraluminal vesicles (0.5-3 μm)	Single-membrane vesicles (30-150 nm)	Single-layered lipid bilayer vesicles with irregular morphology (100 nm-1 μm)	Irregular large vesicles (1-5 μm)	Heterogeneous large vesicles (1-10 μm)
Biogenesis	Cell migration-dependent, formed at retraction fibers	Multivesicular body-plasma membrane fusion	Plasma membrane budding	Apoptotic process	Tumor cell membrane budding
Key components	TSPAN4, TSPAN7, integrin α5β1	Tumor susceptibility gene 101 protein, programmed cell death 6-interacting protein, CD63, CD81	Annexin A1, Annexin A2	Annexin V, caspase 3 metalloproteinases	Tumor-associated antigens, matrix
Lipid composition	Enriched in sphingolipids, including sphingomyelin and ceramide, and cholesterol	Sphingolipid-rich	Phosphatidylserine-rich rich	Phosphatidylserine-sphingolipids	Cholesterol,
Functions	Intercellular communication, migration positioning, mitochondrial quality control, disease association	Intercellular communication, immune regulation	Intercellular communication, inflammatory response	Intercellular communication, debris clearance	Tumor metastasis, microenvironment remodeling

TSPAN, tetraspanin.

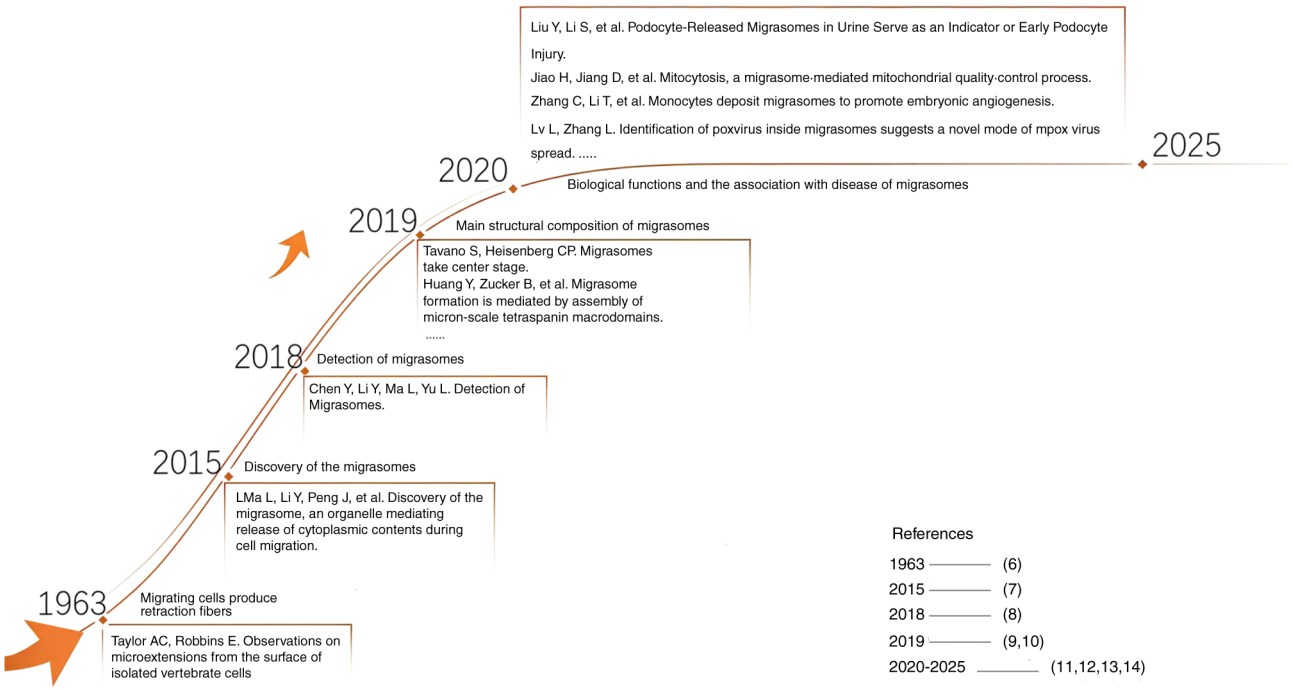

Figure 1. Advances in migrasome research.

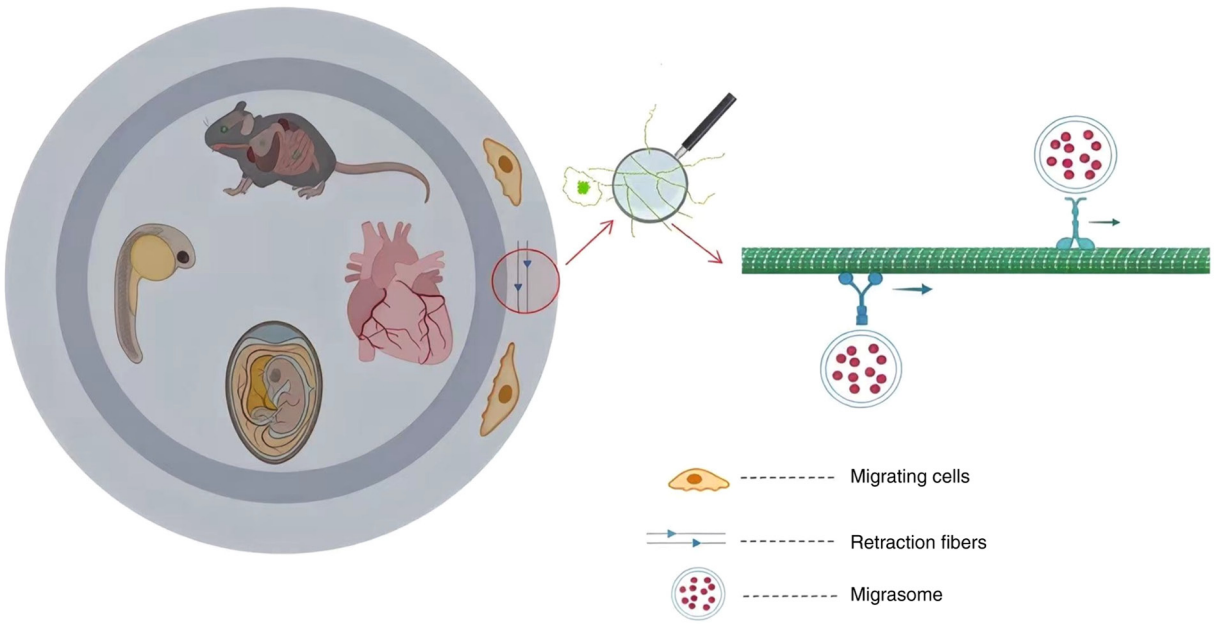

Figure 2. Biogenesis of migrasomes. Migrasomes are found in mice, zebrafish embryos, chick embryos, chorioallantoic membranes and human coronary endothelial cells, and are located on the retraction fibers during cell migration.

components, leading to enhanced nonspecific signals. In addition, different cell lines or tissue types naturally exhibit variations in the glycosylation levels of their cell membrane surfaces, which can also interfere with the results, potentially limiting its application in quantitative migrasome analysis (25). Additional specific protein markers include *N*-deacetylase/*N*-sulfotransferase 1, phosphatidylinositol glycan anchor biosynthesis class K, carboxypeptidase Q and epidermal growth factor domain-specific O-linked *N*-acetylglucosamine transferase; however, due to marked variations in protein content across different cell types, these markers are not uniformly present in migrasomes derived from the same cell source (21,22). Furthermore, migrasome-associated mRNAs can be labelled with the nucleic acid stain SYTO 14, making them secondary markers for migrasomes (24,26).

4. Mechanisms of migrasome formation

During cell migration, RFs are extended from the posterior end of the cell, with migrasomes situated at the termini or

bifurcations of these fibers (6). When RFs break, migrasomes may leak or rupture, thereby releasing their contents into the extracellular space (6). The formation of migrasomes is a complex process that involves the regulation of multiple molecules and signaling pathways.

Migrasome formation depends on cell migration. The formation of migrasomes is contingent upon cellular migration, a finding initially presented by Ma *et al* (6). A study revealed that, among 563 compounds capable of reducing migrasome numbers in cultured cells, 507 also decreased RF formation, reinforcing the association of migrasome production with cell migration (27). Subsequent research conducted by Fan *et al* (28) revealed a lower migrasome count in turning cells compared with those migrating in a straight line, highlighting the importance of migration continuity and speed in migrasome formation. Directional changes during migration lead to fewer RFs and migrasomes, with the removal of vimentin from cells having been shown to impair migration and reduce migrasome numbers (29,30). In conclusion, these findings suggested that the formation of migrasomes is markedly regulated by cell migration behavior.

Nucleation: SM synthase (SMS)2 foci are the starting point of migrasome biogenesis. SM, synthesized from ceramide by SMS, is a key component of the plasma membrane, and is involved in signaling and membrane transport (23). A previous study has shown that SM and ceramide are enriched on migrasomes and are present at the sites of migrasome formation; furthermore, ceramide is unevenly distributed on different migrasomes, and as migrasome biogenesis proceeds, SM levels continuously increase, indicating that ceramide can be converted into SM on migrasomes (23). Hydrolyzing SM on migrasomes or knocking out ceramide synthase 5 to reduce SM synthesis severely impairs the formation of migrasomes, demonstrating the importance of SM for migrasome formation (23).

Mammalian cells contain two principal types of SMS: i) SMS1, which is localized in the Golgi apparatus; and ii) SMS2, which is located in both the Golgi apparatus and the plasma membrane (31). SMS2 synthesizes SM from ceramide in the plasma membrane (23,31). Consequently, it is plausible that SMS2 modulates migrasome formation by facilitating SM production. Experimental evidence, including the knockout of SMS2 and treatment with SMS2 inhibitors that hinder SM synthesis, has demonstrated that migrasome formation and growth are impeded in SM-depleted conditions, whereas the reintroduction of SM restores migrasome production (23). Furthermore, impaired SM synthesis reduces cholesterol recruitment, thereby affecting TEM assembly, since TSPAN4, TSPAN7 and cholesterol assemble into TEMs, the enrichment of which stiffens the plasma membrane, which is an important condition for migrasome formation (9).

Research has revealed that SMS2 localizes to foci on the basal membrane at the leading edge of a cell, which predestines migrasome formation sites (23). These foci mature into migrasomes during cell migration (23). Intracellular SMS2 foci initially adhere to the section of the membrane of the migrating cell that is interacting with a substrate to generate motility, resembling focal adhesions (FAs), which are the sites where cells are linked to the ECM in which integrins are highly enriched. However, previous studies have failed to detect FA markers within migrasomes, and active forms or markers of FA components such as integrin α5, integrin β1 or the FA kinase paxillin do not colocalize with intracellular SMS2 foci, underscoring that SMS2 focus formation is independent of FAs (23,32). To elucidate the role of SMS2 foci in migrasome formation, researchers identified an SMS2 mutant, S217A, that cannot form foci. The formation of migrasomes in cells expressing this mutation has been shown to be markedly diminished (23). Notably, the inability to form SMS2 foci prevents migrasome formation, even when exogenous SM is added (23). These findings suggest that SMS2 foci not only regulate migrasome formation by synthesizing SM, but may also be involved in other important intracellular signaling processes that are required for migrasome biosynthesis and function. Future investigations should explore the precise mechanisms of SMS2 focus assembly, the selection of assembly sites and the adhesive mechanisms of SMS2 foci to fully elucidate the contribution of SMS2 foci to migrasome formation and function.

Expansion: TSPAN4 and cholesterol mediate migrasome formation. TSPANs constitute a family of small hydrophobic proteins characterized by four transmembrane domains, comprising a total of 33 distinct members in mammalian cells. These proteins facilitate the organization of functional higher-order protein complexes on the cell membrane through interactions with adhesion molecules, enzymes and signaling proteins, thereby forming the structures known as TEMs (33,34). Initial research identified TSPAN4 as a marker of migrasomes; however, subsequent investigations have suggested that the roles of TSPAN family members may extend beyond this initial characterization. By establishing a stable normal rat kidney (NRK) cell line that expresses various levels of TSPAN4 and green fluorescent protein (GFP), a study by Huang *et al* (9) demonstrated that the overexpression of 14 types of TSPAN family members enhances migrasome formation in a dose-dependent manner, with TSPAN4 exhibiting the most pronounced effect. Conversely, knockout of the TSPAN4 gene was shown to markedly reduce the number of migrasomes, underscoring the importance of TSPAN4 for migrasome formation. During the migrasome formation process, the signal from TSPAN4-GFP during the growth phase of migrasomes rapidly re-emerges on their surface, whereas no such recovery occurs when migrasomes tend to mature and stabilize (9). Furthermore, high-speed imaging revealed that TSPAN4-GFP forms rapidly-moving-discrete spots on RFs and migrasomes that assemble on the surface of migrasomes during their growth phase. Taken together, these findings suggest that TSPAN4 is recruited to migrasomes specifically during the growth phase (9).

By developing an *in vitro* system to simulate migrasome formation, researchers have demonstrated that TSPAN4 and cholesterol are sufficient to reconstitute migrasome-like structures, further validating their role in this process (9). To elucidate how the assembly of TEMs promotes migrasome formation, a theoretical model was proposed, identifying three key energetic drivers: i) The bending energy of the migrasome and RF membranes; ii) the membrane tension energy; and

iii) the boundary energy at the migrasome-RF interface (9). A subsequent study using a biomimetic system divided migrasome growth into two phases: i) A local swelling phase, driven by membrane tension and potentially other cellular factors (such as the cytoskeleton, specific lipids, ion fluxes, mechanosensitive signaling and adhesion complexes); and ii) a TSPAN4 migration-enrichment phase mediated by TSPAN family proteins (35). Notably, the biomimetic system lacks cytoskeletal components, which may regulate migrasome formation *in vivo*; therefore, discrepancies between artificial and cellular systems may exist (6,17,21,22). TSPAN4, TSPAN7 and cholesterol assemble into TEMs, whose enrichment stiffens the plasma membrane, facilitating migrasome initiation. Changes in TSPAN4 curvature will affect the swelling of the plasma membrane, the reduced intrinsic curvature of TSPAN4 directs TEMs to low-curvature membrane swellings, stabilizing these protrusions and promoting migrasome maturation (9,10,18,35,36). In summary, TEMs composed of TSPAN4 and cholesterol are important for migrasome biogenesis.

Maturation

Integrin and extracellular matrix (ECM) protein pairing determines migrasome formation. Integrins are transmembrane receptors that bind ECM proteins and link to the cytoskeleton via intracellular adapters. These heterodimeric proteins, which are composed of α and β chains, are important for cell adhesion, spreading, migration and matrix remodeling (37). Migrasomes, which adhere to ECM sites during cell migration, are enriched with integrin α5β1, as revealed by mass spectrometry (32). Fluorescence staining confirms that integrin β1 in migrasomes is in an activated, ligand-bound state, demonstrating direct ECM binding. Three-dimensional imaging and total internal reflection fluorescence microscopy have further revealed the localization of integrins α5 and β1 at the migrasome base, supporting their role in migrasome anchorage (32).

Although FAs also contain high integrin concentrations, FA markers are absent in migrasomes, indicating a distinct adhesion mechanism (32,38). A functional study has revealed that NRK cells produce markedly more migrasomes on fibronectin-coated surfaces than on laminin 511- and collagen I-coated surfaces, with minimal migrasome formation on uncoated coverslips. This increase in migrasome formation on fibronectin-coated surfaces compared with other ECM components is associated with an elevated integrin α5 expression in NRK cells, as α5 knockout impairs migrasome production on fibronectin but not on other ECM components (32). Conversely, integrin α3 overexpression increases the number of migrasomes on laminin 511. Similarly, integrin α1 overexpression enhances migrasome formation on collagen IV in Chinese hamster ovarian cells without affecting formation on other ECM components (32). These findings demonstrate that migrasome formation depends on specific integrin-ECM pairings.

Phosphatidylinositol 4,5-bisphosphate (PIP2)-Rab35 axis regulates migrasome formation. PIP2, a plasma membrane lipid synthesized by phosphatidylinositol 4-phosphate 5-kinase type-1α kinases, regulates key subcellular processes, including the regulation of ion channels and transporters, clathrin-dependent and -independent endocytosis, exocytosis regulation, actin polymerization, efficient FA turnover and the regulation of cell-cell contacts) (39,40). PIP2 localizes to migrasomes, as confirmed by phospholipase Cγ-PH domain-GFP fusion protein probes and antibody staining (41). Kinetic experiments have revealed that PIP2 recruitment precedes TSPAN4 and integrin α5 recruitment, both of which are important for migrasome biogenesis. Phosphatidylinositol-4-phosphate 5-kinase type-1α (PIP5K1A) inhibition disrupts migrasome formation, implicating PIP2 synthesis in this process (41).

PIP2 likely functions by recruiting binding partners, such as Rab35, a GTPase involved in organelle biogenesis, endosomal trafficking and actin regulation (42). Rab35 is recruited to migrasome formation sites in a PIP2-dependent manner, and its depletion disrupts RF elongation and migrasome assembly (41). Rab35 also interacts with integrin α5 via the GFFKR motif, recruiting integrins α5 to migrasome sites, although the direct binding mechanism remains unconfirmed (41,43). Thus, the PIP2-Rab35 axis orchestrates migrasome formation by coupling lipid signaling with integrin trafficking. Future studies should address PIP5K1A recruitment dynamics, Rab35-integrin α5 interactions and the clinical relevance of the PIP2-Rab35 signaling axis in cancer and migration-associated diseases.

Roles of Rho-associated protein kinase (ROCK)1 and programmed death-ligand 1 (PD-L1) in migrasome formation. Through a chemical genetic screen designed to identify compounds and protein targets that disrupt migrasome formation, a study by Lu *et al* (27) identified SAR407899, an inhibitor of ROCK1 and ROCK2, which stably suppresses migrasome biogenesis. ROCK1 and ROCK2 are serine/threonine kinases that act downstream of the small GTPase Ras homolog family member A (RhoA), regulating diverse cellular processes, including actin cytoskeleton organization, cell adhesion and migration, via the ROCK-Rho signaling pathway (44). Although ROCK2 knockdown does not affect migrasome formation, ROCK1 depletion markedly reduces the migrasome abundance per cell (27). Notably, ROCK1 knockdown also impairs cell migration. To distinguish the effects of RFs and migration from migrasome formation, researchers have quantified the number of migrasomes per 100 μm RFs (27). The findings of this experiment revealed that ROCK1-depleted cells generate notably weaker traction forces than healthy cells, supporting the premise that migrasome formation depends on ROCK1-mediated traction and other ECM components (such as fibronectin) adhesion (27).

PD-L1 is best known as an immune checkpoint molecule that facilitates cancer cell migration (45). Emerging evidence has indicated that PD-L1 has an intrinsic capability to facilitate sustained cellular migration, a process important for migrasome biogenesis. High-resolution time-lapse microscopy has demonstrated that PD-L1 accumulates at the trailing edge of migrating cancer cells, where it forms distinct structures that move directionally during retraction (46). Given that RFs form at the rear of the cell during migration, a subsequent study demonstrated that PD-L1 localizes not only in RFs, but also in migrasomes. Notably, PD-L1 enhances migrasome formation independently of cell migration (46). PD-L1 closely associates with integrin β4, co-localizing at the rear of the cell, and later

in RFs and migrasomes. A further investigation revealed that PD-L1 recruits integrin β4 to the trailing edge; this recruitment stimulates contractility via the dynamics of the cell, a mechanism by which PD-L1 maintains rear polarity and reduces membrane tension (46). Additionally, PD-L1 activates RhoA by coupling integrin β4 to the cytoskeleton, further promoting rear contraction (actin cytoskeleton-mediated contractility) (46). Taken together, these findings underscore the dual role of PD-L1 in facilitating cell migration and migrasome formation. However, the precise mechanisms of PD-L1 in migrasome biogenesis, and its broader functional implications, warrant further exploration.

5. Other factors affecting migrasome formation

Regarding the formation mechanisms of migrasomes in different cell types, the universal core mechanism involves the following sequence of events: i) Cell migration initiation; ii) the formation of TEMs; and subsequently iii) the recruitment, fusion and maturation of microvesicles (the precursors of migrasomes) (6,9). However, migrasome formation is a complex biological process influenced by multiple factors, and the underlying mechanisms may vary across cell types. Some examples are as follows: i) Triggering signals vary, for example monocytes and macrophages may initiate migrasome generation through tissue damage and clearance signals, with these migrasomes potentially participating in angiogenesis regulation or damaged mitochondrial clearance, whereas cancer cells may trigger migrasome formation via oncogenic or metastasis-driving signals to promote cancer progression; and ii) regulatory factors may be cell type-specific. For example, normal human dermal fibroblasts exhibit modulated migrasome formation through peptide-modified matrices, which affect contractile fiber quantity and length (different peptide-modified substrates influence the strength of cell migration, such as migration distance and duration, thereby affecting the number and length of RFs) (47). Mouse embryonic stem cells exhibit calcium ion and synaptotagmin-1 (Syt1)-regulated migrasome production, where calcium promotes migrasome formation via Syt1 (48). Furthermore, in H4 human glioma cells, osmotic regulation may control migrasome formation, as hypotonic conditions induce the formation of TSPAN4-enriched migrasome-like vesicles on RFs. These cholesterol-dependent vesicles exhibit migrasome characteristics but originate from osmotic stress rather than from cell migration (49). While conclusive identification of these cholesterol-dependent vesicles as migrasomes requires further evidence, these observations provide valuable perspectives on cellular osmoregulation and migrasome biophysical responses in tissues. A previous report indicated that high-salt diets exacerbate ischemic brain injury by promoting excessive migrasome formation in microglia and macrophages, reducing their post-ischemic populations alongside astrocytes (17).

Migrasomes from different cell types participate in distinct biological activities. Nevertheless, research on most cell-type-specific migrasomes remains preliminary, and the generation mechanisms of these migrasomes have not been fully elucidated. Currently, evidence confirms only their existence and functional roles in various biological responses. For example, migrasomes produced by zebrafish embryonic cells can regulate the formation of zebrafish embryonic organs; migrasomes derived from adipose stem cells serve a key role in adipose tissue regeneration; and migrasomes from neutrophils affect the coagulation function of the body (18,50). Specialized investigations into cell-type-specific formation mechanisms remain lacking, preventing targeted discussion of these mechanisms at present. Exploring these heterogeneous-origin migrasomes and their impacts on cellular functions and disease pathogenesis constitute an important future research direction.

6. Biological functions of migrasomes

Migrasomes, notable organelles in cell migration, are increasingly recognized for their roles in cellular physiology and pathology. Their formation and function are closely associated not only with cellular-migratory capacity, but also with intercellular communication, tissue remodeling and immune regulation. These microvesicles serve as carriers for the intercellular transfer of biomolecules, such as proteins, mRNAs and microRNAs, thereby modulating the gene expression and functional states of recipient cells. The present section elucidates the biological functions of migrasomes in organ morphogenesis, angiogenesis, mitochondrial quality control and immune regulation, highlighting their notable roles in maintaining tissue homeostasis and contributing to disease pathogenesis (Fig. 3). A deeper understanding of these functions underscores the complexity and diversity of migrasomes in biological systems and their potential as therapeutic targets in medical research.

Communication and regulatory functions. Migrasomes constitute a notable secretory pathway in migrating cells, encapsulating diverse cytoplasmic contents (6,51). Migrasomes form and mature on RFs of migrating cells before they detach, rupture and release their contents (6) (Fig. 3A). Migrasomes can also be internalized by neighboring cells, or adhere to cell surfaces or the ECM without being engulfed. For example, interactions with the ECM enable migrasomes to attach to specific cell surfaces or tissues, facilitating intercellular communication (32). These vesicles transport intracellular biomolecules, including proteins, mRNAs and microRNAs. Recent studies have indicated that secretory proteins, such as signaling molecules, are actively transported from migrating cells into migrasomes via kinesin-mediated carriers, akin to targeted neurotransmitter release in neuronal systems (51). These molecules can be transferred to adjacent or distant cells, altering recipient cell-gene expression and function. For example, Zhu *et al* (24) added purified migrasomes derived from L929 cells to U87-MG, MDA-MB-468 and PC3 cells that do not express the PTEN protein, and demonstrated that migrasomes mediate the transfer of PTEN mRNA and protein, inhibiting proliferation in recipient cells.

Migrasomes are enriched with cytokines, including chemokines and morphogens, which enables them to act as signaling molecule-carriers, and thereby influence cell behavior. In zebrafish embryos, gastrula-derived migrasomes contain high levels of C-X-C motif chemokine ligand (CXCL)12a (18). These migrasomes, produced during mesoderm and endoderm cell gastrulation, regulate organ development. Mutations that

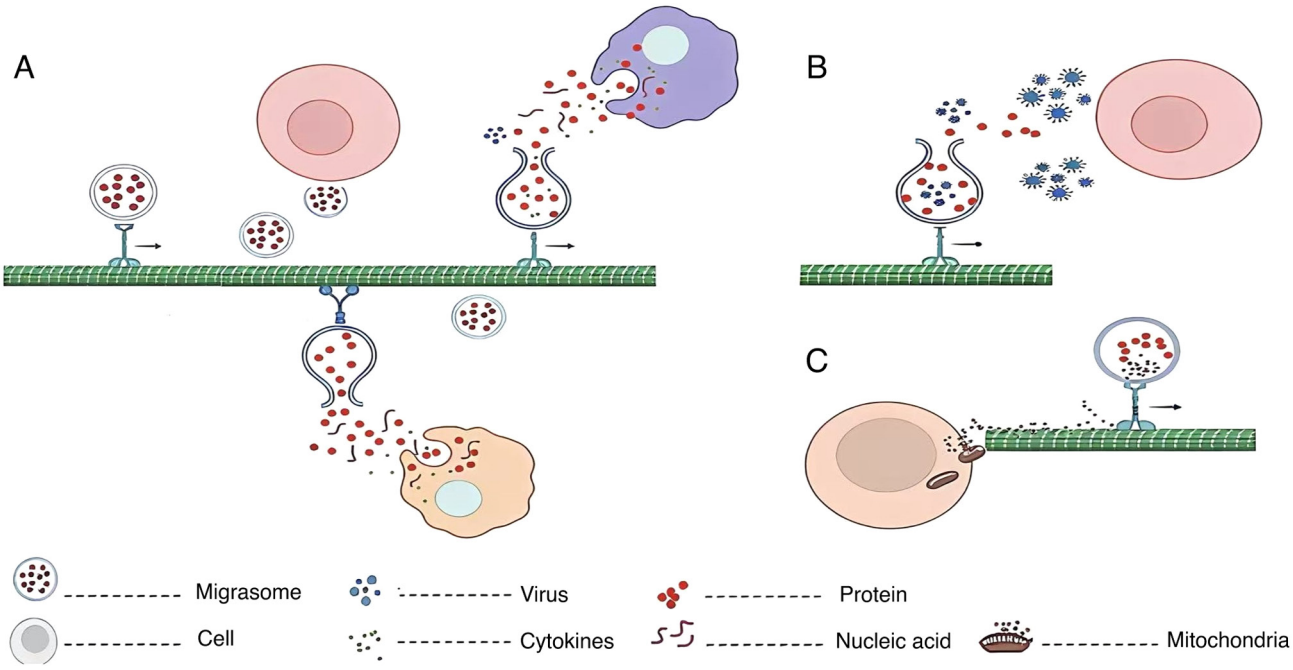

Figure 3. Biological functions of migrasomes. (A) Cell-cell communication and regulation mediated by migrasomes and their cargo. (B) Migrasome-mediated viral transmission. (C) Clearance of damaged mitochondria via migrasomes.

reduce migrasome numbers lead to severe developmental defects, which can be rescued by migrasome supplementation, underscoring their role in organogenesis (18). Further studies have revealed that CXCL12 in migrasomes interacts with C-X-C chemokine receptor type 4 (CXCR4) on dorsal precursor cells (DFCs), inducing chemotaxis and ensuring typical organ morphogenesis (35). Migrasomes thus spatially and temporally distribute signaling molecules, releasing CXCL12 upon rupture to modulate DFC behavior. Similarly, adipose-derived stem cells produce CXCL12-enriched migrasomes that promote adipose tissue regeneration via CXCR4/RhoA signaling (50).

A study by Zhang *et al* (11) identified migrasome-producing monocytes in the chorioallantoic membrane of chicken embryos, where these vesicles are rich in proangiogenic factors, including TGF-β3, VEGFA and CXCL12. In this context, migrasomes induce endothelial tube formation; their depletion via monocyte clearance or TSPAN4 knockout inhibits angiogenesis, whereas supplementation restores monocyte recruitment and capillary formation (11). Monocytes leverage migrasomes to deliver angiogenic factors, thereby creating a microenvironment conducive to blood vessel growth. Notably, migrasome-derived CXCL12 recruits additional monocytes, forming a positive feedback loop (11,52).

Multipotent mesenchymal stem cells (MSCs) are precursors to various cell types, with the ability to support tissue homeostasis, promote hematopoiesis and interact with cancer cells. Previous research on MSCs has focused on MSC-derived EVs (MSC-EVs), indicating that MSC-EVs have functions similar to those of MSC (53-58). A recent investigation demonstrated that MSCs generate migrasomes that attract leukemia KG-1a cells and $CD34^+$ hematopoietic stem cells via the CXCR4-CXCL12 axis (59). These migrasomes, enriched in TSPANs, including CD166 and TSPAN4, and endosomal markers, such as Rab7 and CD63, are influenced by ECM components such as fibronectin and laminins. In addition to influencing cell migration and thereby affecting the formation of retraction fibers, ECM components can also impact the process of TEM formation (59). Migrasomes produced by MSCs attract leukemia KG-1a cells and $CD34^+$ hematopoietic stem cells through the CXCR4-CXCL12 axis, thereby facilitating communication between the MSCs and these cells, thus highlighting the role of migrasomes in MSC-hematopoietic cell interactions, offering insights into their functions in health and disease.

Neutrophil-derived migrasomes adsorb coagulation factors from the plasma; migrasomes actively bind and enrich coagulation factors on their surface by virtue of their unique membrane composition, particularly cholesterol esters, and then localize to injury sites and modulate coagulation by activating platelets (60). These migrasomes also regulate immune responses by delivering cytokines and chemokines to injury sites, enhancing immune cell recruitment during inflammation (60). Conversely, migrasomes have been shown to suppress immunity by transporting immunosuppressive molecules, thereby maintaining immune tolerance (46).

Participation in maintaining cellular homeostasis. Mitochondria, the cellular 'powerhouses', maintain homeostasis through energy production and quality control mechanisms, such as mitophagy (61,62). A previous study demonstrated that migrasomes mediate mitocytosis, a process in which damaged mitochondria are selectively expelled to sustain cellular health (12) (Fig. 3C). Under stress conditions, such as carbonyl cyanide m-chlorophenyl hydrazone treatment, mitochondria undergo fragmentation via kinesin-5B (KIF5B)-mediated transport and myosin head

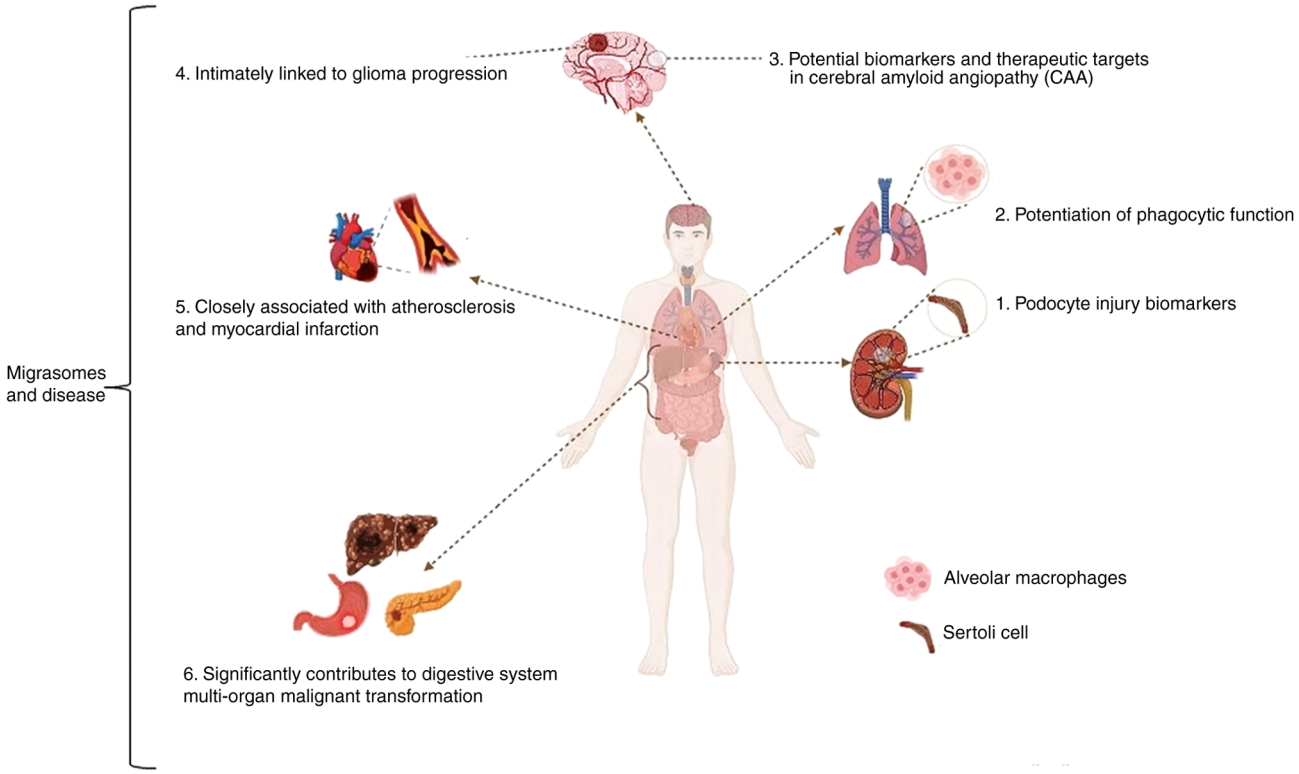

Figure 4. Associations between migrasomes and clinical diseases.

domain-containing protein 1 (MYO19)/density-regulated protein 1-dependent fission, accumulating at the cell periphery for subsequent migrasome encapsulation. Knocking out TSPAN9 or taking other measures to block the formation of migrasomes has been shown to cause migrating cells to lose their mitocytosis capability, leading to the accumulation of damaged mitochondria within the cells and affecting cell viability (12,63,64).

Although both mitocytosis and mitophagy contribute to cellular homeostasis, their mechanisms differ markedly. Mitocytosis, which is mediated by migrasomes, selectively removes mildly damaged mitochondria from migrating cells. In this process, damaged mitochondria selectively bind to intracellular dynein to facilitate their transport out of the cell, they are then transported towards the cell periphery by outwards motor proteins, such as KIF5B. MYO19 further facilitates this process by anchoring mitochondria to cortical actin, thereby promoting their incorporation into migrasomes (12,63,64). By contrast, mitophagy primarily degrades damaged mitochondria via the autophagy pathway. Upon mitochondrial damage, PTEN-induced kinase 1 accumulates on the outer mitochondrial membrane, where it recruits parkin to ubiquitinate outer membrane proteins. This ubiquitination marks the mitochondria for autophagosomal engulfment, and subsequent lysosomal degradation (61,62).

Mitocytosis complements mitophagy by incrementally clearing mildly damaged mitochondria. Migrasomes may also transfer mitochondrial components, including mitochondrial DNA and mitochondrial microRNAs, to recipient cells, influencing their function.

Migrasomes mediate virus spread. Migrasomes facilitate viral dissemination, facilitating the evasion of antiviral therapies (Fig. 3B). Vaccinia virus induces migrasomes containing viral particles, enabling their spread despite tecovirimat treatment (13,65). Similarly, herpes simplex virus-2 exploits migrasomes as 'Trojan horses' for intercellular transmission (66). Taken together, these findings illuminate novel viral spread mechanisms and suggest potential targets for antiviral strategies.

7. Migrasomes and disease

As research advances, the understating of migrasomes is improving, with their structure and physiological functions becoming increasingly elucidated. Studies have demonstrated that migrasomes perform notable roles in intercellular communication and signal transduction, as well as in the pathogenesis of various diseases (Fig. 4). These findings highlight the potential of migrasomes for clinical applications in disease diagnosis and treatment.

The association between migrasomes and kidney disease is particularly notable. Studies have identified podocyte-derived migrasomes in urine as early biomarkers of podocyte injury (14,67). Podocytes, which regulate glomerular permeability, are terminally differentiated cells incapable of regeneration; therefore, early detection of their injury is important for managing glomerular diseases (14). Research indicates that podocytes generate migrasomes during migration, with their numbers markedly increasing during kidney injury. Furthermore, Rac-1 inhibitors that target a small Rho family GTPase that is overactivated in podocyte injury

dose-dependently suppress lipopolysaccharide-induced migrasome release, underscoring the diagnostic potential of the urinary presence of podocyte migrasomes (14).

Migrasomes also exhibit therapeutic relevance for post-stroke pneumonia. Bone marrow (BM)-MSC-derived migrasomes, which are packed with dermcidin, display dual effects that reduce pulmonary bacteria load and enhance LC3-associated phagocytosis (LAP) of macrophages (68). These migrasomes not only exert antibacterial effects, but also augment LAP in macrophages, facilitating bacterial clearance. Consequently, BM-MSC-derived migrasomes represent a promising alternative to conventional antibiotics for preventing and treating post-stroke pneumonia.

In neurodegenerative disorders, migrasomes have been implicated in cerebral amyloid angiopathy (CAA). β-amyloid protein 40-induced macrophage-derived migrasomes adhere to the vasculature in biopsies from patients with CAA and mouse models, delivering the protein CD5L to vascular walls and triggering complement-dependent cytotoxicity, thereby compromising the blood-brain barrier (69). These observations suggest that macrophage-derived migrasomes and complement activation are potential biomarkers and therapeutic targets for CAA.

Emerging evidence further links migrasomes to atherosclerosis, myocardial infarction and malignancies. TSPAN4, a migrasome-forming protein, is strongly associated with atherosclerosis regression-associated macrophages according to single-cell sequencing, Gene Expression Omnibus datasets and The Cancer Genome Atlas analyses, and is also associated with plaque hemorrhage and rupture (70). In another study, low-intensity pulsed ultrasound has been shown to mitigate myocardial ischemia-reperfusion injury via migrasome-mediated mitochondrial quality control; the possible mechanism involves promoting the formation of migrasomes, potentially by enhancing cell motility, which enables migrasomes to exert mitocytosis activity, facilitating the removal of damaged mitochondria from cells (71). TSPAN4 is also upregulated in hepatocellular carcinoma, gastric cancer and glioblastoma (GBM), where it influences tumor-associated macrophages (72). In hepatocellular carcinoma, migrasomes guide cancer cell invasion (73); in pancreatic cancer, pancreatic cancer cell-derived migrasomes modulate immunosuppressive factors in the tumor microenvironment, thereby accelerating progression (74). In GBM, TSPAN4 promotes the progression of GBM by regulating epidermal growth factor receptor stability, whereas migrasome-autophagosome crosstalk alleviates endoplasmic reticulum stress and migrasome-mediated GBM-microenvironment communication may drive recurrence (75-77). Collectively, these findings underscore the therapeutic potential of targeting TSPAN4 and migrasomes in severe diseases.

8. Summary and outlook

Migrasomes, a novel class of EVs, have attracted considerable attention in the field of cell biology, with their important roles in cellular processes gradually being elucidated. Research on migrasomes has advanced markedly, from structural characterization to functional exploration. These vesicles not only serve important roles in normal physiological processes,

Table II. Dual roles of migrasomes in diseases.

Disease type	Functional mechanism	Potential applications
Developmental defects	Loss of $CXCL12^{+}$ migrasomes leads to abnormal organ morphogenesis in zebrafish embryos (18)	Early intervention targets for developmental disorders
Tumor microenvironment	MSC-derived migrasomes recruit leukemia cells; pancreatic cancer migrasomes enrich immunosuppressive factors (59,74)	Blocking migrasome-mediated tumor metastasis
Ischemic injury	Adipose stem cell-derived migrasomes activate Ras homolog family member A via CXCL12, promoting vascular regeneration (50)	Tissue engineering and regenerative medicine
Inflammation and infection	Neutrophil-derived migrasomes enhance coagulation or antibacterial functions, such as releasing dermcidin in post-stroke pneumonia (68)	Novel anti-infection strategies
Autoimmune diseases	Migrasomes deliver immunosuppressive molecules, such as interleukin-10, to maintain immune tolerance (46)	Immunomodulatory therapies for autoimmune disorders

CXCL, chemokine ligand.

but also modulate cell behavior and disease progression under pathological conditions, highlighting their potential as biomarkers and therapeutic targets.

The field of migrasome research is rapidly evolving, but still faces substantial challenges. Firstly, a deeper mechanistic understanding of migrasome biogenesis and its regulatory networks, particularly the contributions of lipid and protein components, is important. Secondly, further experimental validation is needed to clarify how migrasome-derived biomolecules, such as RNAs and proteins, influence recipient cell functions and mediate intercellular communication. Additionally, investigating migrasome heterogeneity across cell types and tissues, as well as their functional alterations in disease states, remains a key research direction. Advances in single-cell sequencing and high-resolution imaging technologies are expected to provide deeper insights into the biology and disease-related functions of migrasomes.

Clinically, migrasome research may offer novel strategies for early disease diagnosis and therapy (Table II). For example, migrasomes could serve as biomarkers for monitoring kidney or neurodegenerative diseases, or their formation and function could be therapeutically targeted. Furthermore, migrasome involvement in viral transmission suggests their potential applications in infectious disease research. As knowledge on the function of migrasomes expands, their impact on research and clinical therapeutics is expected to grow. In summary, migrasome research presents both challenges and opportunities, with future discoveries poised to further elucidate the complexity of cellular processes while advancing diagnostic and therapeutic innovations.

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Authors' contributions

YC and QW wrote the manuscript. YC, XL, BZ and HZ revised the manuscript. XL supervised the present review and guided each author who participated in writing the article. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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