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Shedding light on the cell biology and diverse physiological functions of the migrasome

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Abstract
The migrasome, an organelle that forms behind migrating cells, is connected to the cell body by a retraction fiber. Once released from the retraction fiber, the migrasome transforms into an extracellular vesicle and plays important roles in cell communication, development, angiogenesis, and disease. To date, the biogenesis, regulation of formation, cargo transportation, and physiological functions of migrasomes remain largely unknown. In this review, we summarize the current understanding of the mechanisms underlying migrasome formation and regulation, describe the evidence suggesting that migrasomes serve various physiological functions, compare the differences between migrasomes and other extracellular vesicles, emphasize the limitations in studying migrasomes, and discuss the potential of migrasomes in disease diagnosis and treatment.

Introduction

The migrasome, a newly discovered organelle associated with cell migration, was first reported by the group of Li Yu in 2015 [1]. Using transmission electron microscopy, the authors identified a structure containing small vesicles located outside of a cell. Initially, this structure was named the pomegranate-like structure (PLS), but further research revealed that its formation was closely linked to cell migration. The speed and persistence of cell migration contributes to the formation of migrasomes [2], leading to the renaming of the structure as "migrasome" (Fig. 1). After the discovery of the migrasome, the question arose as to how to identify it. It has been recognized that migrasomes are parts of the cell, prompting researchers to use wheat germ agglutinin (WGA) to stain them [3]. WGA, a lectin found in the germ tissue of wheat kernels, can be labeled with small-molecule fluorescent markers to facilitate the visualization of mammalian plasma membranes [4, 5] and can be used to stain migrasomes. For purification, researchers have developed a method that combines trypsin–EDTA treatment and density-gradient centrifugation [3]. Additionally, quantitative mass spectrometry has led to the identification of four markers for the detection of migrasomes [6]. Consequently, migrasomes have been detected and purified, leading to more and more information about their morphology and function.

The size of migrasomes ranges from 0.5 to 3 μm [1, 3], conferring them a greater ability to carry cargoes than exosomes. Migrasomes are enriched in RNAs, proteins, lipids, chemokines, cytokines, and small organelles [7–10] (Fig. 1). Once the migrasome is taken up by surrounding cells, the mRNA, miRNA, chemokines, and even viruses [11] inside the organelle regulate the growth

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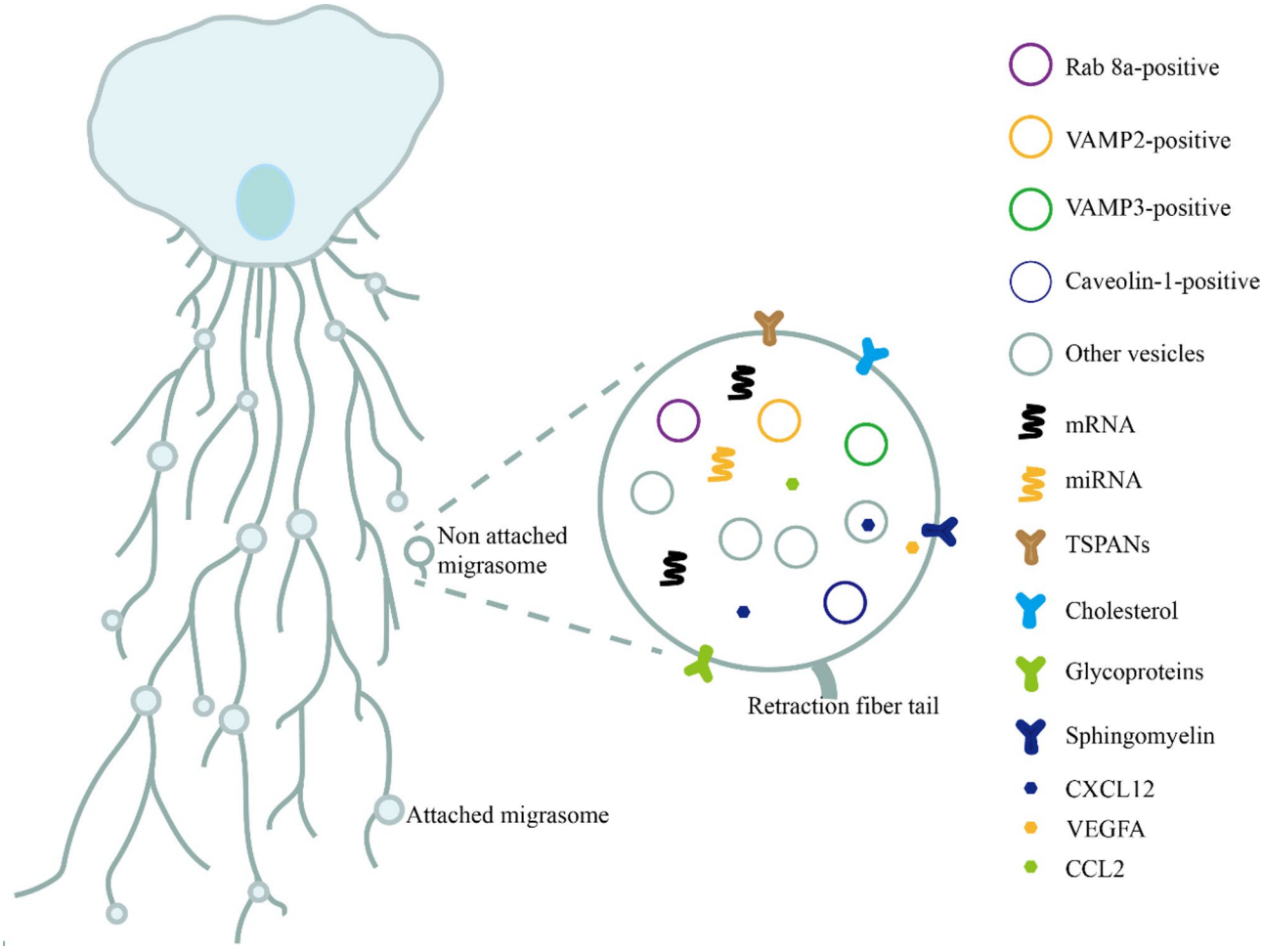

Fig. 1 Properties of migrasomes. The migrasome is more likely formed at the branch point of RFs. It is enriched with small vesicles whose membranes contain high levels of Rab8a, VAMP2, VAMP3, and Caveolin-1. Additionally, macrodomains such as TSPANs, cholesterol, glycoproteins, and sphingomyelin are present on the migrasome membrane. Nucleic acids, chemokines, and morphogens are also enriched in the migrasome

and survival of the recipient cell. It has been reported that mRNA transferred by migrasomes regulates protein levels in the recipient cell [7]. Additionally, mitochondria can be transported into the migrasome, maintaining mitochondrial quality and viability in neutrophils [10]. Migrasomes are enriched with various chemokines such as VEGFA, CXCL12, and TGFβ [8, 9], and induce a localized secretion model in migrating cells. These findings highlight the critical role of migrasomes in organ morphogenesis and angiogenesis. Moreover, migrasomes have been found in human serum, indicating a significant biological function in development and disease [6, 12]. For instance, migrasomes derived from retinal pigmented epithelial cells contribute to the development of proliferative vitreoretinopathy [13].

Despite numerous publications on migrasomes over the last decade, many questions remain regarding their formation and regulation [14]. Additionally, the physiological function of migrasomes remains largely unknown. In this review, we introduce the physical and chemical properties of migrasomes, summarize the mechanisms underlying migrasome formation and regulation, discuss both known and presumed physiological functions, emphasize limitations related to the study of migrasomes, and describe the future direction of migrasome research.

What are the basic physical and chemical properties of migrasomes?

Migrasomes are significantly larger than exosomes [15]. Within the migrasome, there are numerous small vesicles, whose number varies from less than 10 to more than 300. This gives the migrasome a resemblance to a pomegranate, which is why it was initially referred to as pomegranate-like structures. Recently, a study reported that these migrasome intraluminal vesicles can be released from the migrasome through self-rupture or through a process similar to cell plasma membrane budding. They have named these released lipid-bilayer membrane vesicles as migrasome-derived nanoparticles (MDNPs) [16] (Fig. 1). The membrane of MDNPs exhibits a typical

round-shaped morphology and is rich in migrasome biomarkers. Moreover, the MDNPs exhibited an average diameter of 165.3 ± 3.1 nm. This findings suggests that MDNPs originate from migrasome intraluminal vesicles (mILVs). However, not all mILVs can be considered MDNPs. Jiao et al. reported that Rab8, VAMP2, and VAMP3 are enriched on the membrane of mILVs, facilitating fusion with the migrasome membrane [17]. One question that arises is how these mILVs are transported into migrasomes. A recent study reported that the motor protein Myosin Va and the adaptor protein RILPL2 are required for the transport of mILVs marked with Rab10 and Caveolin-1 into migrasomes [18], while Rab10- and caveolin-1-negative mILVs may employ different mechanisms. Inside mILVs, chemokines, coagulation factors, and angiogenic factors provide localized secretion of these signaling proteins [8, 9, 17]. An interesting question is whether any intra-luminal vesicles (ILVs; future exosomes) exist inside migrasomes. The size of ILVs is similar to that of MDNPs. Once ILVs are transported into migrasomes, migrasomes may acquire all the functions of exosomes.

The migrasome is connected to the cell body through retraction fibers (RFs), which are channel-like structures [1]. Ma et al. discovered that GFP can be transported into migrasomes. However, it is still unknown whether mILVs are transported into the migrasome during migrasome maturation. The function of the RFs remains unclear, with one hypothesis suggesting that they serve as a channel for transporting mILVs between the migrasome and cell body. Another hypothesis is that the RFs also act as force transducers, contributing to migrasome formation.

Tetraspanins (TSPANs) are proteins with four transmembrane domains present on the cell membrane [19–21]. There are 33 known TSPAN members in humans, and it has been reported that TSPANs and cholesterol promote migrasome formation, with TSPAN4 appearing to be the most effective. Huang et al. reported that TSPAN4 can migrate to the migrasome formation site and stabilize the migrasome [22]. In addition to TSPANs, integrins and cholesterol localize in the migrasome membrane and are associated with migrasome formation [23] (Fig. 1). Other proteins are also present on the migrasome membrane. Migrasomes have been reported to be internalized by surrounding cells [1, 7], but whether a specific receptor on the recipient cell is responsible for the internalization process has not been clarified.

Migrasomes are quite distinct from other extracellular vesicles in terms of size and morphological properties, and require a different methodology for purification and identification. Jiang et al. reported that centrifugation at 20,000 × *g* is adequate for collecting migrasomes [3]. To separate migrasomes from other extracellular vesicles, density-gradient centrifugation at 150,000 × *g* should be performed. After purification, migrasomes can be detected using immunofluorescence, western blotting, and electron microscopy. Detection of biomarkers such as NDST1, EOGT, PIGK, and CPQ in western blotting can help researchers identify migrasomes. Additionally, electron microscopy imaging allows researchers to determine whether an extracellular vesicle is a migrasome.

What are the differences between exosomes, microvesicles, and migrasomes?

Various types of extracellular vesicles, including exosomes and microvesicles, are recognized as new mechanisms for intercellular communication [24]. These vesicles allow cells to exchange proteins, lipids, and genetic material. Exosomes, which typically range from 50 to 150 nm in diameter, are formed by inward budding of the endosomal membrane during the maturation of multi-vesicular endosomes (MVEs) [25]. Conversely, microvesicles, which range from 50 to 1000 nm in diameter, are produced by outward budding and fission of the plasma membrane, leading to the release of the vesicles into the extracellular space [26] (Table 1).

Unlike exosomes and microvesicles, migrasome formation is dependent on cell migration. Cells that do not migrate cannot produce migrasomes. This suggests that migrasomes generated in vivo are more likely produced by fast-moving cells, such as immune cells or cancer cells. This may provide migrasomes with spatial effects, as cells on the migration pathway are more likely to be influenced by migrasomes. Recently, Jiao et al. reported that secretory proteins, including signaling proteins and cytokines, are enriched in migrasomes through the transportation

Table 1 Differences between exosomes, microvesicles, and migrasomes

	Exosome	Microvesicle	Migrasome
Size	50–150 nm	50–1000 nm	500–3000 nm
Membrane	Integrated, origin from endosome	Integrated, origin from plasma membrane	Non-integrated, origin from plasma membrane
Biogenesis	Cargo clustering and membrane budding occur via ESCR-dependent and ESCRT-independent mechanisms [24, 27, 28]	Cargo clustering and lipid flipping requires an ESCRT-dependent mechanism	Migration-dependent, microvesicles inside
Release	MVEs fuse with the plasma membrane [29, 30]	Pinch off from plasma membrane [31, 32]	Breakdown of retraction fibers

MVE, multi-vesicular endosomes

of secretory carriers [17, 33]. Once released from migrasomes, these secretory proteins influence the behavior of surrounding cells. Hence, migrasomes induce a localized, highly efficient secretion of signaling proteins and cytokines.

Migrasomes are much larger than exosomes or microvesicles (Table 1) and have a much more powerful ability to carry cargo. Mitochondria are reportedly carried by migrasomes [10], while exosomes and microvesicles lack this capacity. Migrasomes also exhibit morphological differences compared to exosomes and microvesicles. Exosomes and microvesicles display a rounded morphology with integrated membranes, preventing the leakage of cargoes inside. In contrast, migrasomes typically have a retraction-fiber tail. Additionally, the migrasome membrane may not be fully integrated because of the breakdown of the retraction fiber, which allows for cargo leakage inside (Table 1).

How can migrasomes be distinguished from exosomes and microvesicles? Migrasomes have a much larger diameter than exosomes, with a unique fiber-like structure that sets them apart. This distinct shape makes them easily identifiable. Additionally, a recent study reported that migrasome contains little CD81, Alix and CD63, the markers for exosomes [34]. This distinction helps to differentiate migrasomes from exosomes. Microvesicles have a similar diameter to migrasomes, making it more difficult to distinguish between the two. Jiang et al. reported that neutrophil-derived migrasomes did not contain phosphatidylserine on the outer membrane leaflet, while phosphatidylserine exposure was present on the outer leaflet of neutrophil-derived microvesicles [12]. Therefore, they were able to differentiate between migrasomes and microvesicles using FACS. Furthermore, migrasomes did not exhibit an enrichment of markers found in microvesicles, such as Arf6 and Kif23 [35, 36]. These distinguishing characteristics can be utilized to distinguish between microvesicles and migrasomes effectively.

Mechanism for migrasome formation

Migrasome localization on the retraction fiber network can be categorized into three types: at branch points, at the tip of RFs and along RFs [2, 37]. Migrasomes appear to be more commonly found at branch points and at the tips of RFs, suggesting that their formation is governed by a series of specific biological mechanisms. A significant amount of research has been dedicated to studying the formation of migrasomes [2, 22, 38–40], which is currently divided into three steps: determination of the formation site, formation of the retraction fiber, and swelling of the membrane (Fig. 2).

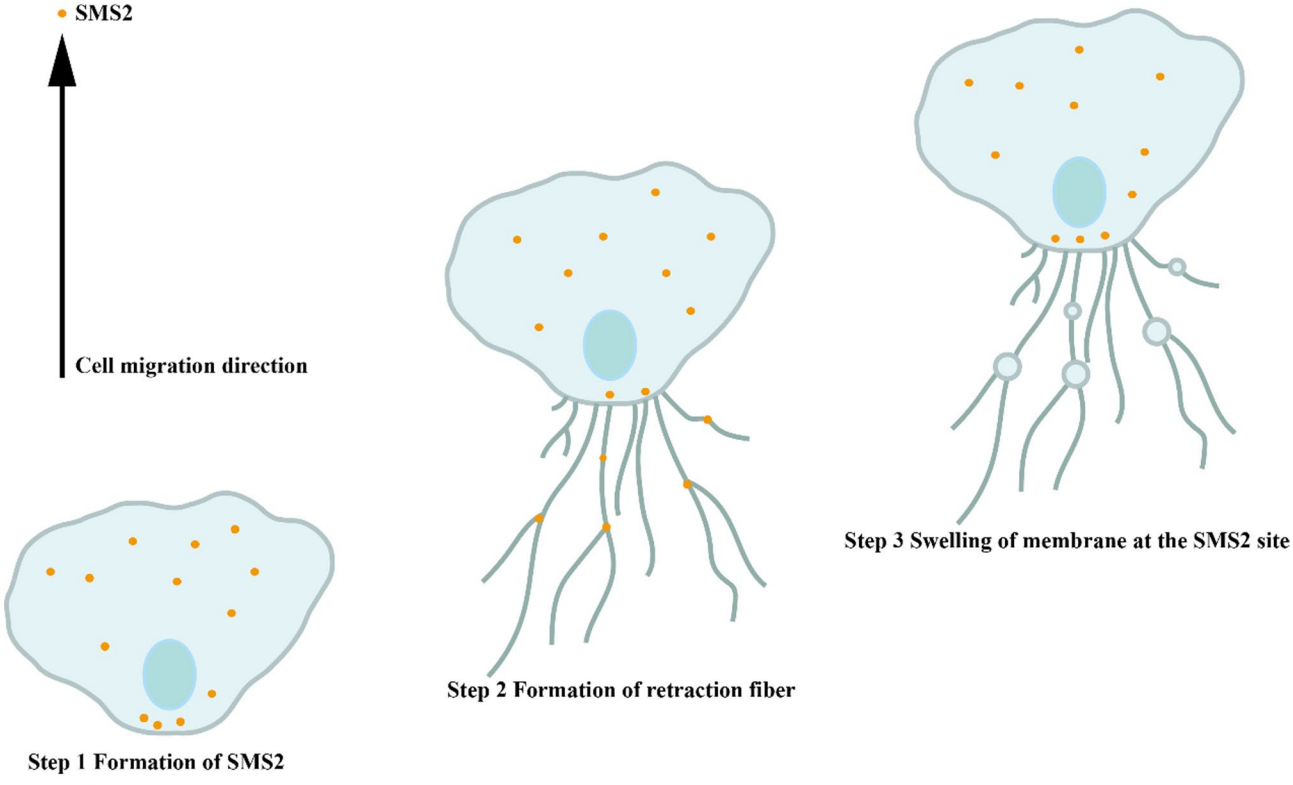

Fig. 2 Mechanism for migrasome formation. SMS2 assembles into immobile foci at the leading edge; with the cell migrating forward, SMS2 is localized in RFs. SMS2 converts ceramide to sphingomyelin, allowing the swelling of the membrane at the SMS2 site

Sphingomyelin synthase 2 (SMS2) is a plasma membrane-localized sphingomyelin synthase that converts ceramide into sphingomyelin [38]. Sphingomyelin is one of the most abundant lipids in the plasma membrane [41] and may contribute to the maintenance of migrasomes. Through high-throughput screening of migrasome-enriched proteins, Liang et al. found that the knockdown of genes associated with ceramide catabolism resulted in significant reductions in the formation of migrasomes, while RFs still formed. This indicates that ceramide-associated genes may play a pivotal role in migrasome formation. Lipidomic analysis of migrasomes and plasma membranes reveals that sphingomyelin and ceramide are enriched in migrasomes and are essential for migrasome formation. SMS2 localizes in RFs prior to the formation of migrasomes (Fig. 2). It likely converts ceramide into sphingomyelin at the retraction fiber and determines the site of migrasome formation.

After identifying the site of migrasome formation, it is essential to establish a RF network for migrasome formation. To create RFs, the cell membrane must be attached to the extracellular matrix. Activated integrins are highly enriched at the base of migrasomes [23] and bind to various components of the extracellular matrix. For example, integrin α5β1 binds to fibronectin, and integrin α3β1 specifically binds to laminins. This binding of integrins to the extracellular matrix results in the anchoring of the cell membrane to the extracellular matrix. With the forward migration of the cell, RFs are formed between the integrin adhesion site and the cell body (Fig. 2).

The cell membrane is enriched with various macrodomains, such as TSPANs, cholesterol, and sphingomyelin, which can swell into the membrane of migrasomes and increase migrasome stiffness. Using mathematical modeling, Huang et al. found that evenly distributed tetraspanin-enriched microdomains (TEMs) can self-organize into microscaled macrodomains (TEMAs) on the retraction fiber [19]. These TEMAs then swell into nascent migrasomes (Fig. 2). Moreover, the migrasome-localized TSPAN4 stabilizes these membrane swellings and aids their maturation.

Although considerable research has been conducted on the mechanism of migrasome formation, many unknowns remain. For example, does the network of RFs contribute to the formation of migrasomes? What is the relationship between the mechanical forces along the RFs and migrasome formation? Are there other proteins that act as clutch factors in migrasome formation? Does integrin-independent adhesion occur during migrasome formation?

Mechanism for migrasome regulation

Directly after formation, the migrasomes are not stable. The number of migrasomes is regulated through various mechanisms. For example, overexpression of TSPANs facilitates migrasome formation [19]. Cell migration speed and persistent direction are closely related to migrasome formation [2]. The PIP2–Rab35 pathway promotes migrasome formation by recruiting and concentrating integrin α5 at migrasome formation sites [39]. Moreover, calcium ions can also promote migrasome formation via synaptotagmin-1 [40].

Overexpression of 14 TSPANs has been reported to enhance migrasome formation (Fig. 3). Huang et al. discovered that TSPANs form discrete, fast-moving puncta that are recruited to the migrasome during its formation [19]. TSPAN recruitment increases the stiffness of the migrasome membrane, thereby stabilizing the migrasome. Apart from TSPANs, other membrane molecules, such as cholesterol, sphingomyelin, and ceramide, are essential for migrasome formation. Overexpression of these macrodomains promotes the formation of migrasomes. Despite this knowledge, migrasome formation may be regulated by still unknown proteins.

Migrasome formation relies on cell migration. Fan et al. found that migrating cells that display turning behavior form fewer migrasomes [2]. By observing cells undergoing sharp, mild, and continuous turning, the authors noticed that turning cells have narrower rear ends and fewer RFs. This indicates that persistent cell migration is closely related to migrasome formation. Using live-cell imaging, Fan et al. also noted that cells that exhibit more persistent migration are more likely to generate migrasomes. Moreover, cells with higher migration speeds tend to form more numerous migrasomes. These findings suggest that both extracellular and intracellular factors that affect the direction or speed of cell migration play a role in orchestrating migrasome formation.

Phosphatidylinositol (4,5)-bisphosphate (PI(4,5)P2) is a crucial lipid primarily found in the cell membrane [42]. Through the use of PLCγ-PH-GFP, a probe for PI(4,5)P2 [43], Ding et al. discovered that PI(4,5)P2 is localized in the migrasome [39]. To investigate the role of PI(4,5)P2 in migrasome formation, they screened for PI(4,5)P2-binding proteins and identified 23, including Rab35 [39]. Additionally, they observed that PI(4,5)P2 recruits Rab35 to the site of migrasome formation. Rab35, a small GTPase, plays a crucial role in regulating phosphoinositide levels [44]. Ding et al. also discovered that Rab35 interacts with integrin α5 and recruits activated integrin α5 to the migrasome formation site, thereby promoting migrasome formation. Taken together, these findings suggest that the PI(4,5)P2–Rab35 pathway acts as an upstream signaling pathway in the regulation of migrasome formation (Fig. 3).

Calcium is an important signaling ion that plays a crucial role in cell migration and adhesion [45, 46]. It can bind synaptotagmin-1 (Syt-1), a vital calcium sensor

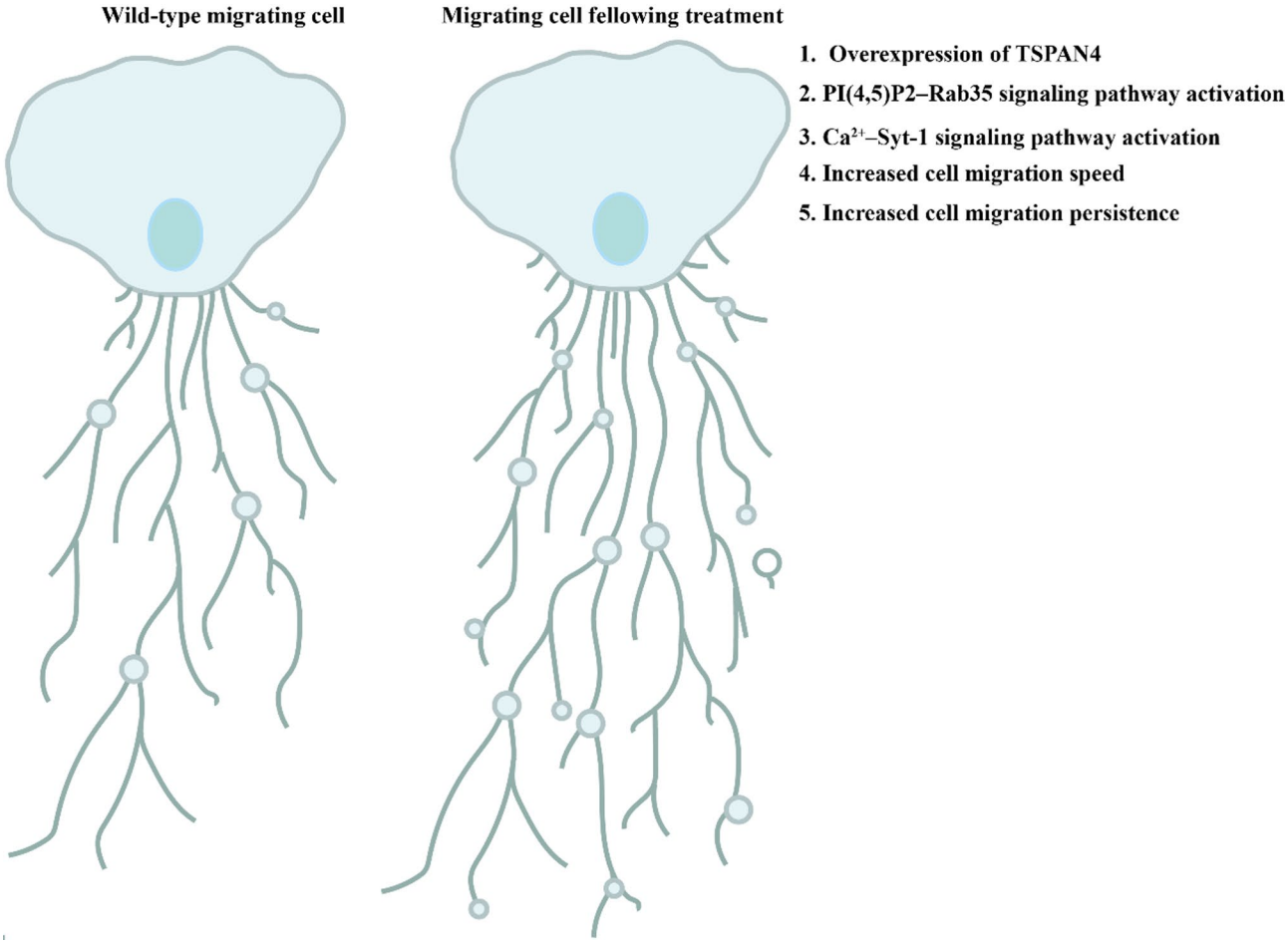

Fig. 3 Mechanisms for migrasome regulation. Overexpression of TSPANs and activation of the PI(4,5)P2–Rab35 and Ca^{2+}–Syt-1 signaling pathways increase persistent cell migration and speed, resulting in enhanced migrasome formation

enriched in migrasomes, according to a study by Han et al. [40]. The binding of calcium to synaptotagmin-1 promotes migrasome formation by recruiting synaptotagmin-1 to the site and inducing swelling. Knocking out synaptotagmin-1 significantly reduces mature migrasomes, highlighting the importance of the calcium–synaptotagmin-1 signaling pathway in migrasome regulation (Fig. 3). However, the question remains as to how synaptotagmin-1 is recruited into the migrasome.

Although much work has been done to understand the mechanisms of migrasome regulation, our comprehension of the mechanisms that regulate migrasome formation is incomplete. New proteins, signaling pathways, or even physical signaling may play a pivotal role in regulating migrasome formation.

Physiological function of migrasomes

Migrasomes in transferring RNAs

Migrasomes have a strong ability to carry cargoes. Using SYTO14, a dye that binds to nucleic acids and emits a fluorescent signal [47, 48], Zhu et al. discovered that RNAs are localized in migrasomes [7]. Total RNA sequencing revealed that mRNA is the main RNA species. To investigate whether these RNAs modify the expression level of proteins in the recipient cell, Zhu et al. incubated migrasomes with a *Pten* knockout cell line and found that *Pten* expression was restored in the knockout cells. Furthermore, they found that mRNA can not only be transferred into the recipient cell but can also modify the functional properties of the recipient cell. The mechanism underlying RNA sorting and transport into the migrasome is currently unknown. Moreover, how RNAs inside the migrasome are released into recipient cells remains to be determined.

Migrasomes in embryonic development

During embryonic development, cell proliferation and migration increase significantly [49, 50]. To investigate whether migrasome generation occurs during embryonic development, Jiang et al. observed shield-stage zebrafish embryos and discovered migrasome generation during gastrulation [9]. Using transmission electron microscopy,

they confirmed that migrasomes are present in extracellular pockets between mesendodermal cells, which are generated by mesodermal and endodermal cells. Additionally, Jiang et al. found that migrasomes are enriched with chemokines, morphogens, and growth factors, and play a pivotal role in zebrafish organ morphogenesis. Whether migrasome formation occurs during human embryonic development remains to be clarified.

Migrasomes in angiogenesis

Migrasomes are enriched with chemokines, morphogens, and growth factors. Using mass spectrometry, Zhang et al. discovered that migrasomes extracted from chicken embryos contain high levels of pro-angiogenic factors [8]. Injecting migrasomes into chicken embryos can aid capillary formation. Mechanistically, monocytes on the chorioallantoic membrane of chicken embryos generate migrasomes, which then promote the sprouting of endothelial cells (ECs) and recruit additional monocytes. This EC sprouting enhances tube formation. The study by Zhang et al. also revealed that CXCL12 and VEGFA in migrasomes play a critical role in angiogenesis. However, whether migrasomes generated in human cells have similar effects on angiogenesis remains to be elucidated.

Migrasomes in virus transmission

The diameter of a virus ranges from 20 to 200 nm [51, 52], which is much smaller than that of a migrasome. Can viruses localize in migrasomes? According to Liu et al., HSV-2 localizes in migrasomes after HSV-2 infection of HaCaT cells [11]. Furthermore, they discovered that HSV-2 can be transmitted to recipient cells after the migrasome is incubated with the recipient cell. Not only can viruses be transmitted through migrasomes but they can also play a role in orchestrating the formation of migrasomes. For example, the non-structural protein CHIKV activates PIP5K1A to generate PI(4,5)P2, contributing to the formation of migrasomes [53]. Besides mature viral particles, viral components can also be localized in migrasomes. Once the components essential for replication are transported into a migrasome, the virus can infect recipient cells through the migrasome.

Migrasomes in proliferative vitreoretinopathy

Activation of cells of the retinal pigmented epithelium (RPE) leads to proliferative vitreoretinopathy [54, 55]. Wu et al. identified migrasome-like extracellular vesicles in the microenvironment of proliferative vitreoretinopathy [13], and reported that TSPAN4 was overexpressed in human PVR-associated clinical samples. Furthermore, the authors found that RPE cells are activated after incubation with the migrasome-like vesicles. Interestingly, the researchers claim that these migrasome-like vesicles are produced by RPE cells. However, the supporting evidence was obtained in vitro, and in vivo confirmation is lacking.

Migrasomes in hemostasis

Neutrophils are fast-moving immune cells in the human body that reportedly produce migrasomes [12, 56]. In a study conducted by Jiang et al., neutrophil-derived migrasomes were enriched with coagulation factors [12]. This discovery prompted investigations of whether migrasomes play a role in hemostasis. After incubating neutrophil-derived migrasomes with platelets, the researchers observed that these migrasomes activated platelets. Furthermore, they found that neutrophil-derived migrasomes trigger coagulation. These findings suggest that neutrophil-derived migrasomes are an essential component of the coagulation system. In conclusion, the study conducted by Jiang et al. highlights the important role of neutrophil-derived migrasomes in regulating the coagulation process.

What are the limitations in studying migrasomes?

It is well established the migrasome is linked to the cell body via RFs. The method used to isolate migrasomes utilizes trypsin–EDTA [3], which effectively breaks down the adhesion between cells and extracellular matrix [57, 58] without severing the bond between the migrasome and cell body. Consequently, migrasomes remain attached to the cells, even after centrifugation, leading to a decrease in migrasome harvesting. Second, the size of a microvesicle ranges from 0.05 to 1 μm, with some microvesicles being similar in size than migrasomes. This similarity makes it difficult to separate migrasomes from microvesicles. Therefore, new methods for the collection and purification of migrasomes are needed.

Microscopy is one of the most commonly used techniques to investigate migrasomes in vitro [59]. Cells in living organs encounter a complex microenvironment, including blood, cytokines, and various extracellular matrices. This complexity presents a challenge for imaging migrasomes in vivo [60, 61]. The team of Dai developed digital adaptive optics scanning light-field mutual iterative tomography (DAOSLIMIT), which features high-speed and high-resolution 3D imaging, and two-photon synthetic aperture microscopy (2pSAM) [62, 63]. Using DAOSLIMIT and 2pSAM, Dai and colleagues imaged neutrophil generation in mice. Despite significant advancements in live-cell imaging in mammalian organs, there is still a need for long-term, high-speed, deep, and super-resolution subcellular mammalian imaging.

Potential of migrasomes in disease diagnosis and treatment

Numerous disease biomarkers are found in the blood and other bodily fluids [64]. These biomarkers have been used

in liquid biopsy, which is now recognized as an important approach for diagnosing diseases. For example, circulating tumor cells and DNA have been identified as new biomarkers in cancer diagnosis [65, 66]. It is intriguing to consider whether migrasomes or migrasome-related genes could be utilized as a novel approach for diagnosing diseases. Qin et al. recently identified migrasome-related genes, including ITGB1, ITGA5, EOGT, CPQ, PIGK, NDST1, and TSPAN4, as potential immunotherapeutic targets [67]. They suggest that the increased formation of migrasomes may be linked to poor prognoses in various types of cancer. Despite this, the specific function of migrasomes in cancer still remains unclear. Migrasomes, which are enriched with various types of RNAs, have a powerful transport ability that makes them ideal for liquid biopsy. Despite this observation, published studies on the use of migrasomes for liquid biopsy are presently lacking. It is imperative that more research is conducted to explore the potential of migrasomes for liquid biopsy.

The migrasome contains signaling proteins that can activate numerous signaling pathways. In patients experiencing significant signaling inhibition, exogenous migrasomes containing these signaling proteins can be used for treatment. Additionally, nanoparticles can derive from migrasomes. With technological advancements, researchers may soon be able to pack drugs into migrasomes. By expressing specific receptors on the migrasome membrane, drugs contained within migrasomes can precisely target cells, which is crucial for effective disease treatment.

Concluding remarks

The migrasome is a recently discovered organelle that functions as an extracellular vesicle. It plays a crucial role in cell communication, development, immune response, and disease. However, much remains unknown in terms of basic cell biology and physiological function. Additionally, the question remains whether migrasomes can provide new strategies for curing diseases. With the development of technologies for migrasome purification, manipulation, and in vivo imaging, migrasomes are poised to play a much more significant role in human health.

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Author contributions
Yuxing Huang and Jian Gao designed the study, Yuxing Huang wrote the manuscript, Yi Huang and Jian Gao contributed to literature collection and language editing, Yuxing Huang and Jian Gao contributed to funding acquisition, revision. All authors read and approved the manuscript.

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Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
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