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REVIEW

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Migrasomes as intercellular messengers: potential in the pathological mechanism, diagnosis and treatment of clinical diseases

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Abstract

Migrasomes are newly identified organelles that were first discovered in 2015. Since then, their biological structure, formation process, and physiological functions have been gradually elucidated. Research in recent years has expanded our understanding of these aspects, highlighting their significance in various physiological and pathological processes. Migrasomes have been found to play crucial roles in normal physiological functions, including embryonic development, vascular homeostasis, material transport, and mitochondrial quality control. Additionally, emerging evidence suggests their involvement in various diseases; however, clinical research on their roles remains limited. Current studies indicate that migrasomes may contribute to disease pathogenesis and hold potential for diagnostic and therapeutic applications. This review consolidates existing clinical research on migrasomes, focusing on their role in disease mechanisms and their use in medical applications. By examining their biological structure and function, this review aims to generate insights that encourage further research, ultimately contributing to advancements in disease prevention and treatment.

Article Highlights

- Evaluates optimal logistics facility locations within Uzbekistan's railway network using a multicriteria decision-making framework.
- Introduces a hierarchical goal tree method for transparent and evidence-based infrastructure placement.
- Highlights how strategic facility placement impacts regional competitiveness, economic growth, employment, and overall logistics sector development.

Keywords Disease, Cell communication, Organelles, Treatment, Pathology, Migrasome

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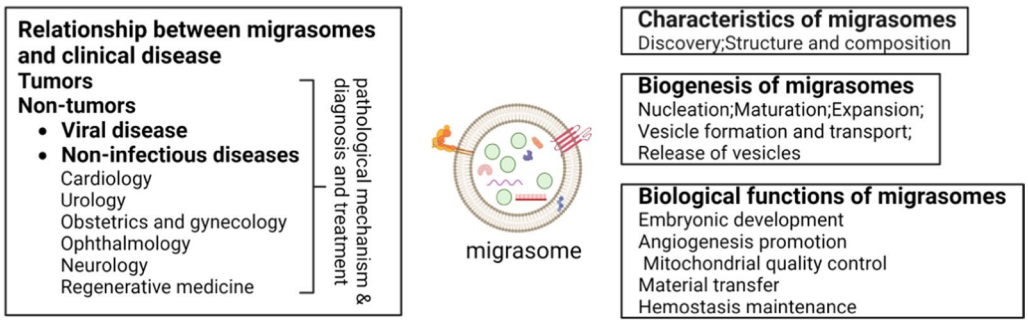
Graphical abstract



Introduction

Migrasomes are newly defined organelles produced by migrating cells, discovered by Professor Yu Li at Tsinghua University in China in 2015 [1]. During cell migration, long tubular "retraction fibers" are produced at the tail of the cells, and large single-layer membranous vesicles are produced at the tail and bifurcation of the contraction fibers. These contain many small vesicles and resemble an unsealed pomegranate. As the formation of these large vesicles depends on cell migration, they are called "migrasomes" [1]. Cytoplasmic contents can be transported into migrasomes and then released from cells; this migration-dependent release mechanism is called "migracytosis" [1]. During the migration process in vivo, cells can release their contents into a specific space at a specific time by producing migrasomes, thus mediating the release of cytoplasmic content and communication between cells, such as signal transmission [2, 3], maintenance of cell homeostasis [4], and material transmission [5]. With the introduction and study of migrasomes, a new cell secretion mode has been proposed in which cells are not in a stationary state; secretory vesicles are randomly transported to the cell edge and fuse with the cell membrane to complete secretion. When the cell enters a migratory state, the secretory vesicles exhibit a highly polar distribution, which is specifically enriched at the cell tail and transported to the migrasome, where it fuses with the migrasome membrane to complete the secretory mode [6]. Therefore, migrasomes can not only release signals at fixed points but also form an important secretion mode for migrating cells [6].

We already know that intercellular communication occurs mainly through direct contact, paracrine signals, and extracellular vesicles [7, 8]. Many studies have demonstrated that extracellular vesicles play an important role in intercellular communication and are crucial for the regulation of disease progression [9, 10]. Multiple studies have shown that migrasomes affect various physiological functions of cells through intercellular communication and signal transduction [11], indicating that migrasomes also play important regulatory roles in the pathological processes of various clinical diseases. Migrasomes are reportedly involved in the occurrence and development of various diseases, including tumors [12–14], viral infections[15–17], and cardiovascular [18], neurological [19], ophthalmic [20], obstetric, gynecological [21], and urological diseases [22]. They have also been found to play a role in regenerative medicine [23]. Moreover, migrasomes released by different cell types are closely related to the diagnosis and treatment of diseases under different pathological conditions. Therefore, to better understand the correlation between migrasomes and clinical diseases, this review aims to summarize the research progress on the role of migrasomes in clinical diseases, highlight their role in the pathological processes of these diseases, and discuss their potential clinical applications as biomarkers in clinical disease diagnosis and treatment.

Migrasome characteristics

Migrasome discovery

In 1963, Taylor et al. [24] revealed that migrating cells presented a long tubular structure after retraction from the matrix. In 2015, Ma et al. [1] identified a unique vesicle structure in the extracellular environment of normal rat kidney (NRK) cells. Furthermore, when NRK cells migrated, long tubular "retraction fibers" (RFs) were observed. As the vesicle structure resembles an open pomegranate, it was originally called a pomegranate-like structure (PLS). Subsequent studies have revealed that PLS production is related to cell migration. With the acceleration of cell migration, the number of PLSs increased, whereas the number of PLSs that inhibited cell

migration decreased. The production of PLSs depends on the migration of cells, which is why they are called "migrasomes."

Structure and composition of migrasomes

The average diameter of migrasomes ranges from 0.5 to 3 μm, indicating a monolayer membrane structure. As migrasomes perform basic cell-autonomy functions before separation, they are regarded as organelles [1]. Migrasomes contain round and oval vesicles with diameters of 30–150 nm. These contain components such as nucleic acids, proteins, damaged mitochondria [4], and autophagosomes [25]. The membrane components of migrasomes from different cell sources differ, but they are rich in transmembrane proteins (TSPANs) [26, 27], cholesterol, and integrins [28]. Mammals express 33 types of TSPANs [29, 30] that are overexpressed in NRK cells, but only 14 relate to the composition of migrasomes. Ma et al. [1] reported that TSPAN4, in particular, is not only highly abundant in migrasomes but also serves as the first protein marker used to identify migrasomes. TSPAN4 binds closely to cholesterol, which is essential for stabilizing the structure of migrasomes and maintaining their normal functions. Huang et al. [26] reported that TSPAN4 binds closely to cholesterol, which is essential for stabilizing the structure of migrasomes and maintaining their normal functions. Wu et al. [28] found that integrins, especially integrin α5β1, are highly enriched at the base of migrasomes. Proper pairing with specific extracellular matrix (ECM) partner proteins is a decisive factor in migrasome formation. Furthermore, migrasomes possess unique proteins. Bifunctional heparan sulfate *N*-deacetylase/*N*-sulfotransferase 1 (NDST1), phosphatidylinositol polysaccharide anchor biosynthesis, class K (PIGK), carboxypeptidase Q (CPQ), and EGF domain-specific O-linked *N*-acetylglucosamine tetratransferase (EOGT) are specific migrasome markers. These proteins, like the exclusive "identity cards" of migrasomes, can clearly distinguish migrasomes from other extracellular vesicles [31] (Fig. 1).

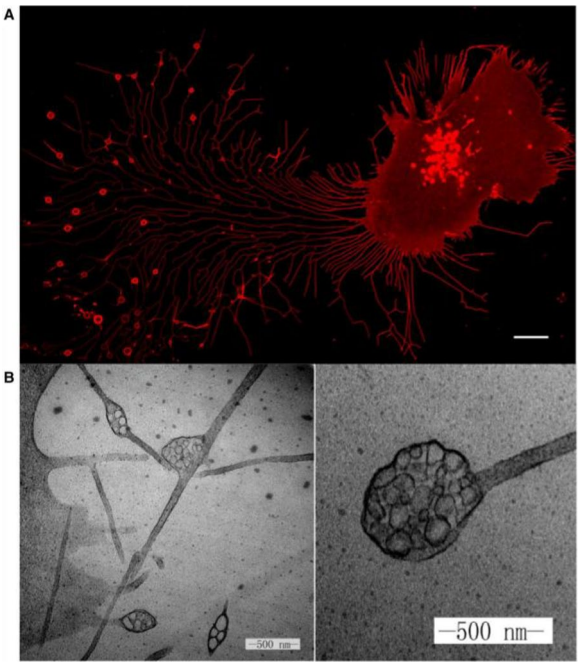


Fig. 1 Structural characteristics of migrasomes. **A** Migrasomes from L929 cells transfected with Tspan4-mCherry were visualized using confocal microscopy. Scale bar, 10 mm. **B** Transmission electron microscopy image of pomegranate-like structures, which were later named migrasomes. Scale bar, 500 nm. © 2021 The Authors. The FEBS Journal was published by John Wiley & Sons Ltd. on behalf of the Federation of European Biochemical Societies

Migrasome biogenesis

Nucleation

Yu Li et al. [32] identified the key enzymes involved in the regulation of migrasomes: ceramide synthase, sphingomyelin synthase (SMS2), and ceramide transporter. The specific nucleation steps are as follows: (I) SMS2 foci on the front edge of cells define the future formation site of migrasomes; (II) the SMS2 foci remain on the RFs and become migrasome formation sites (MFS); (III) ceramide is converted into sphingomyelin at the SMS2 focus, which triggers the growth period of migration; (IV) tetraspanin-enriched macrodomains (TEMAs) are recruited, stabilized, and drive the growth of migrasomes. Essentially, the formation of the SMS2 focus represents the "nucleation" step in the formation of migrasomes, marking the beginning of migrasome biogenesis. In terms of mechanism, de novo synthesis of sphingomyelin mediated by SMS2 is essential for the formation of migrasomes, possibly by maintaining their structural integrity.

Maturation

After the MFS location is determined, PIP5K1A is recruited to the MFSs in the early stage of formation to catalyze phosphatidylinositol (4,5)-diphosphate (PI(4,5) P2) on the migrating membrane. PI(4,5)P2 subsequently promotes migrasome formation by recruiting PI(4,5) P2-binding proteins. In general, Rab35 is initially distributed uniformly along RFs and then recruited to the MFS as a binding protein. Next, activated Rab35 recruits integrin α5 to the MFS. Successful recruitment of integrins is a sign of migrasome maturity [33]. It accumulates at the bottom of migrasomes in the form of heterodimers, each consisting of an α and β subunit, and binds to specific ECM proteins, anchoring migrasomes and tethering RFs to the ECM. The correct pairing of

integrins and their corresponding ECM proteins is key to migrasome formation [28].

Expansion

After the migrasome matures, it expands on the RFs. The initial expansion was stabilized by TSPAN supplementation. TSPAN is a transmembrane protein with four transmembrane domains. The TSPAN family has 33 members and is present in every cell type. TSPAN4 is enriched in the membrane of migrasomes and combines with cholesterol and other proteins to form TEMAs; these domains then expand into migrasomes [26]. TEMAs can be further assembled into larger TEMAs in an SM-dependent manner during the growth stage of migrasomes. In vitro reconstruction has shown that TEMAs promote the growth and stability of migrasomes through physical mechanisms, which is why migrasome membranes have high bending stiffness [34].

Vesicle transport in migrasomes

The transport of intraluminal vesicles within migrasomes is complex and involves multiple proteins and regulatory processes. Li et al. [35] discovered that Rab10 and caveolin-1 (CAV1) are co-localized inside migrasomes, and the activation of Rab10 promotes the transport of CAV1 on migrasomes. Both proteins jointly participate in the transport of intraluminal vesicles in migrasomes. The transport process requires Myosin Va and RILPL2. As an adaptor protein, RILPL2 binds to Myosin Va and Rab10 through its specific domains, and the three proteins work synergistically. Furthermore, the phosphorylation of Rab10 is critical in regulating the transport process, as its phosphorylation directly influences the binding between Rab10 and downstream effector proteins. Knockdown of leucine-rich repeat kinase 2 (LRRK2), which can phosphorylate Rab10 at the T73 site, reduces Rab10 phosphorylation and vesicle transport, while activation or overexpression of LRRK2-related mutants promotes vesicle transport. These jointly constitute the mechanism of intraluminal vesicle transport to migrasomes.

Transport and release of substances in migrasomes

Migrasomes are rich in signaling molecules, including chemokines, cytokines, and angiogenic factors. These molecules are transported into migrasomes and exert their biological functions through spatially directed delivery. Jiao et al. [6] found that secreted proteins, especially signaling proteins, are shuttled into migrasomes via secretory carriers through either constitutive or regulated secretion pathways. Specifically, during cell migration, myosin-5a plays a pivotal role in driving a substantial number of secretory carriers to re-localize towards the posterior part of the cell. Subsequently, it mediates the transport of vesicles from diverse secretory pathways into migrasomes. These vesicles are typically labeled with specific proteins, such as Rab8a, Rab11, Rab5, and Rab10. Once secretory carriers reach migrasomes, they fuse with the migrasome membrane through a precisely regulated SNARE-mediated mechanism. Among the SNARE proteins involved, VAMP2, a v-SNARE associated with constitutive exocytosis, is precisely localized on the membrane of intraluminal vesicles within migrasomes. It forms a highly specific SNARE complex with t-SNAREs (syntaxin4 and SNAP23), which is crucial for promoting the fusion of intraluminal vesicles with the migrasome membrane. This fusion event ultimately facilitates the release of secreted proteins, and the mechanism by which migrasomes release secreted proteins bears a striking resemblance to the process by which neurons release neurotransmitters through synaptic vesicles. Furthermore, this study strongly suggests that migrasomes serve as the predominant pathway for migrating cells to secrete proteins (Fig. 2).

Biological functions of migrasomes

Embryonic development

The transmission of signal molecules between cells plays an important role in regulating the development of embryonic organs, and their concentration gradient also determines the position of different organs during embryonic development. Jiang et al. [2] employed mass spectrometry to separate and purify migrasomes from zebrafish embryos. Their findings showed that migrasomes are abundant in chemokines, morphological factors, growth factors, and cytokines. These molecules play crucial roles in embryo development, indicating that migrasomes may also be indispensable. Therefore, the team established a Tspan4a or Tspan7 knockout model and reported that organ formation was strongly inhibited, but this could largely be reversed by supplementing and purifying migrasomes. Migrasomes accumulate in the embryo shield cavity, releasing Cxcl12a and Cxcl12b, which regulate organ morphogenesis by activating the Cxcl12a–Cxcr4b signaling axis. In this way, migrasomes can release the factor to establish a combined signal with clear spatial and potential time constraints, thus generating the complex information needed to encode embryonic development tissue. Although embryo-derived migrasomes contain a variety of cytokines, this study only analyzed the relationship between migrasomes and organ morphology; other related mechanisms remain to be further elucidated.

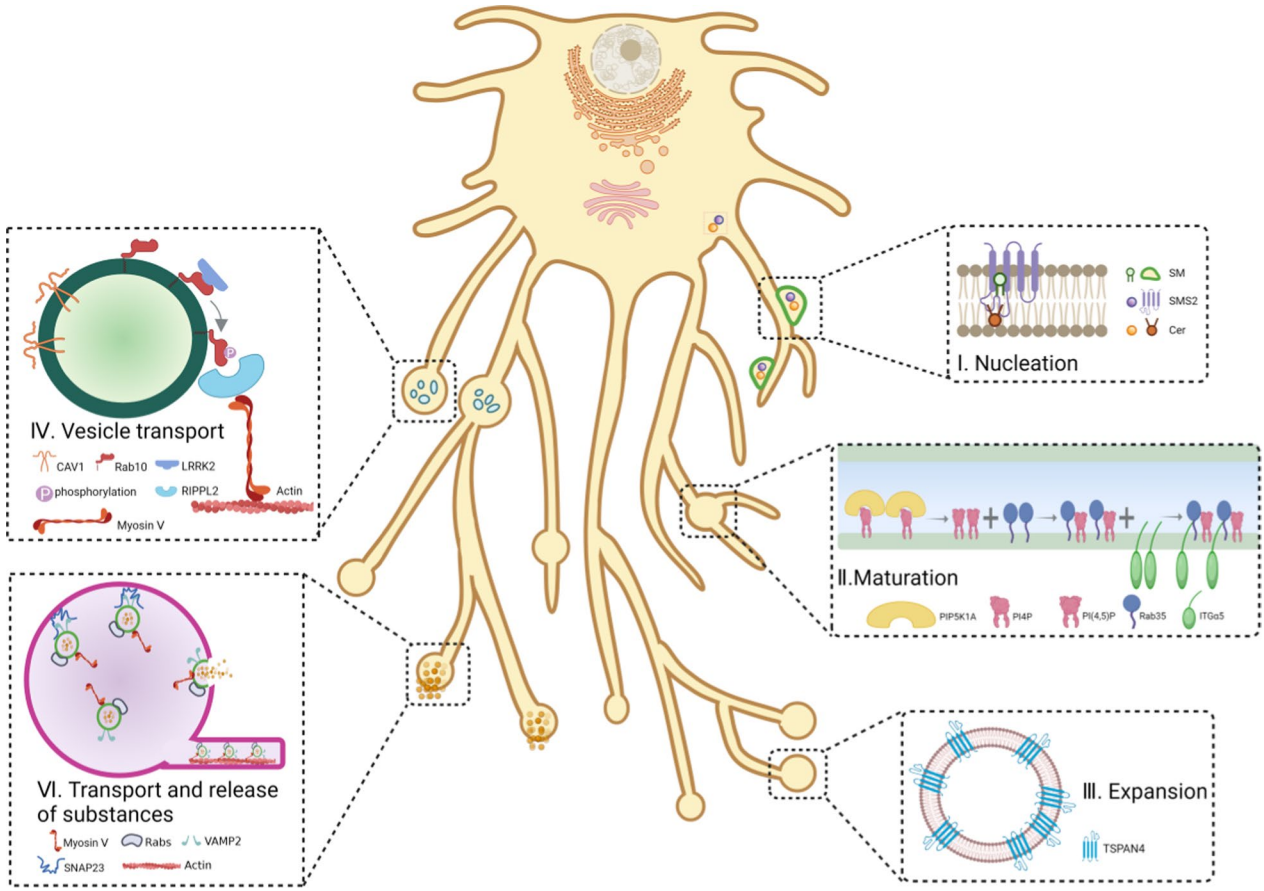


Fig. 2 The process of migrasome biogenesis encompasses the following five steps: I Nucleation. The aggregation of SMS2 determines migrasome formation sites and promotes the conversion of ceramide to sphingomyelin, thereby driving the growth of migrasomes. II Maturation. PIP5K1A catalyzes the generation of PI(4,5)P2. Subsequently, PI(4,5)P2 binds to Rab35 and recruits integrins, marking the maturity of migrasomes. III Expansion. TSPAN4 is enriched in the migrasome membrane and combines with cholesterol and other proteins to form tetraspanin-enriched microdomains that expand within migrasomes. IV Vesicle transport. Rab10 and CAV1 jointly participate in vesicle transport within migrasomes. During transport, LRRK2 promotes the phosphorylation of Rab10. Phosphorylated Rab10 binds to RILPL2, which then links to myosin V, and these three proteins work synergistically. V Transport and release of substances. Myosin drives vesicles labeled with different Rabs into the migrasomes. VAMP2 forms a complex with SNAP23 to promote the fusion of intraluminal vesicles with the migrasome membrane, ultimately releasing substances within migrasomes

Promotion of angiogenesis

Vascular endothelial growth factor (VEGF) is important for angiogenesis [36–38]. VEGF is usually secreted by cells near developing blood vessels and interacts with receptors on endothelial cells (ECs) to promote angiogenesis [39, 40]. Macrophages and monocytes play important roles in angiogenesis [41, 42]. Zhang et al. [3] found that monocytes in the chorioallantoic membrane (CAM) of chicken embryos produce migrasomes rich in VEGF and CXCL12; VEGF is transferred to the capillary formation area through migrasomes, creating a microenvironment conducive to angiogenesis, whereas CXCL12 recruits more monocytes through migrasomes, thus establishing a positive feedback cycle and promoting the rapid formation of capillaries in the CAM. Based on this, we propose a "pioneer" model of angiogenesis, in which monocytes establish a microenvironment to promote angiogenesis by producing migrasomes before angiogenesis. In this model, migrasomes provide a mechanism to coordinate angiogenic signals in time and space, and the delayed effect caused by the release of VEGF from migrasomes provides more opportunities for fine-tuning the signal pattern. Angiogenesis plays an important role in embryonic development and is closely related to angiogenesis under pathological conditions, such as injuries or tumors [43]; thus, migrasomes may also participate in these processes.

Mitochondrial quality control

The clearance of damaged mitochondria contributes to the quality control of mitochondria and the

maintenance of cell homeostasis [44]. Mitochondria can be shed from cells through various mechanisms [44–46]. Currently, most known mechanisms for removing damaged mitochondria are based on the degradation of mitochondria or mitochondrial proteins, which is mediated by proteases or proteasomes. Mitophagy is a special form of autophagy in which autophagosomes are formed to encapsulate and degrade damaged mitochondria [47, 48]. In L929 cells, mitochondria are engulfed by migrasomes [4]. The accumulation of mitochondria in migrasomes has been confirmed through the detection of protein markers and transmission electron microscopy (TEM). The study also revealed that mitochondria triggered by mild mitochondrial stress were transported to migrasomes for clearance from cells. This process is called mitocytosis. TEM revealed that damaged mitochondria were transported to the tail of the cell and excreted through mitocytosis, and the mechanism mediating mitocytosis has been previously reported. First, kinesin family member 5B (KIF5B) transports mitochondria to the vicinity of the cell membrane at the tail of the cell. Myosin 19 (Myo19) links mitochondria to cortical actin, which is closely associated with the cell membrane. Dynamin-related protein 1 (Drp1) subsequently mediates mitochondrial division and is transported to migrasomes. KIF5B, myosin19, and Drp1 mediate mitocytosis by regulating the transport, localization, and division of mitochondria, respectively. In mitocytosis, migrating cells selectively remove damaged mitochondria to maintain an internal balance. The increase in mitocytosis related to migration is a selective mechanism of mitochondrial quality control in migrating cells, and mitocytosis organically couples mitochondrial homeostasis with cell migration.

Material transfer

Zhu et al. [5] found in L929 cells that migrasomes contained RNA, and the RNA was transferred to the recipient cell for translation, thus affecting the function of the recipient cell. However, RNA content differs among migrasomes. This study revealed that approximately 30% of migrasomes contain RNA, suggesting that the RNA in migrasomes is mRNA. Gene Ontology (GO) analysis revealed that mRNAs in migrasomes were highly correlated with metabolism, intracellular transport, cell connections, and vesicle fusion. A previous study revealed that the lateral transfer of Pten mRNA and Pten protein by migrasomes inhibits tumor cell proliferation. This study revealed that mRNAs can be transferred laterally into recipient cells by migrasomes and translated into proteins that can functionally modify recipient cells. However, further study is required on how mRNAs are sorted and transported to migrasomes.

Hemostasis maintenance

Hemostasis is complicated and involves a dynamic balance between the coagulation, anticoagulation, and fibrinolysis systems [49]. It can maintain blood fluidity and quickly repair injured blood vessels. In addition to established components, such as activated coagulation factors, platelet aggregation and activation, and fibrin production [50, 51], Zhu et al. [52] found that neutrophils produce many migrasomes during intravascular migration in both mice and humans. Neutrophil-derived migrasomes in the separated serum did not play a role in material transfer in the past but adsorbed and enriched coagulation factors in plasma on their surface, quickly gathered at the wound site, and activated platelets through rich adhesion molecules. Additionally, researchers have used lipopolysaccharide to induce an inflammatory reaction in mice and reported that the number of neutrophil migrasomes in the blood increases sharply, indicating that the production of neutrophil migrasomes is part of the immune response to infection or inflammation and that hemostasis system disorders caused by infection or inflammation may involve migrasomes (Fig. 3).

Relationship between migrasomes and clinical disease

In addition to basic biological research on migrasomes, studies on the relationship between migrasomes and diseases have also begun to increase. This study summarizes the clinical diseases currently linked to migrasomes, classifying them as tumor or nontumor, dividing nontumors into infectious and noninfectious, and finally categorizing noninfectious diseases in detail. For each disease, we explain the relationship between migrasomes and clinical disease from two aspects: the pathological mechanism and diagnosis and treatment, to provide reference ideas for future clinical research into migrasomes (Fig. 4 and Table 1).

Tumors

Role of migrasomes in the occurrence and development of tumors

Promotion of tumor cell invasion and metastasis The formation of migrasomes is related to the migration ability of cells [1], and tumor cells with high invasive and metastatic abilities can theoretically produce many migrasomes. Qin et al. [53] conducted a pan-cancer analysis, which revealed that the expression of migrasome-related proteins was elevated in numerous types of tumors. Additionally, they found that the expression of migrasomes varied among different cell types within the tumor microenvironment (TME). The tetraspanin protein is not only an important part of migrasomes but

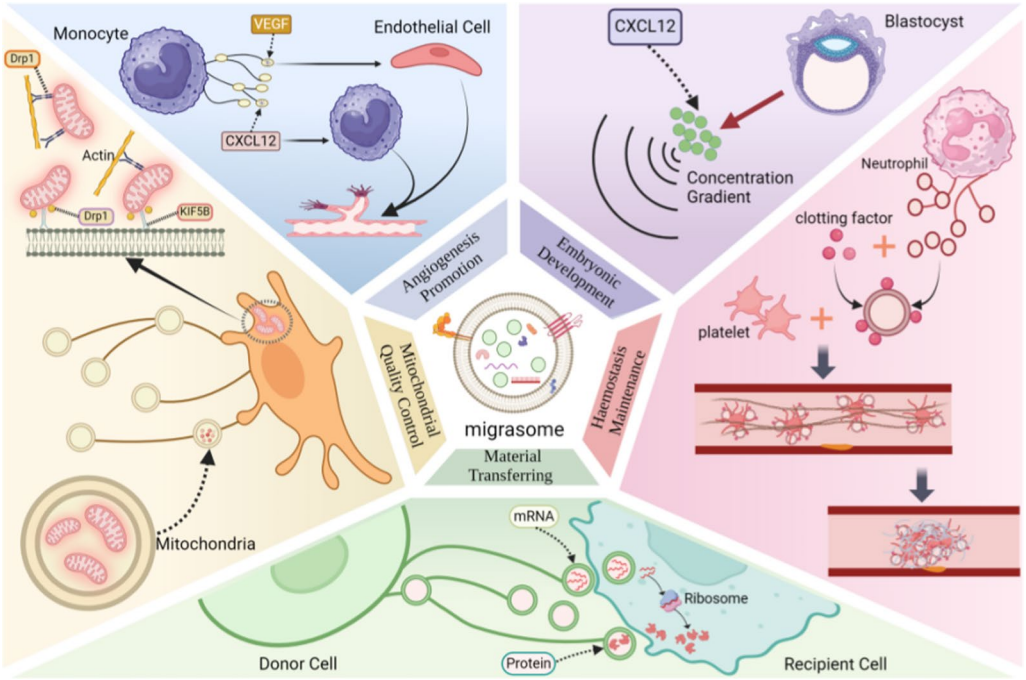


Fig. 3 Biological functions of migrasomes. Migrasomes play important roles in five aspects: embryonic development, angiogenesis promotion, mitochondrial quality control, material transfer, and hemostasis maintenance

also closely related to the occurrence of tumors [54, 55]. Zhang et al. [12] concluded that the poor prognosis of patients with liver cancer is related to the high expression of CD151, which is a member of the tetraspanin protein family, and that high expression of CD151 can promote the production of migrasomes, thus promoting the invasion of tumor cells. Additionally, the evolution of the tumor microenvironment is crucial for tumor progression and metastasis. This microenvironment typically includes fibroblasts, immune cells, inflammatory cells, and extracellular matrix components [56]. Zhang et al. [13] reported that pancreatic cancer cells can induce the transformation of macrophages in the tumor microenvironment into immunosuppressive subtypes via migrasomes. These macrophages, in turn, hinder the body's immune response by overexpressing secretory proteins, such as ARG1, and suppressing CD4+/CD8+T-cell proliferation, thus promoting cancer cell migration and invasion. In terms of metastasis, migrasomes facilitate angiogenesis by carrying VEGF, thereby aiding tumor metastasis. Specifically, in the context of the cytoplasmic matrix, Huang et al. [14] discovered that during the growth phase of glioblastoma (GBM), tumor cells predominantly release ECM-associated proteins, namely, p21-activated kinase 4 (PAK4) and laminin alpha 4 (Lama 4), through the generation of migrasomes. These proteins affect the surrounding cells, thereby promoting the migration and invasion of GBM cells. Tumor metastasis is a leading cause of cancer treatment failure, with the bone being a frequent site of metastasis in many cancers. Gu et al. [57] found that tumor cells transport their own cancer cell mRNAs to osteoclast precursor cells through migrasomes, leading to the abnormal differentiation of osteoclast precursor cells into osteoclasts, which then secrete many acidic substances that promote bone absorption and eliminate obstacles to the bone metastasis of cancer cells. For a long time, the mechanism of high invasion and metastasis of tumors has been unclear, and migrasomes may be an important link. However, further research is needed to clarify the detailed mechanisms of action of migrasomes.

Transport of accumulated autophagosomes in tumor cells The remarkable survival ability of tumor cells has long been a perplexing issue. Research has revealed that autophagy is a survival strategy for tumor cells. It supplies essential nutrients to cells, enabling them to survive in harsh microenvironments, thus promoting tumor development [58, 59]. In a recent study, Lee et al. [25] made a significant discovery that autophagosomes were present in migrasomes derived from GBM. Intriguingly, inhibiting autophagy enhanced the formation of migrasomes in GBM cells. Given the well-established association between the autophagy pathway and endoplasmic reticulum (ER) stress, this study further demonstrated

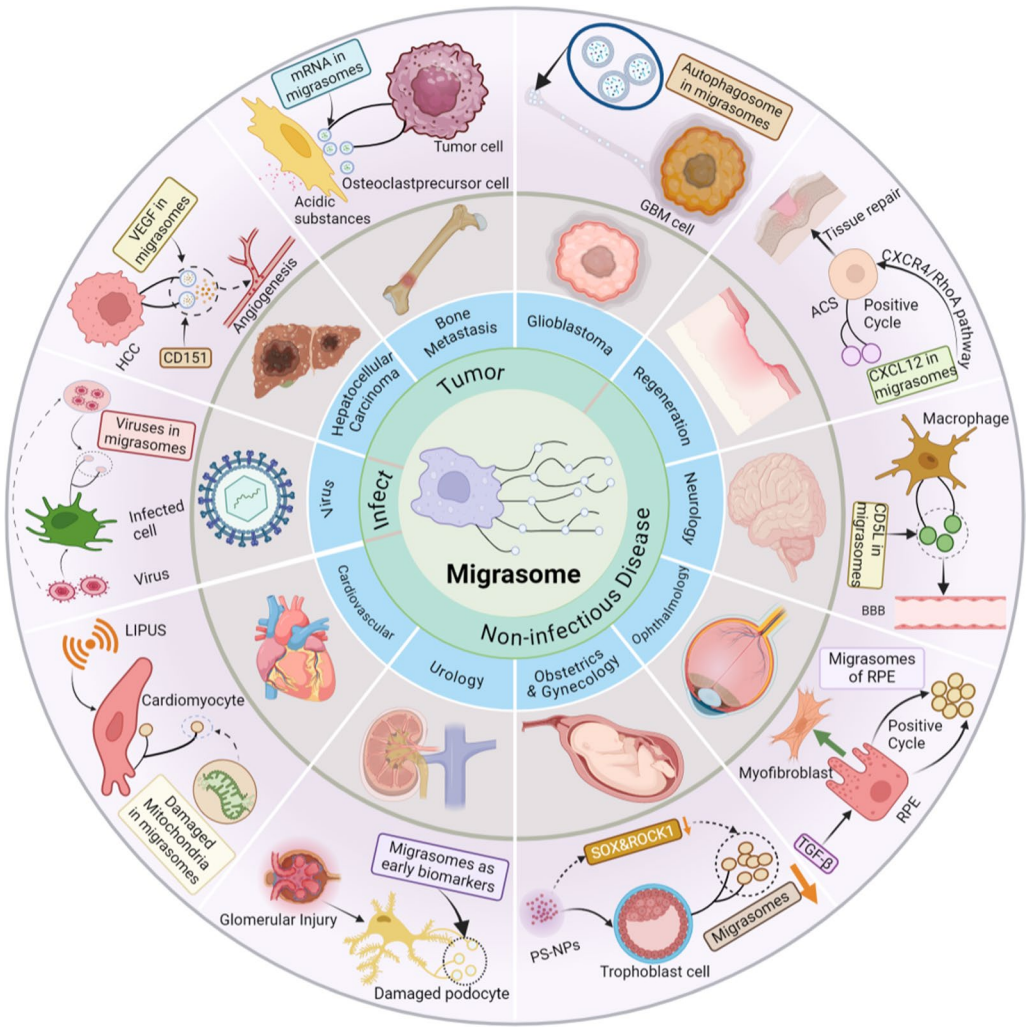


Fig. 4 Relationship between migrasomes and clinical disease. This review summarizes the clinical diseases associated with migrasomes. Diseases are classified as tumors or nontumors; nontumor diseases are divided into infectious and noninfectious; noninfectious diseases are classified into the cardiology, urology, obstetrics, gynecology, ophthalmology, and neurology categories. Regenerative medicine research was also considered

that GBM-derived migrasomes can alleviate ER stress in tumor cells. Based on these findings, we propose a novel mechanism by which migrasomes contribute to tumor progression: when cancer cells accumulate stress-induced damage, leading to an upregulation of autophagy, the accumulated autophagosomes are not degraded using the cell's intrinsic energy resources. Instead, they are managed by migrasomes generated through cell motility, which ultimately enhances cancer cell survival.

Role of migrasomes in tumor diagnosis and treatment

Improving the therapeutic effect of drugs With the continuous development of nanotechnology, its application in tumor treatment is also increasing [60]. Targeted drug delivery with nanomaterials can improve drug delivery efficiency, increase the drug intake of tumor cells [61], and significantly reduce drug toxicity to normal cells, improving the overall effect of tumor treatment in vivo [62, 63]. However, nanodrugs interact with a variety of high-affinity biological components, especially the ECM in the TME, which forms a large net that hinders the transmission of nanodrugs around the tumor and limits the efficiency of nanodrug delivery [64, 65]. Cheng et al. [66] were the first to discover that nanoparticles inhibit cell movement by combining with the ECM and interfering with cell-ECM interactions; specifically, nanoparticles combine with the surface of migrasomes in the ECM, organizing tumor cells to absorb migrasomes in this way, thus inhibiting cell migration. These results

Table 1 Mechanism of migrasome involvement in different diseases

Category	Disease	Source	Cargo	Mechanism	Effect	References
Tumor	Hepatocellular carcinoma	Cells	VEGF	Increased expression of CD151 promotes the production of migrasomes	Affects the invasiveness of liver cancer cells and promotes HCC migration	[34]
	Bone metastasis	Cells	RANKL	Tumor cells activate osteoclasts via migrasome-mediated cytoplasmic transfer	Bone metastasis promoted by stimulation of osteoclasts to secrete acidic substances	[35]
	Glioblastoma	Cells	Autophagosomes	GBM cells accumulate autophagosomes through migrasomes	Alleviates the accumulation of stress damage and does not consume its own energy	[9]
Infectious	Viral	Cells	Virions	The infected cells release migrasomes encapsulating virions	Promoting virus infection in the mode of cell-to-cell spread by migrasomes	[50–52]
Noninfectious	Cardiovascular	Cells	Mitochondria	Migrasomes selectively remove damaged mitochondria by mitocytosis	Providing mitochondrial quality control to improve cardiac dysfunction	[62]
	Urology	Cells and urine	–	Podocytes secrete more migrasomes when injured	Using migrasomes as a potential diagnostic marker for early kidney injury	[75, 86]
	Gynecology and obstetrics	Cells	–	Nanoplastics activate autophagy and suppress migrasome formation	Affects trophoblast cell migration and induces miscarriage	[96]
	Ophthalmology	Cells	–	The migrasomes of RPE are induced through the TGF-β1/Smad2/3 pathway	Increases the migration and proliferation of RPE to induce PVR	[105]
	Neurology	Cells and plasma	CD5L	Migrasomes of Aβ40-stimulated macrophages facilitate CDC in CAA	Injuring endothelial cells and causing the destruction of the blood—brain barrier	[120]
	Regenerative medicine	Cells	CXCL12	Migrasomes from ASCs enrich CXCL12 to recruit stem cells via CXCR4/RhoA	Promoting stem cell migration and mediating tissue regeneration	[147]

suggest a new approach for studying the interaction between nanotumors in the future. Additionally, how nanoparticles restrict tumor metastasis by interacting with migrasomes can also provide a new direction for improving the antitumor efficacy of nanodrugs.

Inhibition of tumor migrasomes Migrasomes, generated by tumor cells, enable cells to exchange information among tumor cells, promote the occurrence and development of tumors, and maintain a favorable state. Therefore, inhibiting tumor growth via the inhibition of migrasomes may become a new target for tumor treatment. Lee et al. [25] found that the migrasomes produced by GBM can alleviate endoplasmic reticulum damage to cells; however, by reducing the TSPAN4 level in glioblastoma cells, that is, reducing the generation of migrasomes, glioblastoma cells exhibit lower growth rates and higher mortality. Concurrently, Zhang et al. [12] found that inhibiting migrasomes can inhibit liver cancer invasion and metastasis and improve its prognosis. Gu et al. [57] proposed an in situ decoupling killing strategy in which sodium bicarbonate and disodium hydrogen phosphate were encapsulated in tetracycline-modified nanoliposomes. When tumor cells contact osteoclasts, they release high concentrations of dihydrogen phosphate ions and calcium ions into the microenvironment to form calcium-phosphorus crystals, thus reducing the calcium concentration, inhibiting the formation of migrasomes, and inducing tumor cell death by physically destroying their cell membranes, thus achieving early prevention of tumor bone metastasis. Therefore, inhibiting the formation of tumor migrasomes may be a strategy to inhibit tumor

growth and metastasis. However, considering that it may also affect the normal function of other cells, the targeted inhibition of tumor cells to produce migrasomes will become a research hotspot in the future.

Viral diseases

Role of migrasomes in viral infection

An intermediate carrier in virus transmission Virus transmission occurs through two main routes: direct infection of cells by the virus and direct contact of virus-infected cells with uninfected cells [67]. Zhang et al. [15] proved for the first time that migrasomes and viruses may interact. This study revealed that NSP1, a nonstructural protein of the Chikungunya virus, can promote the production of inositol PI(4,5)P2 by regulating PIP5K1A and that inositol PI(4,5)P2 is an important regulator of actin polymerization, thus inducing the formation of migrasomes and promoting cell migration. This study highlights the possible relationship between migrasomes and viruses in terms of the colocalization of specific proteins and RNA. Lv et al. [16] were the first to demonstrate that migrasomes contain virus particles induced by viral infection. In this study, vaccinia virus (VACV) was observed using TEM, and it was proven that VACV infection promoted the formation of migrasomes. After infection, the vaccinia virus extensively remodels the actin cytoskeleton to produce actin to form the extracellular envelope virus. Actin is closely related to the formation of migrasomes, and virus particles are found in migrasomes; therefore, migrasomes are likely to constitute a new mechanism of virus transmission. Liu et al. [68] were the first to demonstrate using a model of herpes simplex virus type 2 (HSV-2) that migrasomes play a role in virus transmission and that cells can also be infected with HSV-2 when the isolated migrasomes act on cells. Using TEM, this study revealed that virus particles exist in migration-like structures in the intestine and cervix of HSV-2-infected mice. Many studies have shown that viruses may regard migrasomes as Trojan horses and as one of the routes of cell-to-cell transmission.

Assisting viruses escape drug attacks It has been demonstrated that migrasomes can function as intermediate virus carriers to facilitate virus propagation, whereas migrasomes, being monolayer organelles, possess a stable structure. Therefore, we hypothesize that when the environment is unfavorable, especially when therapeutic drugs attack it, the virus may use migrasomes as a refuge to protect itself from external damage. Zhao et al. [69] utilized treatment with the vaccinia virus as a background. Currently, the main drug used for MPXV treatment is tecovirimat/ST-246, which can reduce plaque formation and cell-to-cell transmission of the virus by targeting the F13 family protein of the vaccinia virus. Zhao et al. [69] reported the presence of vaccinia virus particles in migrasomes, but ST-246 treatment did not reduce the number of virus-induced migrasomes. Therefore, viruses can resist common antiviral drugs via the protection of migrasomes, which is also a way to promote and expand their spread.

Migrasomes as a target of virus therapy

Although many antiviral drugs are available, the diseases caused by viral infections still seriously threaten human health, and researchers have been looking for new antiviral treatments to achieve better therapeutic effects. Many studies have shown that migrasomes are a novel route of viral spread between cells. Zhao et al. [69] emphasized the limitations of using ST-246 as an antiviral drug. Therefore, further research should focus on blocking the formation of virus-induced migrasomes, which may be potential targets for future antiviral drug development. Nevertheless, Xu et al. [17] revealed that during VACV infection, dasabuvir can inhibit the further spread of extracellular envelope virus (EEV) by blocking the formation of migrasomes. Additionally, COVID-19 infection leads to the rapid death of platelets, but platelets concurrently release their contents through migrasomes, thereby promoting thrombosis and inflammation [70]. Therefore, migrasomes can be used as intervention targets for viral infections. With the gradual deepening of related research, the special clinical application value of migrasomes in the field of antiviral therapy will continue to be explored in the future.

Cardiology

Role of migrasomes in cardiovascular disease

Alleviating cardiac cell damage The pathological mechanism of myocardial infarction involves damage to cardiac cells such as cardiomyocytes, endothelial cells, and immune cells [71]. Coronary artery disease is the most common cause of acute myocardial infarction [72]. In this case, clinical guidelines recommend that myocardial blood perfusion can be effectively restored by timely revascularization, thus reducing myocardial injury and ischemia-induced necrosis [73]. However, reperfusion after ischemia may aggravate cardiac dysfunction and injury. Myocardial ischemia–reperfusion not only affects the function, metabolism, and structure of the heart but also exacerbates necrosis of cardiac cells, leading to irreversible damage, such as myocardial bleeding and necrosis [74, 75]. The mechanism of reperfusion injury involves free radicals, intracellular calcium overload, inflammation, apoptosis, and other factors. Among

them, the production of oxygen free radicals and calcium overload are closely related to mitochondrial damage. After reperfusion, damaged mitochondria accumulate in cells, leading to inflammatory activation, further affecting heart metabolism and aggravating the heart burden [76, 77]; thus, mitochondrial injury is considered a key trigger for pathological progress. Jiao et al. [4] identified a new mechanism for clearing damaged mitochondria in cells, mitocytosis. This is a quality control method for mitochondria that is mediated by migrasomes. Cells excrete damaged mitochondria through migrasomes, thereby maintaining mitochondrial homeostasis. Recently, Sun et al. [18] used mice with reperfusion injury as a model and observed migrasomes with damaged mitochondria in myocardial tissue using TEM. They then established a reperfusion model in transgenic mice with specific TSPAN4 knockout, which confirmed the importance of migrasomes in maintaining mitochondrial homeostasis during reperfusion injury. They also studied myocardial and endothelial cells under simulated reperfusion in vitro, indicating that myocardial and endothelial cells may expel damaged mitochondria through migrasomes to reduce their own damage; however, this issue still lacks clear in vivo evidence and requires further study.

Maintaining vascular homeostasis Most cardiovascular diseases damage blood vessels to varying degrees, and vascular injury and repair and regeneration mechanisms after injury have been extensively researched. Atherosclerosis is one of the most common vascular diseases. During development, vascular endothelial cells are initially damaged, leading to dysfunction. Endothelial cells have a strong migrasome ability in vivo. Macrophages and smooth muscle cells actively migrate to injury sites to promote the progression of atherosclerosis. According to reports in the literature, cells with stronger migrasome ability have a stronger ability to produce migrasomes [1]; thus, it can be hypothesized that migrasomes may play an important role in this process. Studies have shown that TSPAN4 is abundant in the membrane of migrasomes and is the clearest marker of migrasomes. Zheng et al. [78] showed that the expression of TSPAN4 in macrophages was detected through single-cell sequencing data, a GEO dataset, and the TCGA database, which revealed a significant correlation between the expression of TSPAN4 and that of macrophages in the process of atherosclerosis, especially when atherosclerotic plaques bleed or rupture, indicating that macrophages may pass through migrasomes. Although the effect of migrasomes produced by endothelial cells on atherosclerosis progression has not been reported, a study revealed that TNF-α can promote the release of migrasomes from primary human coronary endothelial cells (pHCAECs) and that migrasomes participate in intercellular signal transduction during the directional migration of activated pHCAECs, thus coordinating the movement direction of cells [79]. Moreover, in a model of ischemia–reperfusion injury, Sun et al. [18] showed that endothelial cells subjected to ischemia–reperfusion can also eliminate damaged mitochondria to protect themselves and alleviate injury caused by migrasomes. Therefore, endothelial cells are primarily involved in angiogenesis and cellular repair, and migrasomes derived from endothelial cells possess significant research potential for future investigations.

Role of migrasomes in the diagnosis and treatment of cardiovascular disease

Biomarkers for early diagnosis The common diagnostic methods for cardiovascular diseases are complex imaging or blood tests, and researchers are constantly exploring simpler and more accurate diagnostic measures [80, 81]. New surrogate markers for cardiovascular disease should be accurate, sensitive, specific, and rapidly and noninvasively collected from easily available body fluids [82, 83]. Migrasomes are present in human blood and urine. Zheng et al. [78] showed that compared with that in the sham-operated group, the expression of TSPAN4 in the myocardial tissue of Acute Myocardial Infarction (AMI) model mice increased one day after myocardial infarction. Therefore, monitoring the number of migrasomes after myocardial infarction may be a new factor for disease evaluation and prognosis prediction. With the continuous study of migrasomes, biomarkers contained in migrasomes may be found, providing new ideas for the treatment of myocardial infarction.

Potential intervention targets for cardiovascular disease Many studies have shown that migrasomes are closely related to the progression of cardiovascular diseases. Migrasomes have complex functions and are likely to become new targets for the prevention and treatment of cardiovascular diseases. Sun et al. [18] proved that low-intensity pulsed ultrasound can improve myocardial injury caused by ischemia/reperfusion, but the protective effect of low-intensity pulsed ultrasound was weakened in reperfusion-induced mice with TSPAN4-specific knockout, suggesting that migrasomes are key for the therapeutic role of low-intensity pulsed ultrasound. Additionally, the interaction between cardiovascular disease and tumor progression can be linked to migrasomes. Monocytes in myocardial infarction can change the microenvironment of breast cancer in patients with both myocardial infarction and breast cancer, thus promoting the progression of early stage breast cancer. In patients with atherosclerosis, abnormal lipid metabolism can also affect blood vessel formation, thereby affecting

tumor growth and metastasis. Zheng et al. [78] showed that migrasomes may be the link between cardiovascular diseases and tumors, but more research is needed.

Urology

Migrasomes reflect podocyte damage

Podocytes are common injury sites in renal diseases [84, 85]. Podocyte injury decreases glomerular filtration rate, leading to proteinuria [86, 87]. As podocytes are terminally differentiated cells and cannot self-proliferate and renew, they migrate to fill the lost space when they are damaged in disease states [88, 89]. Ma et al. [1] proved that cells release migrasomes during migration; therefore, the number of migrasomes secreted by podocytes may increase when podocytes are damaged. Liu et al. [22] proved that podocytes release more migrasomes when kidney diseases damage them by investigating the urine samples of mice with different types of nephropathy and patients with active diabetic nephropathy. This investigation not only demonstrated that migrasomes in urine primarily originate from podocytes in nephropathy but also revealed elevated migrasome levels in urine on the second day in model mice, preceding the onset of proteinuria. This study suggests that elevated urinary migrasome levels may serve as a more sensitive indicator of early podocyte injury compared to proteinuria.

Role of migrasomes in the diagnosis and treatment of renal disease

As an early diagnostic marker of renal disease Urine is an ideal biological sample for detecting biomarkers of renal disease; clinicians widely use it because of its noninvasive and convenient collection [90, 91]. Proteinuria is common in various renal diseases and is an early clinical indicator of disease [92]. However, Liu et al. [22] proved that the change in the urine migration level occurs earlier than that in the urine protein level in the early stage of renal injury, indicating that urine migration can be a potential diagnostic marker of early renal injury. Additionally, in the early stage of renal disease, the release of extracellular vesicles from various cells usually increases, with exosomes being the most studied extracellular vesicles. Thus, whether the exosomes released by renal cells can be used as potential sensitive biomarkers of renal disease has also been extensively studied [93, 94]. However, two problems exist with the use of urine exosomes as markers of early podocyte injury. First, the cell source of exosomes is complex; they can come from renal and non-renal cells, making it difficult to determine whether changes in the exosome level damage the kidney. Second, exosomes released by renal cells, such as podocytes or renal tubular cells, are not unique to cell injury but are also released under normal physiological conditions [95, 96]. Migrasomes are newly discovered organelles [1] that function similarly to exosomes and promote information exchange between cells. Unlike exosomes, the production and release of migrasomes depend on cell movement, and podocyte movement is closely related to cell injury. The number of migrasomes released by podocytes directly reflects the degree of podocyte injury, and urine migrasomes are derived mainly from podocytes in the early stage of nephropathy. Therefore, considering the relationship between changes in urine migrasomes and podocyte injury, the level of urinary migrasomes is likely to be a diagnostic index for early nephropathy [22].

Quantification of PLA2R autoantibodies in patients with primary membranous nephropathy Ma et al. [1] proved that the membrane composition of migrasomes is very similar to that of their source cells; therefore, migrasomes naturally have some characteristics of their source cells. Membranous nephropathy can be divided into primary and secondary nephropathy, and their treatment methods are very different; thus, distinguishing between them is very important [97, 98]. The phospholipase A2 receptor (PLA2R) is a transmembrane glycoprotein that is mainly expressed by podocytes. Serum anti-PLA2R autoantibodies are important for diagnosing primary membranous nephropathy. Currently, renal biopsy or synthetic human recombinant PLA2R proteins are required to detect autoantibodies in the blood [97]. However, as an invasive procedure, renal biopsy may be accompanied by infection and bleeding complications, and the detection of serum PLA2R autoantibodies from synthetic human recombinant PLA2R protein is not very sensitive for diagnosing primary membranous nephropathy [99]. Liu et al. [22] proved that migrasomes in urine are derived mainly from podocytes during early renal injury, and Yang et al. [100] demonstrated PLA2R expression in migrasomes through mass spectrometry and western blot (WB) analysis of migrasomes in the urine of patients with primary membranous nephropathy on the premise that the composition of membrane proteins of migrasomes was similar to that of their source cells. These findings further verified that PLA2R autoantibodies in patient serum can recognize PLA2R expressed on the membrane of migrasomes and that the method of quantitatively detecting PLA2R autoantibodies in serum using migrasomes is superior to the commonly used ELISA in terms of sensitivity and specificity. Therefore, the use of migrasomes as an antigen source for detecting PLA2R autoantibodies is expected to be a novel method for diagnosing primary membranous nephropathy.

Potential drug therapy targets Rac-1 is a member of the small G protein of the Rho family and is involved

in regulating cell signals and controlling migration and inflammation [101]. Studies have shown that Rac-1 is overactivated when podocytes are injured, and that inhibiting the activity of Rac-1 can protect the structure and function of podocytes [102, 103]. However, the specific protective mechanisms remain unclear. Liu et al. [22] used a Rac-1 inhibitor to treat damaged podocytes and revealed that the greater the dose of theRac-1 inhibitors, the greater the decrease in the number of migrasomes in urine, indicating that the protective effect of the Rac-1 inhibitor on damaged podocytes may be related to the inhibition of the release of migrasomes in podocytes. As the release of migrasomes relates to podocyte damage, migrasomes will likely become an effective drug target for future development of renal disease treatments.

Obstetrics and gynecology

Migrasomes maintain the normal development of embryos

Unexplained miscarriage represents a major challenge in female reproductive health [104]. Among the various factors, environmental pollutants are likely to be significant contributors to adverse pregnancy outcomes [105, 106]. Studies have shown that plastic particles with a diameter of 20 nm can be transferred from the lungs of pregnant mice to the placenta and fetal tissues, thereby affecting fetal development [107–109]. Jiang et al. [2] used zebrafish as a model and demonstrated that migrasomes provide specific signaling molecules to coordinate organ morphogenesis during embryonic development. Lu et al. [110] showed that ROCK1 regulates the adhesion of cells to fibronectin, which is an important factor in regulating the formation of migrasomes. Similarly, Wan et al. [21] found that after exposure to polystyrene nanoplastics (PS-NPs), the number of migrasomes produced by trophoblast cells decreased, leading to miscarriage. The specific mechanism is that PS-NPs activate the autophagy of sex-determining region Y-box 2 (SOX2), inhibiting the SOX2-mediated transcription of ROCK1, thus suppressing the ROCK1-mediated formation of migrasomes. In summary, migrasomes play a crucial role in embryonic development.

Migrasomes provide a potential target for treating miscarriages

Jiang et al. [2] demonstrated that migrasomes play an important role in embryonic development. Recently, Wan et al. [21] showed that trophoblast cells also produce migrasomes to maintain the healthy development of embryos under normal conditions, but under exposure to nanoplastics, the generation of migrasomes is inhibited, leading to miscarriage. In this process, PS-NPs inhibit the transcription of ROCK1 by activating SOX2 autophagy, thus inhibiting human trophoblast migration and leading to miscarriage. This study identified three potential targets for treating PS-NP-induced miscarriages. First, pregnant mice exposed to PS-NPs were supplemented with mouse ROCK1, which restored the number of migrasomes, thus reducing the probability of miscarriage in these mice. Second, overexpression of SOX2 in PS-NP-exposed trophoblast cells restored the downregulated levels of ROCK1 mRNA and protein, which alleviated the inhibition of migrasomes at the cellular level. Supplementation with SOX2 in a mouse model also reduced the miscarriage rate. Third, chloroquine was used to treat trophoblasts exposed to PS-NP, which effectively inhibited the autophagy degradation pathway of SOX2 and promoted the recovery of the number of migrasomes [21]. This study reveals the relationships among PS-NP, migrasomes, and miscarriage and provides a potential intervention target for reducing unexplained miscarriages in the future.

Ophthalmology

Migrasomes promote cell proliferation and differentiation

Retinopathy is a major cause of blindness, and retinal detachment is a common pathological mechanism [111]. Retinal detachment can be rhegmatogenous or non-rhegmatogenous. Rhegmatogenous retinal detachment occurs due to retinal breaks, and liquefied vitreous enters between the neuroepithelium and pigment epithelium through these breaks, causing retinal detachment [112–114]. Under pathological conditions, destruction of the blood-retinal barrier or the formation of retinal tears leads to the exposure of the pigment epithelium to many cytokines, including VEGF, TGF-β, and platelet-derived growth factor BB (PDGF-BB). The pigment epithelium differentiates into myofibroblasts, which can proliferate and contract and will do so widely on the retinal surface, causing retinal detachment due to traction [115–117]. Information exchange between cells is an important method for promoting cell proliferation. Migrasomes are important in cell-to-cell communication because they transmit information about time and space. Wu et al. [20] showed that migrasomes play a key role in the occurrence and development of proliferative retinopathy, that is, in the microenvironment of proliferative retinopathy, pigment epithelial cells are exposed to large quantities of TGF-β, and under stimulation, many migrasomes act on themselves, establishing a positive circulation pathway to promote their differentiation into fibroblasts, increasing the severity of the disease. Therefore, migrasomes can participate in the occurrence and development of retinopathy by transmitting their contents. However, research on the role of migrasomes in

ophthalmic diseases is still in its early stages, and much work is needed to determine their clinical implications. The different functions of migrasomes from different cell sources in ophthalmic diseases require further discussion.

Migrasomes as potential targets for treating retinopathy

Currently, the main treatment for retinopathy is surgery, and drug therapy plays a preventive role. As an invasive operation, surgery requires considerable experience and technology for doctors because of the delicate and complicated eyeball structure, while the recurrence of blindness post-surgery is also common [118]. Additionally, the curative effect of drug therapy is very limited [119], and the clinical treatment of retinal detachment still faces great challenges; thus, exploring other treatment methods remains important [120]. Wu et al. [20] found a relationship between migrasomes and proliferative retinopathy and demonstrated in a rabbit model that suppressing the production of migrasomes by knocking down the expression of TSPAN4 can alleviate retinal detachment and decrease the progression of the disease. Therefore, this study suggests that targeting migrasomes may be an effective strategy for preventing or treating proliferative retinopathy.

Neurology

Role of migrasomes in the occurrence and development of neurological diseases

Promotion of complement activation The complement system is an important part of the immune system that can promote phagocytosis, stimulate verification, and induce microbial lysis [121, 122]. Moreover, after complement activation, the resulting membrane-attacking complex has a lytic effect on target cells, that is, complement-dependent cytotoxicity (CDC). In an abnormal state, the complement system activated after immune system disorders may also damage normal cells through CDC, thus promoting the occurrence and development of diseases [123, 124]. Cerebral amyloid angiopathy (CAA) is one of the most common cerebrovascular diseases [125]. The deposition of fibrous amyloid β protein (Aβ) in small blood vessels and capillaries is a characteristic feature of CAA [126–128], and macrophage phagocytosis is important for Aβ clearance [129–131]. However, Hu et al. [19] found that macrophages that engulf Aβ are severely destructive to the tissue. Specifically, when Aβ is engulfed by macrophages, it promotes migrasome production in macrophages, which are rich in CD5 antigen-like protein (CD5L). CD5L stops on the blood vessel wall through migrasomes, and the local concentration of CD5L is increased to the injury level through the transport of migrasomes; complement is then activated to start CDC to damage vascular endothelial cells, thus destroying the blood–brain barrier and promoting disease progression. Migrasomes play an important role in this phenomenon. When ultrasound destroys the structure of migrasomes or the expression of TSPAN4 is knocked down, the destruction disappears. Complement inhibition therapy can therefore improve vascular destruction mediated by migrasomes, indicating that migrasomes can promote complement activation in CAA, leading to disease aggravation.

Adjusting immunosuppression As an organ of immune tolerance, the brain is immune-suppressive, and acute ischemic stroke (AIS) leads to brain injury and suppression of the entire immune system. At this time, the ability of the human body to resist foreign pathogens is greatly reduced, rendering it prone to severe infections [132, 133]. Post-stroke pneumonia is one of the main causes of death in patients with AIS [134, 135]. The main clinical treatment for this infection involves the use of multiple antibiotics. However, the use of antibiotics not only leads to a further decrease in macrophage phagocytosis but also aggravates the disorder of microorganisms; therefore, the therapeutic effect of antibiotics is not ideal [136, 137]. Many studies have shown that mesenchymal stem cells (MSCs) can improve the clinical outcomes of pulmonary infections, but the specific mechanism is unclear [138–140]. Li et al. [141] showed that the fine-tuned immune function of MSCs may be due to the production of migrasomes containing the antibacterial peptide dermcidin (DCD) which enhances macrophage-related phagocytosis through contact between migrasomes and macrophages, thus promoting bacterial clearance and digestion. Therefore, in the immunosuppressed state, MSCs can reduce the inhibitory effect of the organism on the immune system and enhance the phagocytic function of macrophages through migrasomes, thus improving the clinical prognosis of AIS patients. Additionally, in ischemic stroke, a high-salt diet can promote the ability of microglia to produce migrasomes, which can integrate and dispatch the cytosol of surrounding neurons and find neuronal fragments in migrasomes [142]. Therefore, this study hypothesized that microglia induce neuronal death and aggravate damage to ischemic cells through migrasomes, but concurrently, microglia perform a cleavage function by removing neuronal fragments through migrasomes.

Role of migrasomes in the diagnosis and treatment of neurological diseases

As indicators of early disease prediction and evaluation of disease progression Hu et al. [19] collected peripheral blood from patients with clinical CAA, and Spearman correlation analysis revealed that the percentage of TSPAN4 + monocytes was greater than that of common plasmaneurofilament, light polypeptide (NeF), and other diagnostic markers of brain injury in CAA. Additionally, the number of migrasomes in the peripheral blood of patients with CAA was positively correlated with cognitive impairment. The number of migrasomes in patients with mild cognitive impairment was not significant; however, peripheral blood of patients with moderate and severe cognitive impairment contained an abundance of migrasomes. Owing to the limited sampling of clinical patients, this study revealed that the expression of TSPAN4 in brain macrophages was consistent with that in circulating peripheral blood macrophages in the coronal brain slices of the CAA mouse model. In addition, the increase in plasma NeFL in mice was related to the increase in TSPAN4 + macrophages in the brain, in addition to the increase in TSPAN4 + macrophages in the blood. Therefore, migrasomes have potential value as a clinical detection index for CAA disease. In central nervous system diseases, identifying biochemical changes in peripheral blood in the early stages is difficult because of the blood–brain barrier [143, 144]. However, it has been proven that the macrophage lineage of the brain can produce migrasomes and is correlated with certain diseases. Therefore, the detection of biological information related to migrasomes in the cerebrospinal fluid should be considered in the future to obtain more relevant information in the early stages of the disease.

As transport carriers for carrying therapeutic substances Although the transplantation of bone marrow mesenchymal stem cells (BM-MSCs) can alleviate pulmonary infection after stroke and reduce the bacterial load in the lung, the antibacterial effect of BM-MSCs is significant on the third day after transplantation and seems to persist until the fourteenth day. However, Li et al. [141] found that after transplantation, the retention time of BM-MSCs in the lung was short and subsided within 24 h, but migrasomes could remain in the lung to perform immunomodulatory and antibacterial functions. Migrasomes are vesicles derived from MSC migration. This study revealed that cytochalasin D inhibited the migration of bone marrow MSCs and that the ability of macrophages to promote the phagocytosis of bacteria was lost. Although DCD is the main molecule that promotes phagocytosis, packaging DCD with migrasomes can enhance the phagocytic function of macrophages more than direct DCD treatment and has a better effect on lung infections. Stem cell transplantation has been a popular research topic in recent years; however, risks such as cell embolism, microvascular injury, and malignant differentiation are associated with stem cell therapy [145–147]. Treatment based on stem cell-derived migrasomes carrying therapeutic substances can improve the safety of treatment; therefore, migrasomes containing DCD are a promising treatment for post-stroke pneumonia.

Regenerative medicine

Migrasomes enrich chemokines and promote stem cell recruitment

Transplantation and in situ regeneration of adipose tissue are important parts of regenerative medicine [148] because adipose tissue can not only repair human soft tissue defects but also reduce fibrosis and pain, as well as improve skin quality. Adipose stem cells are the main cells that play a regenerative role in adipose tissue [149–151]. However, when the tissue is injured, the number of adipose stem cells is insufficient due to the poor environment at the injured site; therefore, the tissue regeneration effect is not good [152, 153]. Chemokines can attract more adipose-derived stem cells to metastasize [154]. However, chemokines are degraded when tissues are damaged or inflamed, making it difficult to form an effective concentration gradient [155, 156]. Therefore, to meet the need for chemokine diffusion, packaging with a membrane structure is crucial [2, 157]. Migrasomes form a diffusion gradient by transporting chemokines, which promotes blood vessel formation in chicken embryos and organ development in gastrula embryos [2, 3]. Based on this research, Chen et al. [23] found that adipose-derived stem cells can activate the CXCR4/RhoA pathway by producing migrasomes rich in CXCL12, promoting further enrichment of adipose-derived stem cells. This positive feedback pathway creates a favorable microenvironment for soft tissue regeneration.

Migrasomes improve treatments for degenerative diseases

Stem cell transplantation is commonly used clinically to treat degenerative diseases, such as diabetic wound healing, musculoskeletal regeneration, and neurodegenerative diseases [158–160]. However, the therapeutic effect is often not ideal, mainly because the microenvironment of the transplanted site is poor, which makes it difficult for the transplanted stem cells to survive and play an effective role [161, 162]. Migrasomes can carry cytokines, growth factors, and

chemokines to recipient cells, essential for stem cell proliferation and differentiation [2, 3, 6]. Migrasomes can establish a positive feedback pathway by carrying various chemokines, thus maintaining the space and time required to recruit adipose-derived stem cells during regeneration [23]. Therefore, migrasomes may become a novel therapeutic target for degenerative diseases in the future. Additionally, MSC-derived migrasomes carry cell surface molecules from parent cells [163]. Cultured adipose-derived stem cells typically exhibit minimal immunogenicity due to the absence of antigen-presenting cell-related surface proteins [164]. This characteristic potentially underscores the advantages of adipose-derived stem cells as candidates for allogeneic applications in regenerative medicine, a topic that warrants further investigation.

Conclusions

In this review, we emphasize the biological mechanisms of migrasomes, including their characteristics, formation mechanisms, and functions. Migrasomes, a new type of organelle, play a role in intercellular communication, thus affecting the physiological functions of embryo development, angiogenesis, maintenance of homeostasis, substance transport, and promotion of blood coagulation [2–5, 52]. With the gradual clarification of the physiological function of migrasomes and progress in research methods, many studies have revealed that migrasomes also participate in the occurrence and development of clinical diseases and have great potential in diagnosing and treating these diseases.

Before studying the clinical application of migrasomes, we must clearly understand the potential mechanisms of migrasome biogenesis. First, we only knew that migrasomes were composed of domains rich in TSPAN4 [26], with many vesicles inside, and containing proteins, RNA, mitochondria, and other substances [4, 5]; however, the mechanism by which the vesicles were transported into migrasomes was unclear. However, the latest evidence shows that vesicles are driven to the back of cells by the myosin-5a motor protein during cell migration, then transferred to migrasomes, and finally released by the fusion of SNARE proteins and migrasome membranes [6].

Biological evolution is known to develop in a favorable direction. As cells produce migrasomes, they must have physiological significance. Although migrasomes are known to be involved in organ development [2], mitochondrial quality control [4], and other functions, recent research has revealed that neutrophils enrich coagulation factors and adhesion molecules in plasma through generated migrasomes, thus gathering at the wound site and quickly initiating the coagulation reaction [52]. Therefore, another function of migrasomes has been identified, but their physiological function is certainly more significant.

With the gradual clarification of migrasome function, clinical research on migrasomes has gradually emerged. Although migrasomes are important for physiological function, they may be a double-edged sword in disease states. In this review, we summarize the current research on the relationship between migrasomes and clinical diseases. We divided clinical diseases into tumor and nontumor diseases and nontumoral diseases into infectious and noninfectious diseases. The pathological mechanism and diagnostic and therapeutic value of migrasomes have been elucidated for different diseases. First, in the study of migration and tumors, it was found that tumor cells can promote the invasion and metastasis of tumor cells via migration [12] and improve the survival rate of cancer cells by transferring autophagosomes [25]. Although current research shows that migrasomes can promote tumor progression, does reduced adhesion during tumor metastasis also reduce the formation of migrasomes and, in turn, affect tumor metastasis? Additionally, can immune cells regulate the TME by producing migrasomes, thus inhibiting tumor growth? Among infectious diseases, current research has focused primarily on migrasomes and viral infections; that is, virus-infected cells can promote their spread by packaging virus particles into migrasomes [15, 16, 68], and the virus can also escape drugs [69]. In addition to promoting spread, can migrasomes be temporary resting places for viruses during incubation or latent infection periods? Can virus-infected cells excrete the virus invading the cell through migrasomes, such as transporting damaged mitochondria, to maintain their stability? We examined disease categories for noninfectious diseases. In cardiovascular disease, myocardial and endothelial cells transport damaged mitochondria through transporters, thus alleviating injury after ischemia/reperfusion [18]. In addition to myocardial injury, atherosclerosis is a common cardiovascular disease. Cholesterol is an important component of migrasomes and is the main pathogenic factor. Does it also play an important role in this process? In urinary diseases, early renal injury can be identified by detecting migrasomes produced by podocytes in the urine [22, 100]. However, can migrasomes aggravate or alleviate renal injuries? In gynecological diseases, nanoplastics can induce miscarriage by preventing trophoblast cells from producing migrasomes [21]. We already know that migrasomes play an important role in embryonic development [2]; therefore, if we can find substances that promote the production of migrasomes, we can compensate for the shortage of migrasomes in

the disease state. In ophthalmic diseases, the positive feedback pathway established by pigment epithelial cells through migrasomes stimulated by cytokines promotes their transformation into fibroblasts, leading to proliferative retinopathy [20]. However, can fibroblasts also migrate to stimulate the transformation of pigment epithelial cells, thus accelerating disease progression? In neurological diseases, macrophages stimulate Aβ40 to produce migrasomes that damage endothelial cells and destroy the blood–brain barrier, thus aggravating CAA [19]. However, can damaged endothelial cells produce migrasomes to promote the repair of the blood–brain barrier? In regenerative medicine, adipose-derived stem cells attract more adipose-derived stem cells to generate a chemotactic gradient, promoting tissue regeneration [23]. However, can other cells that migrate to the repair site also promote tissue regeneration through migrasomes?

Migrasomes are not only related to pathological mechanisms but also have great potential in the diagnosis and treatment of diseases. First, migrasomes are expected to become new biomarkers that play important roles in early prediction, staging, and prognosis. For example, the number of podocyte-derived migrasomes reflects early renal injury better than urine protein levels [22], and the number of migrasomes in the peripheral blood of patients with CAA is positively correlated with cognitive impairment [19]. However, sufficient evidence for the use of migrasomes in clinical diagnosis still lacks. Therefore, we should first establish various animal disease models to study the role of migrasomes in these biological processes and then prove their feasibility using multiple sets of clinical data. Improving the sensitivity and specificity of migrasomes as biomarkers is also necessary.

Two main approaches exist for disease treatment. First, migrasomes can be directly targeted for disease intervention, and increasing or decreasing the number of migrasomes can improve the prognosis of diseases. For example, the in situ decoupling killing strategy can reduce the production of migrasomes, thereby inhibiting the bone metastasis of tumor cells [57]. Inhibiting migrasome production by virus-infected cells can impede viral spread. Among the existing drug treatments, dasabuvir has been shown to prevent the spread of the virus through migrasomes.

Second, considering the ability of migrasomes to transport substances, they can be considered carriers of drugs for the treatment of diseases. For instance, MSCs can promote the phagocytosis of bacteria by macrophages through the production of migrasomes containing dendritic cell-derived chemokine (DCD), which has a better effect than the direct stimulation of DCD [141]. Therefore, we envision the use of migrasomes rich in DCD to treat bacterial infections in immunosuppressed states, which can avoid the disadvantage of antibiotics damaging the immune environment. Subsequent research will focus on efficiently loading disease treatment drugs into migrasomes and achieving targeted delivery, enabling the drugs to act precisely on specific cells, improving the efficacy of the drugs, and reducing toxicity and side effects on normal tissues. Migrasomes are promising carriers in gene therapy. Gene editing technology has great potential in clinical treatment. Research on the use of migrasomes to precisely deliver gene-editing tools to target cells and achieve the regulation of specific genes may lead to breakthroughs in disease treatment. For example, loading the CRISPR/Cas9 system into migrasomes allows them to specifically target relevant genes in diseased tissues, correcting genetic defects or regulating the expression of disease-related genes. Meanwhile, studying the efficiency and safety of migrasome-mediated gene editing in different tissues and disease models, and optimizing the gene editing strategy can provide more precise and effective methods for the treatment of genetic diseases. In addition, biomaterials are widely used in clinical medicine to construct tissue engineering scaffolds, providing physical support for the growth of cells and tissues. The combination of migrasomes with biomaterials is expected to facilitate the development of composite scaffolds with improved performance. Research on how to integrate migrasomes rich in bioactive factors into biomaterials can enable scaffolds to provide physical support and continuously release migrasomes and the factors they carry, promoting cell adhesion, proliferation, and differentiation. For example, by compounding migrasomes with biomaterials such as hydrogels and nanomaterials, bio-scaffolds with a biomimetic microenvironment can be constructed to simulate the physiological environment of tissues in vivo, guiding the differentiation of stem cells into specific cell types and promoting tissue growth. Moreover, studying the adsorption and release patterns of migrasomes on the surface of biomaterials, as well as the interaction mechanism between migrasomes and biomaterials, can provide a theoretical basis for optimizing the design and performance of the composite scaffolds.

However, bioengineering research on migrasomes currently does not exist. First, the dependence of migrasomes on cell migration may lead to difficulties in their preparation. Nevertheless, important issues remain to be addressed, such as the selection of donor cells, drug loading methods, carrier safety, and the use of targeting peptides on the surface of migrasomes. Additionally, ensuring the efficient transportation and treatment of migrasomes is necessary. Despite all this, the use of migrasomes as drug carriers has great application

prospects, value, and significance in the treatment of diseases in the field of bioengineering.

Abbreviations

Aβ	Amyloid β protein
AIS	Acute ischemic stroke
ASC	Adipose-derived stem cell
BBB	Blood–brain barrier
BM-MSCs	Bone marrow mesenchymal stem cells
CAV1	Caveolin-1
CD5L	CD5 antigen-like protein
CDC	Complement-dependent cytotoxicity
CAA	Cerebral amyloid angiopathy
CAM	Chorioallantoic membrane
CPQ	Carboxypeptidase Q
DCD	Dermcidin
Drp1	Dynamin-related protein 1
ECM	Extracellular matrix
EEV	Extracellular envelope virus
EOGT	EGF domain-specific O-linked *N*-acetylglucosamine transferase
ER	Endoplasmic reticulum
GBM	Glioblastoma
GO	Gene Ontology
HSV-2	Herpes simplex virus type 2
KIF5B	Kinesin family member 5B
Lama 4	Laminin alpha 4
LIPUS	Low-intensity pulsed ultrasound
LRRK2	Leucine-rich repeat kinase 2
MFS	Migrasome formation sites
MSCs	Mesenchymal stem cells
Myo19	Myosin 19
NDST1	*N*-Deacetylase/*N*-sulfotransferase 1
PAK4	P21-activated kinase 4
PDGF-BB	Platelet-derived growth factor BB
pHCAECs	Primary human coronary endothelial cells
PI(4,5)P2	Phosphatidylinositol (4,5)-diphosphate
PIGK	Phosphatidylinositol polysaccharide anchor biosynthesis, class K
PLA2R	Phospholipase A2 receptor
PLS	Pomegranate-like structure
PS-NPs	Polystyrene nanoplastics
RF	Retraction fibers
SMS2	Sphingomyelin synthase
SOX2	Sex-determining region Y-box 2
TSPANs	Transmembrane proteins
TEM	Transmission electron microscopy
TEMAs	Tetraspanin-enriched macrodomains
TME	Tumor microenvironment
VACV	Vaccinia virus
VEGF	Vascular endothelial growth factor
WB	Western blot

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