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Migrasome and cancer - from cellular to clinical perspectives

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Abstract

Migrasomes, a newly discovered class of extracellular organelles, have emerged as pivotal mediators of intercellular communication, signaling gradient establishment, and organelle homeostasis. Their unique biogenesis—arising from retraction fibers of migrating cells—positions them as critical regulators in both physiological and pathological processes, particularly in cancer. Recent studies have revealed that migrasomes play multifaceted roles in cancer initiation, progression, metastasis, and drug resistance by orchestrating cell-cell communication, modulating the tumor microenvironment (TME), and facilitating the transfer of oncogenic biomolecules. This review systematically summarizes current knowledge on migrasome biogenesis and functions, critically analyzes their multifaceted involvement in cancer biology, and evaluates their potential as diagnostic biomarkers and therapeutic targets. Importantly, we highlight recent advances in migrasome-based cancer research and discuss future directions for translating these findings into clinical applications.

Keywords Migrasome, Cell migration, Cancer, Cancer biology, Tumor microenvironment, Clinical application

Background

Cell migration is a fundamental biological process essential for embryonic development, wound healing, immune responses, and cancer progression, [1] where it drives metastasis through signaling pathways, cytoskeletal reorganization, and cell adhesion changes [2, 3]. In recent years, the role of organelles in these biological processes has garnered increasing attention. Organelles such as mitochondria, the Golgi apparatus, and endosomes have been shown to play significant roles, offering new insights into tumor development and progression. Notably, a novel membrane-associated organelle, termed the "migrasome," has been identified as playing a crucial role in cell migration [4].

Migrasomes, as novel organelles, are large vesicular structures formed by local expansion of cell membranes during migration [5]. Unlike conventional organelles like endosomes and exosomes, migrasomes not only participate in the extracellular secretion of signaling molecules

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but also influence cellular dynamics by expanding the membrane and interacting with the extracellular environment [6]. Beyond their role in migration, migrasomes are involved in processes such as cell proliferation, differentiation, and tissue repair [7], suggesting that they may also impact tumor development and metastasis.

Thus, recent studies have increasingly focused on the role of migrasomes in cancer [8]. Pan-cancer analyses have demonstrated that migrasomes are pivotal in tumor cell migration and metastasis across various cancer types, particularly in malignant tumors like liver, breast and colorectal cancers [9–11]. Moreover, the presence of migrating bodies has been observed in these cancers through electron microscopy and other methods. In certain cancers, migrasomes regulate tumor growth, invasion, and metastasis by influencing signaling pathways in tumor cells and modulating cell-cell interactions within the TME [12, 13]. Moreover, They also show promise as biomarkers for detection and drug resistance [4, 14]. The significance of migrasomes extends beyond tumor biology, offering new avenues for cancer clinical treatment and research direction, particularly in targeted therapies and immunotherapies.

As a novel organelle, migrasomes are gaining increasing attention in both cell biology and clinical research. While recent reviews have provided foundational insights—such as the general biological characteristics explored by Tan et al.[15] or the clinical therapeutic potential discussed by Zhang et al. —few studies have yet to comprehensively synthesize the multifaceted roles of migrasomes specifically within the context of tumor progression and metastasis [16]. Notably, existing literature often overlooks the intricate mechanisms of migrasome-mediated intercellular signaling in tumor cells and its profound impact on tumor microenvironment regulation. Furthermore, while Deng et al. highlighted biomarkers, a systematic integration of how these mechanisms contribute to drug resistance and immunotherapy remains underexplored [4]. This review aims to address this critical gap by offering an innovative perspective that bridges basic biology with clinical oncology. Unlike existing literature, we emphasize underexplored areas, including migrasome-mediated intercellular signaling in tumor cells, their contributions to regulating the tumor microenvironment, and their impacts on tumor initiation, metastasis, immune evasion, and resistance mechanisms. Additionally, we highlight the translational value of migrasomes as diagnostic biomarkers, therapeutic targets, and tools for early cancer detection, personalized treatment strategies, and immunotherapy. This targeted approach provides fresh insights not fully articulated in prior works, serving as a vital resource for researchers at the intersection of migrasomes and cancer therapy to drive future investigations.

Biological characteristics of migrasomes

Migrasomes, first identified by Yu et al. in 2015 [5], are a novel type of extracellular vesicles characterized by their large spherical morphology (500–3000 nm in diameter) and phospholipid bilayer structure. Although morphologically similar to exosomes, migrasomes exhibit distinct membrane protein compositions, including integrins and tetraspanins (e.g., ITGA5, TSPAN4), which mediate interactions with the extracellular matrix and cell membranes [17, 18]. Migrasome distribution varies among cell types, with a higher prevalence in cells with strong migratory capacity. They tend to accumulate in specific regions of the cell membrane, particularly at the leading edge of migration, highlighting their importance in this process. Notably, tumor cells exhibit enhanced migrasome production under the influence of the tumor microenvironment (TME) [19]. This suggests that migrasomes play a key role in tumor cell migration, invasion, and adaptation to the TME.

Migrasome formation is a complex process involving membrane swelling, molecular assembly, and mechanical forces [20]. The formation process occurs in three stages: (1)Initiation - Sphingomyelin synthase 2 (SMS2) accumulates at the cell's leading edge to form membrane spots, initiating the assembly of the migrasome generation site; (2) Maturation - Integrins bind to retraction fibers, promoting migrasome protrusion, while localized stretching and remodeling of the cell membrane further support their formation; (3) Release - Mature migrasomes accumulate cytoplasmic components and small vesicles during their formation, ultimately forming large vesicular structures [21], Upon rupture of the retraction fibers, migrasomes are released into the extracellular space and internalized by neighboring cells, which termed "migracytosis" [18, 22]. Migrasome formation process is precisely regulated through multiple molecular mechanisms and signaling pathways. For instance, Tetraspanin 4 (TSPAN4) plays a central role in stabilizing and assembling the four transmembrane protein domains required for migrasome formation [23]. Additionally, Rab GTPases such as Rab35 and Rab10 control cell membrane dynamics and regulate membrane component transport, thereby influencing migrasome formation and function [24, 25]. Other signaling molecules, such as ROCK1, a Rho-associated kinase, also participate by regulating membrane tension and migrasome release [26]. This process has been illustrated in several publications, such as the manuscript by Jiang et al. [7].

Beyond serving as a marker for cell migration, migrasomes have multiple biological functions, including intercellular content transfer, molecular regulation, and cellular homeostasis maintenance [27]. These substances influence cell adhesion and dissociation by interacting with specific adhesion molecules and receptors, thereby

regulating both the rate and direction of cell migration. This process is particularly important in tissue regeneration and repair [28]. Moreover, migrasomes carry specific mRNAs and proteins that, upon uptake by surrounding cells, modulate the physiological functions such as proliferation, metabolism and secretion of the recipient cells, playing a critical role in immune responses [28]. Migrasomes also contribute to mitochondrial homeostasis by translocating and removing dysfunctional mitochondria and maintaining mitochondrial quality [29].

It is important to note that migrasomes differ fundamentally from exosomes in biogenesis and function (Table 1). Extracellular vesicles (EVs) are heterogeneous, membrane-bound particles released by virtually all cell types into the extracellular space, serving as key mediators of intercellular communication by transferring bioactive cargos such as proteins, lipids, nucleic acids, and metabolites. Based on their biogenesis, size, composition, and function, EVs are broadly classified into subtypes, including exosomes, microvesicles (also known as ectosomes), apoptotic bodies, and more recently, migrasomes [30]. Among these, exosomes represent a distinct subset originating from the endosomal pathway, characterized by their small diameter (30–150 nm) and the presence of specific surface markers such as CD63, CD81, and TSG101 [31]. In contrast, migrasomes are a specialized type of EV that arises not from intracellular trafficking but through direct outward protrusion of the cell membrane during collective cell migration. Structurally, migrasomes are significantly larger (500–3000 nm) and possess a unique morphology defined by a single large internal vesicle connected to the parent cell via a narrow neck [6]. Functionally, migrasomes uniquely mediate organelle transfer (e.g., mitochondria), establish long-range signaling gradients through migracytosis, and enable direct cell-to-cell contact and communication, whereas exosomes primarily mediate ligand-receptor signaling [6]. The functional consequences of these divergent biogenesis pathways are profound for tumor progression. While exosomes contribute to a "broadcasting" model of communication, influencing the tumor microenvironment (TME) and pre-metastatic niches through diffuse signaling, migrasomes facilitate a more "targeted" and "high-capacity" mode of information transfer [32]. For instance, the migration-dependent biogenesis of migrasomes allows them to form along retraction fibers, facilitating localized delivery of cargos in the TME to promote directed metastasis, unlike the more diffuse, systemic release of exosomes from multivesicular bodies. Besides, exosomes are limited to molecular cargo, whereas migrasomes can selectively package and expel damaged mitochondria [4, 33]. Notably, despite these differences, the shared vesicular characteristics of migrasomes and exosomes indicates that established exosome research frameworks could be adapted to migrasome

Table 1 The differences between migrasomes and exosomes

	Migrasomes	Exosomes
Diameters	500–3000 nm	30–150 nm
Features	An organelle, a large vesicle of cupular or spherical shape with a single membrane structure, containing many smaller vesicles, with a high degree of heterogeneity	A double-membrane, cup-shaped vesicles with a high degree of homogeneity
Biogenesis	Onset and growing in the tails of migrating cells, attaching to stretched fibers, and being released when the contractile fibers break	Formation of multivesicular bodies by endocytosis, subsequently fusing with the plasma membrane and releasing into the extracellular space
Contents	Enriched in damaged mitochondria, autophagosomes, longer mRNAs (e.g., Pten), chemokines (e.g., CXCL12), growth factors (e.g., VEGFA), cytokines (e.g., TGFB2, IL1B), proteins (e.g., PDGFD), lipids (e.g., sphingomyelin, PI(4,5)P2), and selective signaling molecules; overlaps like cholesterol, integrins (specific α5β1), miRNA	Proteins, lipids (including cholesterol), DNA, miRNA, mRNA (often shorter), lncRNA, MHC molecules
Biomarkers	CPQ, Ndst1, EOGT, PIGK, Integrins (ITGA5/ITGB1 (α5β1), ITGA1, ITGA3), Tetraspanins (TSPAN4, TSPAN7)	Tetraspanins (CD9 (TSPAN29), CD63, CD81 (TSPAN28))、Alix、TSG101、HSP70、HSP90, etc.
Fuctions	Cell migration, releasing of specific factors for specific intercellular communication, intercellular substance exchange, exocytosis of organelles	Intercellular communication
Sedimentation coefficients	High, more centrifugal force required for separation	Low, less centrifugal force required for separation
Extraction methods	Density gradient centrifugation, centrifugation and filtration	Ultracentrifugation, density gradient centrifugation, ultrafiltration separation technology, chemical precipitation, peptide affinity method
Functional implications in cancer	Migration-dependent localized cargo delivery promotes directed metastasis (e.g., CD151-enriched migrasomes in HCC enhance invasion via EMT and VEGF signaling); organelle transfer (e.g., mitochondria in glioma for stress alleviation); immunosuppressive TME remodeling (e.g., CXCL5 release in pancreatic cancer for M2 macrophage polarization)	Diffuse systemic signaling alters gene expression (e.g., miRNA transfer in HCC for proliferation); PD-L1 carriage for immune evasion; general oncogenic cargo delivery without migration specificity

studies in cancer research, thereby facilitating research on migrasomes in cancer.

Migrasome and carcinogenesis

Migrasome promotes cancer development

Migrasomes, with their unique structure and function, play a significant role in tumor biology. Their high abundance in certain cancers is closely associated with tumorigenesis and progression [9]. Cancer development is typically driven by dysregulated expression of oncogenes and tumor-suppressor genes, leading to alterations in a series of intracellular signaling pathways. Notably, key regulators of migrasome formation, including ROCK1 and TSPAN4, along with migrasome-associated markers such as NDST1, PIGK, EOGT, WGA and CPQ, exhibit aberrant expression in various cancers, including breast, colorectal, and hepatocellular carcinoma [4, 26, 34] (Table 2). Additionally, genes related to migrasomes are involved in cancer-related signaling pathways. For example, TSPAN4 promotes glioblastoma progression by interacting with epidermal growth factor receptor (EGFR) and regulating its stability, while TGF-β1 stimulates migration of type II endometrial cancer cells by down-regulating PTEN via activation of SMAD2/3 and ERK1/2 signaling pathways, and PTEN is known to be enriched in migrasomes, affecting recipient cell signaling [35, 36]. Furthermore, the chemokine CXCL5 promotes proliferation and invasion in hepatocellular carcinoma by activating PI3K/AKT and ERK1/2 signaling pathways [11]. While bioinformatics analysis and phenotypic studies have identified migrasome-related gene signatures, direct relationships between migrasome formation and cancer development still remain lacking in many contexts, with much evidence being correlative rather than causative.

To address this gap and distinguish causative roles, functional experiments using loss-of-function and gain-of-function approaches have provided initial evidence of causality in specific cancer models. For instance, TSPAN4 knockdown in glioblastoma cell lines and mouse models significantly impairs migrasome formation, leading to reduced cell migration, invasion, and tumor growth, demonstrating a causal link between TSPAN4-mediated migrasome biogenesis and GBM progression via EGFR stabilization [37, 38]. Similarly, in osteosarcoma, loss-of-function via TSPAN4 silencing or migrasome formation inhibitors (e.g., targeting tetraspanin-enriched domains) reduces migrasome release, which in turn attenuates M2 macrophage polarization in the tumor microenvironment, suppresses metastasis, and slows tumor proliferation in vitro and in vivo, providing causative evidence for migrasomes' role in promoting malignant progression [39, 40]. Furthermore, in pancreatic cancer cells, ROCK1 inhibition not only decreases migrasome production but also impairs cell migration and invasion, linking migrasome biogenesis causally to metastatic potential [41, 42]. These functional manipulations contrast with correlative data, such as ROCK1 overexpression correlating with poor prognosis in breast and colorectal cancers, and underscore the need for more targeted gain-of-function experiments (e.g., ROCK1 overexpression in migrasome-deficient models) to fully elucidate causal pathways. Overall, while correlative bioinformatics dominates current evidence, emerging loss- and gain-of-function studies in GBM, osteosarcoma, and pancreatic cancer models provide stronger causal support for migrasomes' promotional role in tumor biology, though broader validation across cancer types is warranted.

Beyond genetic programs in individual cells, migrasomes orchestrate multiple pro-tumorigenic processes within the cancer ecosystem. First, migrasomes mediate horizontal transfer of oncogenic materials to adjacent cells, initiating malignant transformation. Migrasome facilitates the direct transfer of mRNAs and proteins between cells, promoting intercellular communication and regulating recipient cell behavior [43]. In cancer cells, migrasomes transmit heterogeneous information that influences cancer progression and therapeutic resistance [44]. Studies have confirmed that migrasomes can deliver diverse mRNAs (e.g., *Actb*, *Tuba1a*, *Gapdh*) and proteins (e.g., PTEN, integrins, adhesion proteins, transmembrane proteins), thereby enabling intercellular communication and reprogramming recipient cells. Within the tumor microenvironment, these cargoes modulate signaling pathways, metabolic states, and stress responses, ultimately affecting tumor progression and therapeutic resistance [34, 45]. For example, in pancreatic cancer, tumor-derived migrasomes enriched with chemokines such as CXCL5 and TGF-β1 are internalized by macrophages, inducing M2 polarization and fostering an immunosuppressive tumor microenvironment that accelerates tumor progression and immune evasion [46]. In breast cancer, migrasomes harboring ATF6 promote disease progression by inducing ER stress resistance and modulating the tumor microenvironment [47]. Yu et al. demonstrated that PTEN mRNA carried by migrasomes restores PTEN expression in recipient cells, reduces AKT phosphorylation, induces oncogenic changes, and promotes cancer proliferation [28]. Importantly, this process involves selective, rather than random, cargo loading. Specific mRNAs, such as *Pten*, preferentially accumulate, indicating an active sorting mechanism. At the biosynthetic level, transmembrane proteins like TSPAN4 cooperate with RNA-binding proteins to selectively enrich specific RNAs and proteins [16, 48]. Nevertheless, the precise molecular determinants and adaptors that mediate mRNA and protein incorporation into migrasomes remain to be elucidated. Second,

Table 2 Markers of migrasomes in cancers

Migrasome-Associated Factor	Role Classification	Cancer Type	Alteration	Functional Role	Evidence Type
Tetraspanins	Marker & Functional Driver	CESC	Upregulated	Essential for migrasome biogenesis; promotes cell migration, invasion, and immune infiltration in cancer	TCGA data, bioinformatics analysis
		COADREAD	Upregulated	Facilitates migrasome formation; associated with tumor progression and poor prognosis	TCGA data, bioinformatics analysis
		LIHC	Upregulated	Promotes HCC invasion by conditioning cancer cells and promoting angiogenesis via CD151-enriched migrasomes	TCGA data, in vitro experiments
		PAAD	Upregulated	Involved in migrasome-mediated intercellular communication; may promote tumor progression	Review article, bioinformatics analysis
		BRCA	Upregulated	Contributes to migrasome formation; associated with chemoresistance and metastasis	TCGA data, bioinformatics analysis
		STAD	Upregulated	Promotes cell growth and migrasome biogenesis; linked to poor prognosis	TCGA data, bioinformatics analysis
		LUNG	Upregulated	Enhances migrasome formation; involved in tumor progression and immune escape	TCGA data, bioinformatics analysis
Integrin	Functional Driver	BRCA	Upregulated	Promotes cell motility and migrasome formation; contributes to metastasis	TCGA data, in vitro experiments
		LUNG	Upregulated	Dual role in migration and migrasome biogenesis; facilitates tumor invasion	Review article
		CESC	Upregulated	Involved in migrasome anchoring to ECM; promotes cancer cell migration	TCGA data, bioinformatics analysis
		PAAD	Upregulated	Facilitates migrasome-mediated immune suppression and tumor progression	TCGA data, bioinformatics analysis
		PRAD	Upregulated	Supports migrasome formation and cell communication in cancer	TCGA data, bioinformatics analysis
WGA	Marker	BRCA	N/A	Probe for detecting migrasomes; higher signal on migrasomes aids in monitoring biogenesis	In vitro experiments
		COADREAD	N/A	Used for migrasome visualization in cancer cells; facilitates study of migrasome roles in progression	In vitro experiments
		STAD	N/A	Probe for migrasomes; enables detection in fixed and living cancer cells	In vitro experiments
		PRAD	N/A	Aids in identifying migrasomes in prostate cancer cells; minimal impact on biogenesis	In vitro experiments
		BLCA	N/A	Probe for migrasome detection; useful for studying migrasome biology in bladder cancer	In vitro experiments
NDST1	Marker	LUNG	Mutated	Targets DC glycan sulfation; reduces tumor volume by affecting maturation and trafficking	Review article
		BRCA	Upregulated	Involved in tumor angiogenesis, proliferation, migration, invasion, and chemoresistance	Review article, in vitro experiments
		STAD	Upregulated	Promotes cell growth; acts as a migrasome marker	Review article
		PRAD	Upregulated	Associated with migrasome-related prognostic model	TCGA data, bioinformatics analysis
		BLCA	Upregulated	Involved in migrasome biology; linked to advanced stages	TCGA data, bioinformatics analysis
		KIRC	Upregulated	Prognostic marker; suppresses HS production inhibiting invasion	Review article
PIGK	Marker	COADREAD	Upregulated	Component of GPI transamidase; associated with migrasome enrichment and tumor progression	TCGA data, bioinformatics analysis
		LIHC	Upregulated	Migrasome marker; correlated with immune infiltration	TCGA data, bioinformatics analysis
		BLCA	Upregulated	Linked to migrasome score and advanced stages	TCGA data, bioinformatics analysis

Table 2 (continued)

Migrasome-Associated Factor	Role Classification	Cancer Type	Alteration	Functional Role	Evidence Type
CPQ	Marker	GBMLGG	Upregulated	Hydrolyzes peptides; involved in migrasome-mediated communication	TCGA data, bioinformatics analysis
		COADREAD	Upregulated	Migrasome protein marker; associated with tumor microenvironment	TCGA data, bioinformatics analysis
		PAAD	Upregulated	Promotes immunosuppressive microenvironment via migrasomes	Review article, bioinformatics analysis
EOGT	Marker	PAAD	Upregulated	Glycosylates NOTCH1; promotes pancreatic cancer development	Review article, in vitro experiments
		LIHC	Upregulated	Correlated with immune infiltration; prognostic biomarker	TCGA data, bioinformatics analysis
		LUNG	Mutated	Targets DC glycan sulfation; reduces tumor volume by affecting maturation and trafficking	Review article

CESC, Cervical Cancer; COADREAD, Colorectal Cancer; LIHC, Hepatocellular Cancer; STAD, Stomach Cancer; BRCA, Breast Cancer; LUNG, Lung Cancer; PAAD, Pancreatic Cancer; PRAD, Prostate Cancer; BLCA, Bladder Cancer

by coupling with cell migration, migrasomes establish permissive microenvironments for metastatic spread. For instance, migrasomes regulate cytoskeletal dynamics and promote cell-matrix interactions, providing a "niche" for specific cell types to migrate, which is crucial in the early colonization of tumors [7]. Critically, under metabolic or oxidative stress, migrasomes ensure tumor cell survival through damaged cargo clearance (e.g., mitocytosis) and ROS scavenging. Migrasomes help expel damaged cellular components, promoting cellular stability under stress [49]. In gliomas, cancer cells alleviate stress and reduce cell death by increasing the autophagic clearance of damaged substances, which are subsequently exocytosed via migrasomes, thereby promoting tumor growth [50]. During cytokinesis, migrasomes exocytose damaged mitochondria through a process known as mitocytosis [29]. This mechanism is crucial for mitochondrial quality control and maintaining metabolic homeostasis, which supports cell migration and proliferation [51]. While initially observed in myocardial repair, mitocytosis-mediated mitochondrial quality control has direct implications for tumor survival, as evidenced by reactive oxygen species (ROS) removal in glioma models [52]. By exporting copper-loaded mitochondria via mitocytosis, migrasomes may enable cancer cells to evade Cu-proptosis. These findings suggest that migrasomes help cancer cells maintain homeostasis under intense stress by exocytosing organelles, particularly mitochondria, which aids in the escape from Cu-proptosis and scavenging ROS [53]. Furthermore, recent studies highlight the role of mitochondria in cancer cell transformation and in determining the metabolic adaptation of cancer cells [54]. In melanoma, cholesterol synthesis inhibition upregulates migrasome biogenesis through SREBP2-dependent membrane remodeling, thereby enhancing metastatic potential [55]. This suggests that mitochondrial exocytosis not only maintains cellular homeostasis but may also support the specific metabolic needs of cancer cells, contributing to their survival and progression. Thus, migrasomes act as central signaling hubs in the cancer ecosystem, integrating intercellular communication, stress adaptation, and metabolic reprogramming to drive tumor progression.

Migrasome interaction with the tumor microenvironment

The TME plays a crucial role in cancer development and progression. It consists of tumor cells, immune cells, stromal cells, blood vessels, and the extracellular matrix (ECM) [56], which dynamically interact to either promote or suppress tumor growth and metastasis [57]. The TME influences key processes such as immune escape, angiogenesis, and extracellular matrix remodeling by altering tumor cell behavior and altering intercellular interactions [58]. The importance of the TME in tumor progression and therapy has been demonstrated across various cancers [59, 60]. As a novel extracellular vesicle produced during cell migration, migrasomes are closely linked to the TME. Existing studies have shown that migrasomes play a significant role in tumor immune modulation and in shaping the TME [44] (Fig. 1) .

Multi-functions of the migrasomes within the TME and tumor development. In the TME, tumor cells, immune cells, MSCs, and normal cells form a complex network through their interactions. By modulating these interactions, the migrasome facilitates key processes such as immune evasion, extracellular matrix remodeling, immune cytokines enrichment, tumor angiogenesis, and regulation of biophysical barriers. CAF, cancer-associated fibroblasts; ECM, extracellular matrix; MIGS, migrasomes; MSCs, mesenchymal stromal cells; TME, tumor microenvironment.

Migrasome and immune escape

Migrasomes contribute to immune escape and tolerance mechanisms within the TME by interacting with immune

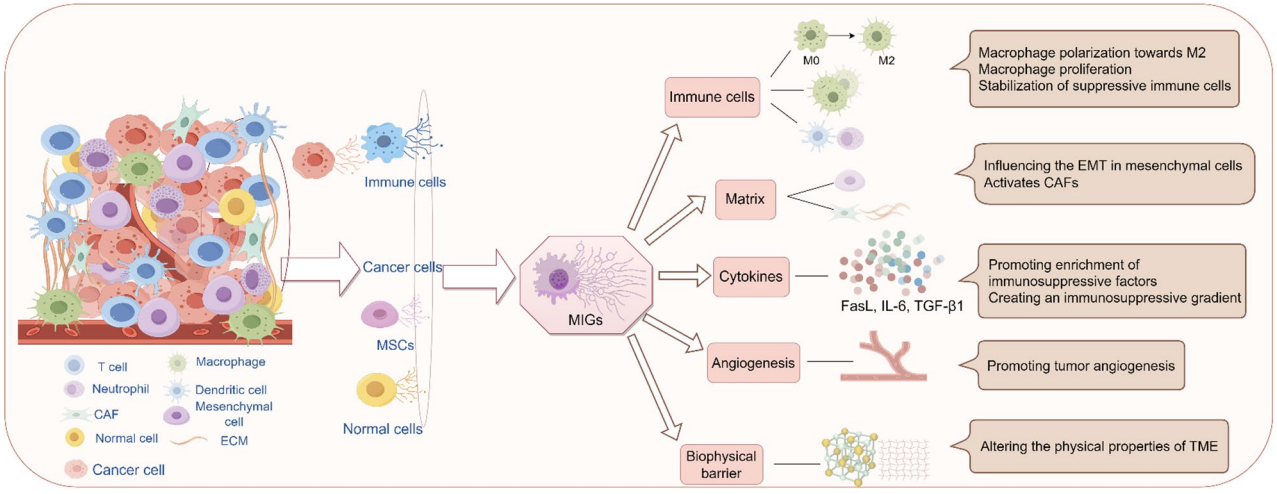

Fig. 1 Migrasomes and TME

cells such as macrophages, dendritic cells (DCs), and neutrophils. These interactions modulate immune activation and influence anti-tumor immunity. Pan-cancer data analysis revealed a significant correlation between macrophage abundance in the TME and migrasome scores [9]. Migrasomes can promote macrophage polarization toward the immunosuppressive M2 phenotype by releasing bioactive factors or inducing autophagy. M2 macrophages, in turn, suppress antitumor immune responses through the secretion of anti-inflammatory mediators [12, 61]. Omics analyses of pancreatic cancer-derived migrasomes have revealed enrichment of TGF-β1, CXCL5, integrin-associated proteins, and Rab family proteins. These factors may reprogram macrophages by facilitating receptor-mediated uptake or activating downstream immunosuppressive signaling pathways. Consistently, TGF-β1 signaling is well known to induce M2 polarization through TβR-SMAD2/3 and PI3K/AKT cascades, resulting in increased expression of CD206, Arg1, and IL-10 and suppression of pro-inflammatory programs [12, 62]. Additional evidence suggests that migrasomes from other sources carry proteins such as MFG-E8, which has been shown to promote M2 polarization by enhancing phagocytosis and activating the SOCS3/STAT3 pathway or other downstream signaling cascades [63]. TSPAN4, a key factor in migrasome formation, has also been found to enhance cell proliferation and promote macrophage polarization toward the M2 phenotype in gliomas [39]. Besides, some studies suggest that migrasomes can carry miRNAs, including miR-21, miR-155, and miR-146a, although direct profiling remains under development. Within the TME, miR-21, miR-146a, and other migrasome- or exosome-delivered miRNAs activate the TLR7/8 pathway in macrophages, which subsequently triggers NF-κB signaling and promotes M2 polarization, leading to the secretion of immunosuppressive cytokines. In contrast, miR-155 drives pro-inflammatory M1 polarization by inhibiting SOCS1 and activating the JAK/STAT pathway. Additionally, members of the miR-34 and miR-200 families can modulate antitumor immunity and influence immunotherapy responses by regulating PD-L1 expression or downstream T-cell signaling [64, 65]. Therefore, comprehensive miRNA profiling of cancer-derived migrasomes remains a critical research priority. In dendritic cells and neutrophils, migrasomes contribute to antigen transport, chemokine delivery, and the exclusion of damaged mitochondria, maintaining organelle homeostasis. These processes facilitate cell-to-cell communication and may induce an immunosuppressive response in the TME [65, 66].

Migrasome and extracellular matrix remodeling

Migrasomes also influence stromal cell behavior and tumor cell interactions with the ECM. The ECM is essential in tumor progression, providing a molecular network that supports biomechanical activity and function [67]. Multipotent mesenchymal stromal cells (MSCs), which serve as precursors to various cell types, interact with migrasomes in cancer. In leukemia, CXCL12 (SDF-1)-containing mesenchymal stromal cell-derived migrasomes attract hematopoietic stem and progenitor cells via the CXCR4 axis. By promoting their retention and uptake, these migrasomes enhance the stem-like properties of leukemia cells through interactions with bone marrow mesenchymal stem cells, thereby facilitating cancer cell-directed migration [68]. In gliomas, the migrasome factor TSPAN4 positively correlates with tumor stemness scores (including DNAss and DMPss) and enhances cellular proliferation and migration capacities [69]. Additionally, migrasomes enhance osteogenic differentiation of MSCs in bone and promote lung macrophage

phagocytosis in anti-infective immunity [70]. These findings support the role of MSCs and migrasomes in the TME [71]. Migrasomes have also been implicated in activating cancer-associated fibroblasts (CAFs) and modulating the epithelial-mesenchymal transition (EMT) in TME stromal cells, thereby influencing tumor cell migration and invasion by altering ECM composition and structure [72–74].

Furthermore, migrasomes can regulate the immune status and physical properties of the TME by modulating the expression and distribution of extracellular factors. Migrasomes deliver signaling molecules such as FasL, IL-6, and immunosuppressive mediators like transforming growth factor-beta (TGF-β) [7,75]. In pancreatic cancer, migrasomes drive the enrichment of immunosuppressive factors through targeted movement and cytokine release, creating an immunosuppressive gradient that promotes tumor immune escape (12). Monocyte-derived migrasomes accumulate in the inflammatory milieu, generating a signaling gradient that favors tumor development [76]. Migrasome abundance correlates positively with immune checkpoint genes and immune-associated markers, such as tumor mutational burden (TMB) and microsatellite instability (MSI), suggesting that migrasomes contribute to an immunosuppressive TME that supports tumor growth [9]. Additionally, a neurotrophic factor in gliomas has been shown to increase migrasome abundance, promoting tumor migration [77].

Migrasome and angiogenesis

Migrasomes also actively participate in tumor angiogenesis. In hepatocellular carcinoma, migrasomes stimulate vascular endothelial cell migration, thereby supporting tumor growth [13]. While the exact mechanism remains unclear, previous studies suggest that migrasomes secreted by monocytes can enhance embryonic angiogenesis via the vascular endothelial growth factor (VEGF) signaling pathway [48, 78]. Additionally, neutrophil-derived migrasomes promote vascular repair and angiogenesis in tissue injury through adhesion-aggregation mechanisms [79]. These studies suggest that migrasomes may contribute to angiogenesis in the TME through pathways such as the classical VEGF pathway. However, further research is needed to clarify these mechanisms. Biophysical barriers within the TME, such as acidity, metabolic changes, and genetic factors, play a crucial role in cancer progression [80]. Migrasomes may modify the TME by interacting with these biophysical barriers, potentially reshaping its structural and chemical properties. In stroke pathogenesis, migrasome formation has been linked to extracellular sodium chloride concentrations [81]. In breast cancer, sodium chloride concentrations have been also thought to be strongly associated with cancer development, suggesting a role for migrasomes in this process. Lactic acid produced by tumor cells contributes to the acidification of the TME, facilitating immune evasion and promoting angiogenesis. In GBM cells, the migrasome was found to be enriched with ECM-associated proteins such as PAK4 and LAMA4, which have been linked to lactate accumulation in the extracellular environment [38, 82]. Thus, the release of migrasomes may also contribute to the formation of this acidic environment [83]. Future studies should explore the relationship between migrasomes and the physical properties of the TME.

Differences of migrasomes and other EVs

As previously mentioned, migrating cells play a unique and crucial role within the TME. In shaping the TME, various types of EVs contribute accordingly. In comparison to other EVs like exosomes, migrasomes exhibit distinct TME effects due to their unique migration-dependent biogenesis and larger size, enabling localized, directional cargo delivery along migratory paths rather than diffuse systemic release [45]. While exosomes often promote TME remodeling through miRNA transfer (e.g., exosomal miR-155 inducing M2 polarization in colorectal cancer via JAK/STAT signaling) or PD-L1 delivery for broad immune checkpoint inhibition [84, 85], migrasomes facilitate more targeted interactions, such as organelle transfer or chemokine gradients that specifically enhance localized M2 polarization and ECM remodeling. Micro vesicles, another EV subtype, share some plasma membrane origin with migrasomes but lack migration specificity, typically mediating rapid inflammatory responses in the TME (e.g., pro-angiogenic effects via VEGF transfer) rather than sustained immunosuppressive shifts [86, 87]. Thus, migrasomes' TME contributions appear more niche and migration-centric, potentially offering complementary or synergistic roles with other EVs in fostering tumor heterogeneity [88].

Migrasome and cancer metastasis

Cancer metastasis is one of the most critical stages of cancer progression and a leading cause of cancer-related death [89]. It is a complex, multistep process in which tumor cells invade from the primary site into the bloodstream or lymphatic system, and colonize distant organs, where they proliferate [90]. This process requires not only that tumor cells possess invasive characteristics, but also that they can adapt to and exploit various signaling and molecular mechanisms within the host microenvironment [91]. As an organelle closely linked to cell migration and playing a key role in the TME, migrasomes are integral to cancer metastasis through regulating processes such as the cytoskeleton, angiogenesis, signaling pathways, and immune modulation.

Cancer metastasis can be divided into several key stages, and migrasomes contribute to each step of the process (Fig. 2). Metastasis begins when tumor cells develop invasive characteristics, enabling them to breach the extracellular matrix and enter the circulatory system [92]. Tumor cells often stimulate surrounding cells to adopt similar invasive traits through genetic mutations or epigenetic modifications [93]. During this process, migrasomes enhance cell-cell interactions by releasing signaling molecules that alter the characteristics of surrounding cells, thereby activating their metastatic potential [44]. Migrasomes may also directly transfer miRNAs and proteins to recipient cells, promoting their invasive potential [43, 94]. In glioblastoma cells, migrasomes facilitate tumor metastasis by transporting migration-associated structures to other sites [39, 77]. Once in circulation, circulating tumor cells (CTCs) colonize distant organs, settling in "niches" where conditions are favorable for proliferation [58]. Unlike other extracellular vesicles, migrasomes exhibit directional guidance, assisting cancer cells in reaching a suitable "niche" for colonization during metastasis [19]. This directional effect also allows migrasomes to serve as signaling sources that promote collective cell migration, a process critical for metastatic efficiency [95, 96]. Furthermore, migrasomes regulate interactions between the extracellular matrix and retraction fibers, promoting tumor cell localization and adhesion at metastatic sites—an essential step in migration [7]. It has been demonstrated that certain non-drug nanoparticles (NPs), when bound to migrasomes and retraction fibers, form a rigid shell that restricts cellular morphological changes, reduces motility, and modifies adhesion, thereby inhibiting tumor migration [97]. This further emphasizes the crucial role of migrasomes in tumor metastasis.

Migrasomes promote cancer metastatic progression. In primary sites, tumor cells promote the transformation of other cells by secreting signaling molecules, miRNAs, and proteins. During metastasis, with the assistance of migrasomes, cancer cells can overcome biological barriers, enter the bloodstream, and eventually form metastatic foci in distant tissues such as the lungs, liver, and brain. In these metastatic foci, the migrasome supports cancer cell growth and colonization by inducing directional migration, remodeling and regulating the extracellular matrix, and modulating the immune environment of the TME. ECM, extracellular matrix; MIGS, migrasomes; TME, tumor microenvironment.

Additionally, interactions between tumor cells and the TME during metastasis are essential [98]. Molecular interactions between metastatic cells and the stromal "seed" and TME "soil" play a key role in the metastatic cascade [99]. Immunosuppressive cells such as tumor-associated macrophages, CAFs, and myeloid-derived suppressor cells (MDSCs) secrete immunosuppressive factors that promote metastasis [60]. Migrasomes facilitate this process by promoting M2 polarization of macrophages and supporting the survival and migration of CAFs and DCs, and can fosters an immunosuppressive TME, diminishing anti-tumor immune responses and promoting tumor progression [12, 65, 66]. Tumor metastasis also requires stromal adaptation to support tumor cell colonization [100]. Migrasomes, enriched with inflammatory factors such as matrix metalloproteinases (MMPs), facilitate tumor invasion by inducing EMT and remodeling the stromal matrix [72, 73, 89]. Moreover,

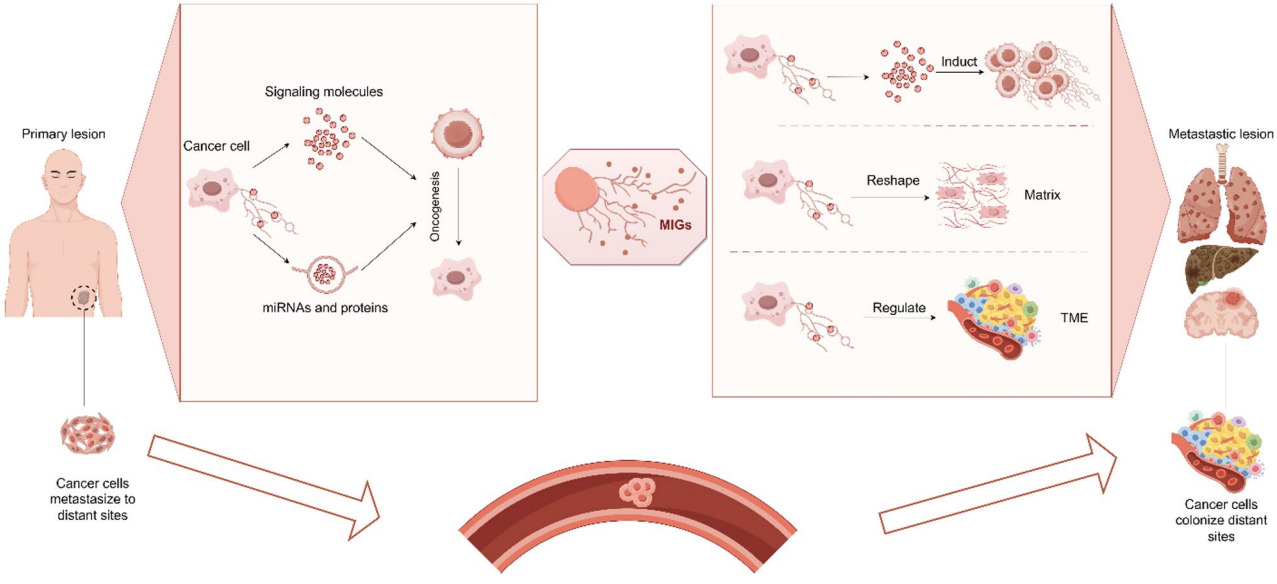

Fig. 2 Migrasome and cancer metastasis

migrasomes modulate stromal cell function, creating a microenvironment conducive to tumor cell colonization. For example, in bone metastasis in breast cancer, osteoclasts alter the bone environment to aid tumor cell colonization. Migrasomes facilitate bone metastasis by promoting the formation of an osteoclast subtype in bone metastasis induced by tumor-mitochondria-mediated cytoplasmic transfer through spatiotemporally coupled interactions between tumor cells and osteoclasts [10, 101]. In leukemia, migrasomes promote directional migration of cancer cells by mediating interactions between MSCs and tumor cells [68]. Furthermore, migrasomes drive metastasis by promoting angiogenesis within the TME. In primary tumors, this facilitates tumor cells' entry into circulation. At metastatic sites, migrasomes enhance tumor perfusion by stimulating vascular endothelial cell migration, ensuring adequate oxygen and nutrient supply for sustained tumor growth and dissemination [13, 78, 102]. In conclusion, migrasomes play a pivotal role in cancer metastasis, and further studies are needed to elucidate the detailed mechanisms across various cancer types and in pan-cancer contexts.

Cancer type-specific migrasome biology

The preceding discussion has revealed extensive associations between the migrasome and the progression, immune infiltration, and metastasis of various malignant tumors, indicating that the migrasome plays a crucial role throughout the entire biological process of tumor development. However, it is important to further note that emerging evidence highlights tumor-specific patterns in migrasome expression, function, and therapeutic relevance. Current research on the role of migrating cells in cancer primarily focuses on solid tumors such as hepatocellular carcinoma, colorectal cancer, lung cancer, and neuroblastoma [9]. In contrast, current literature shows limited migrasome involvement in hematologic malignancies, possibly due to differences in cellular migration dynamics—solid tumors often exhibit collective or mesenchymal migration conducive to migrasome formation along retraction fibers [16], whereas liquid tumors like leukemias rely more on circulatory dissemination without extensive ECM interactions [103, 104]. This disparity underscores a potential bias toward solid tumors in migrasome research, with hematopoietic studies remaining scarce and warranting further exploration to determine if migrasomes play analogous roles in blood cancers. Patterns also differ between epithelial and mesenchymal cancer phenotypes. In epithelial-dominant cancers such as breast cancer, gastric cancer) [105], migrasomes facilitate early-stage processes like biogenesis and immune modulation, often through tetraspanin-enriched structures that support cell-cell communication and ECM anchoring [106]. Conversely, in cancers with strong mesenchymal features post-EMT such as hepatic cancer, migrasomes enhance invasive migration and metastasis by delivering pro-metastatic cargos like chemokines or tsRNAs, aligning with EMT's role in promoting mesenchymal migration modes [13]. At primary sites, migrasomes primarily regulate local TME remodeling and proliferation (e.g., via NDST1 in breast cancer for angiogenesis) [4], while in metastatic sites, they exhibit organ-specific tropism; for instance, in breast cancer brain metastasis, tumor-derived migrasomes harboring ATF6 disrupt the blood-brain barrier via ER stress, promoting site-specific colonization not observed in other organs like liver or lung [107].

These patterns suggest that migrasome-targeted interventions may be most amenable to cancers with high migratory and mesenchymal traits, such as adenocarcinoma and hepatocellular carcinoma, where inhibiting biogenesis (e.g., via TSPAN4 or ROCK1 blockade) has shown preclinical efficacy in reducing invasion and metastasis. In contrast, epithelial cancers like breast cancer might benefit from diagnostic applications leveraging migrasome biomarkers [108], while hematologic malignancies require foundational studies before targeting viability. Future research should prioritize comparative models to refine these context-specific strategies.

Migrasome and cancer: a clinical perspective

Migrasome and tumor drug resistance

Cancer drug resistance remains a major challenge in current therapy, particularly with the continued advancement of chemotherapy and targeted therapies. Over time, tumor cells adapt to these treatments through various mechanisms such as genetic mutations, epigenetic modifications, and microenvironmental remodeling, leading to reduced therapeutic efficacy [109]. Drug resistance has become a leading cause of therapeutic failure [110]. The mechanisms underlying cancer drug resistance are complex and multifactorial, involving adaptive changes in tumor cells, alterations in the TME, and drug tolerance [111]. As previously discussed, migrasomes play critical roles in cancer progression, including tumor genesis, invasion, immune evasion, and metastasis. Notably, Pan-cancer data analysis has revealed that migrasome-related genes and signaling pathways are linked to resistance to multiple therapeutic agents [9]. Research on drug resistance has shown that overexpression of TSPAN4 in esophageal squamous cell carcinoma cell lines promotes paclitaxel resistance by inhibiting apoptosis [15]. Additionally, the migrasome marker NDST1 correlates with chemotherapy resistance in breast cancer, where its upregulation through miR-149 hypermethylation reduces drug sensitivity. Broader members of the Tetraspanin family, such as TSPAN1 and TSPAN3, also modulate resistance. In cisplatin-resistant head and neck squamous

cell carcinoma, depletion of TSPAN1 reduces proliferation by inhibiting SRC signaling, induces apoptosis, and restores drug sensitivity. Conversely, upregulation of TSPAN3 in doxorubicin-resistant acute myeloid leukemia enhances drug resistance and invasiveness [4, 112]. In pancreatic cancer, tumor-derived migrasomes promote gemcitabine resistance by remodeling the TME, including M2 macrophage polarization and immune suppression [46]. In hepatocellular carcinoma (HCC), POSTN + cancer-associated fibroblast (CAF)-derived migrasomes drive tumor progression and induce drug resistance by enhancing proliferation and disrupting ER homeostasis [113]. Given their functional versatility, migrasomes may serve as key mediators of drug resistance, suggesting that targeting them could offer novel strategies to overcome treatment failure and improve clinical outcomes [114]. However, direct studies investigating the link between migrasomes and cancer drug resistance, as well as the intrinsic mechanisms driving this connection, remain limited, highlighting the need for further investigation into their roles as therapeutic targets to overcome treatment failure. Thus, we outline hypothetical roles of migrasomes in drug resistance below, emphasizing gaps in experimental validation. Figure 3 summarizes three potential mechanisms by which migrasomes contribute to drug resistance.

Potential mechanisms of the migrasome in cancer drug resistance. Part A of the figure shows that migrasomes transmit drug resistance signals, promoting other tumor cells to acquire drug resistance functions and facilitating the migration of tumor cell clusters to areas with low drug concentration. Part B illustrates that migrasomes function to efflux damaged organelles, metabolic waste, and drugs, thereby maintaining the stability of cancer cells. Part C demonstrates the role of migrasomes within the TME by regulating immune cells, angiogenesis, and ECM remodeling. All of which significantly impact

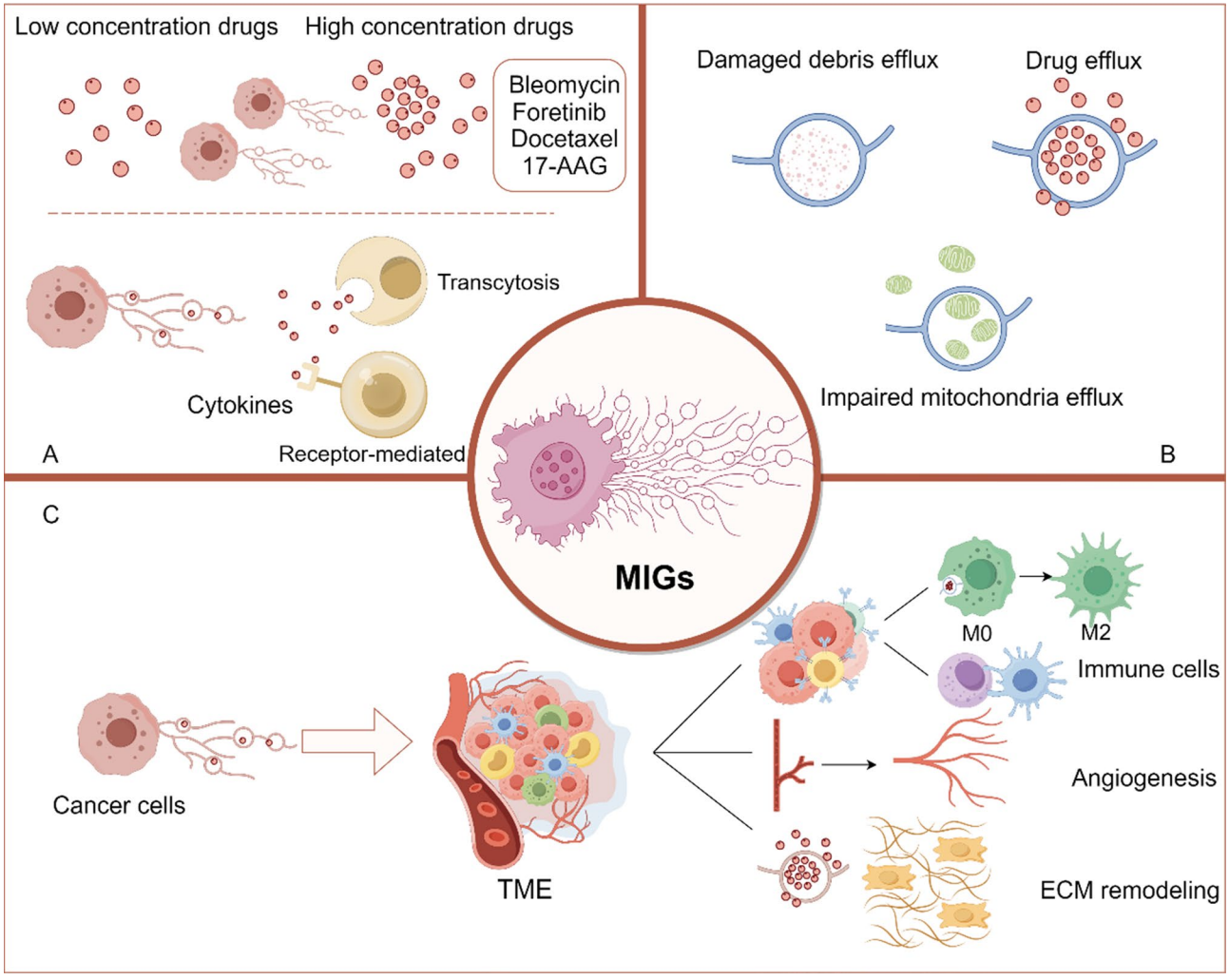

Fig. 3 Migrasomes and drug resistance in cancer therapy

tumor drug response. ECM, extracellular matrix; MIGs, migrasomes; TME, tumor microenvironment.

First, migrasomes may facilitate adaptive changes in tumor cells via intercellular transfer. Genetic and epigenetic adaptations enable alterations in drug targets, DNA repair, and apoptosis inhibition, leading to intrinsic or acquired resistance [115]. According to the tumor ecosystem model, tumor cells acquiring drug resistance traits through adaptive changes can survive natural selection, prompting neighboring cells to adopt similar resistance mechanisms [58, 116]. Migrasomes may play a role in this process by delivering mRNAs and proteins, stimulating surrounding tumor cells to assist them acquire drug resistance traits [43, 44]. Furthermore, migratory tumor cells might use migrasomes to evade high-drug areas, clustering in low-concentration regions [117]. This hypothesis warrants further investigation through migrasome detection in drug-resistant tumor cells and co-culture experiments [13]. Beyond cellular trait alterations, tumor cells enhance their drug tolerance as a strategy to counteract therapy [118]. Drug tolerance refers to the reduction of effective drug concentration in cancer cells due to increased drug efflux and changes in drug metabolism [119, 120]. Migrasomes selectively transport substances during formation and release; hypothetically, they could expel drugs, especially in highly migratory cells forming more migrasomes, though no studies confirm this or show resensitization upon blockade [42, 121]. This suggests that cancer cells with greater invasive potential are more likely to exocytose drugs, potentially creating a self-reinforcing cycle of resistance. From a metabolic perspective, tumor cells often exploit altered metabolic pathways, such as aerobic glycolysis, to sustain drug metabolism and energy balance [122]. Migrasomes aid mitochondrial quality control by exocytosing damaged organelles, potentially maintaining homeostasis for drug metabolism—another area needing experimental support.

Additionally, the TME plays a critical role in cancer drug resistance by providing tumor cells with resistance mechanisms through immune escape and extracellular matrix remodeling [123]. The role of migrasomes in shaping the TME directly influences drug resistance. As previously discussed, migrasomes promote M2 polarization of macrophages in the TME, which in turn supports the survival and migration of immune cells such as CAFs and monocytes [12, 65, 66]. These immune cells foster an immunosuppressive TME, reducing tumor sensitivity to immunotherapy [61, 124]. In pancreatic cancer, migrasomes promote immunosuppression through M2 macrophage polarization and T cell suppression via ARG-1[12]. In glioblastoma (GBM), migrasomes containing autophagosomes alleviate endoplasmic reticulum stress, potentially supporting stem cell-like cells under therapeutic stress [69]. Macrophages and CAFs can also alter the metabolic pathways of tumor cells within the TME, contributing to drug resistance, as observed in triple-negative breast cancer [124]. Furthermore, migrasomes can modulate the composition and architecture of the ECM in the TME [72, 73]. ECM remodeling can impede tumor perfusion, limiting effective drug delivery [125]. Finally, migrasomes contribute to tumor angiogenesis, increasing nutrient supply to tumor cells and exacerbating drug resistance [13, 126]. Therefore, considering the impact of migrasomes in TME-targeting studies for cancer therapy or exploring migrasomes as a novel therapeutic target may yield significant therapeutic benefits.

Potential clinical applications of migrasomes: cancer treatment and detection

As discussed earlier, recent studies highlight the role of migrasomes in tumorigenesis, metastasis, and drug resistance. Targeting migrasomes could modulate tumor proliferation, migration, and immune evasion, making them a promising therapeutic focus. Besides, migrasome-specific targeting, such as inhibiting TSPAN4 or the PIP5K1A-Rab35 axis, offers advantages over pan-EV approaches by selectively disrupting migration-dependent metastasis and TME remodeling without broadly affecting exosome-mediated physiological processes like immune surveillance or tissue repair, potentially reducing off-target effects in therapies [127]. Consequently, migrasomes have become a focal point of medical oncology research [128]. While current cancer therapies including chemotherapy, radiotherapy, and immunotherapy remain mainstream, migrasomes are emerging as a novel potential therapeutic target in cancer treatment, with growing evidence supporting their role in multiple cancers through pathway modulation [114, 129]. For instance, HDAC inhibitors in neuroblastoma have been shown to inhibit tumor cell migration and invasion by targeting migrasome-related pathways, offering a novel strategy for treating neuroblastoma metastasis [130]. Periplocin, a recently developed glioma drug, targets migrasomes by inhibiting TSPAN6 to effectively suppress tumor cell migration and invasion, significantly reducing cell proliferation and promoting apoptosis [131]. Building on the mechanistic understanding of migrasome-tumor interactions, nanotechnology offers a translational approach that nanoparticles (NPs) constructed using nanotechnology can directly target migrasomes, blocking their recognition and endocytosis by surrounding tumor cells. By forming a protective layer on migrasomes and retraction fibers, these NPs serve as a potential anti-metastatic strategy [97]. In studies on breast cancer bone metastasis, nanomedicines designed with an in situ decoupling strategy have been used to target and inhibit migrasome formation, providing a preventive approach to bone

metastasis [10]. Beyond oncology, targeting migrasomes has shown therapeutic potential in antiviral infections and myocardial infarction [52, 132], and studies on abortion have demonstrated that polystyrene nanoplastics can inhibit ROCK1-mediated migration/invasion and migrasome formation [133]. These clinical studies highlight the promise of migrasomes as therapeutic targets, encouraging further exploration of their direct inhibition and associated pathways in cancer treatment.

Additionally, migrasomes modulation may enhance cancer immunotherapy. The immunosuppressive environment in the TME is a critical factor enabling tumor cells to evade immune surveillance. As mentioned earlier, migrasomes in the TME correlate with macrophage abundance and polarization, which promote the immunosuppressive nature of the TME [12, 61]. Although no current therapies directly target migrasomes and macrophages, studies in cerebrovascular and cardiac diseases have shown that complement inhibition and targeted drug interventions can modulate macrophage abundance and polarization, leading to therapeutic benefits [14, 134]. By targeting migrasomes, it may be possible to reduce immunosuppressive factors within the TME, improve the cytoskeleton and extracellular matrix, and regulate tumor angiogenesis, thereby enhancing the efficacy of immunotherapy and increasing tumor cell sensitivity to chemotherapy or immunotherapy [12, 123]. Further research on migrasomes and TME interactions could lead to breakthroughs in cancer immunotherapy.

Beyond therapy, migrasomes also hold promise as biomarkers for early diagnosis and prognosis in cancer [128]. The abundance and distribution of migrasomes can reflect key processes such as tumorigenesis, progression, and metastasis. In cancers such as glioblastoma, hepatocellular carcinoma, and colorectal cancer, migrasome expression is closely linked with tumor progression. Notably, specific surface markers on migrasomes, such as EOGT and NDST, have been identified as potential diagnostic indicators. For instance, elevated EOGT expression in HCC tissues is associated with advanced stages and poor survival. NDST1 is implicated in tumor angiogenesis, cell proliferation, and migration in lung cancer, breast cancer, prostate cancer, and clear cell renal cell carcinoma, where it forms part of prognostic signatures [11, 35, 36, 135]. This correlation suggests that migrasomes could possibly serve as biomarkers for cancer prognostication and metastasis prediction. Furthermore, recent studies have demonstrated that migrasomes can be efficiently isolated from body fluids. Zhao et al. successfully detected all four specific migrasome markers (NDST1, EOGT, CPQ, and PIGK) in human serum fraction 7, confirming the presence of intact migrasomes in circulation [136]. A study by Yang et al. developed a method utilizing wheat germ agglutinin (WGA)-coated magnetic beads combined with flow cytometry (WBFC) to efficiently capture and quantify migrasomes from urine samples. This approach demonstrated a significant increase in migrasome concentration in the urine of kidney disease patients compared to healthy individuals. Notably, receiver operating characteristic (ROC) analysis revealed an area under the curve (AUC) of 0.90 for distinguishing kidney disease from healthy controls, with 90% sensitivity and specificity. This performance surpasses traditional biomarkers. Furthermore, urinary migrasomes outperformed exosomes (marked by CD63), which showed no significant elevation and an AUC of only 0.5379. In preclinical models, migrasome levels increased prior to elevations in serum creatinine or proteinuria, underscoring their superior sensitivity for early detection. This indicates the potential of urinary migrasomes as a novel diagnostic biomarker [137, 138]. Therefore, by tracking the presence and abundance of migrasomes in blood, urine, or other body fluids, noninvasive methods for early cancer screening may become increasingly feasible [139]. Moreover, because migrasomes are released during tumor cell migration, monitoring their dynamic changes could offer valuable insights for the early detection of micro-metastases, allowing for early intervention during the micro-metastasis stage [34]. Thus, migrasome monitoring has the potential to become a critical tool for early cancer diagnosis and dynamic assessment of treatment outcomes [140]. Collectively, migrasomes represent a dual-purpose tool in oncology: as therapeutic targets (e.g., via nanomedicine or TME modulation) and as dynamic biomarkers for early detection and treatment monitoring. In conclusion, as a novel therapeutic target and biomarker, migrasomes could significantly impact the clinical landscape of cancer treatment and management (Fig. 4).

The clinical applications of the migrasome. The left section depicts targeted therapies, including the direct targeting of the migrasome by NPs to prevent its action and the targeting of cancer cells with drugs to reduce migrasome production. The middle section demonstrates immunotherapy targeting migrasomes, using drugs or therapeutic approaches to modulate their production and function, as well as altering their effect on the TME to enhance the anti-tumor immune response. The right section highlights the use of migrasomes as clinical biomarkers to monitor disease progression and treatment efficacy by analyzing their abundance and species in tissue and body fluid samples. ECM, extracellular matrix; MIGS, migrasomes; NPs, nanoparticles ; TME, tumor microenvironment.

Translational challenges and requirements

Current research on the clinical application of migrasomes faces several significant challenges. The primary

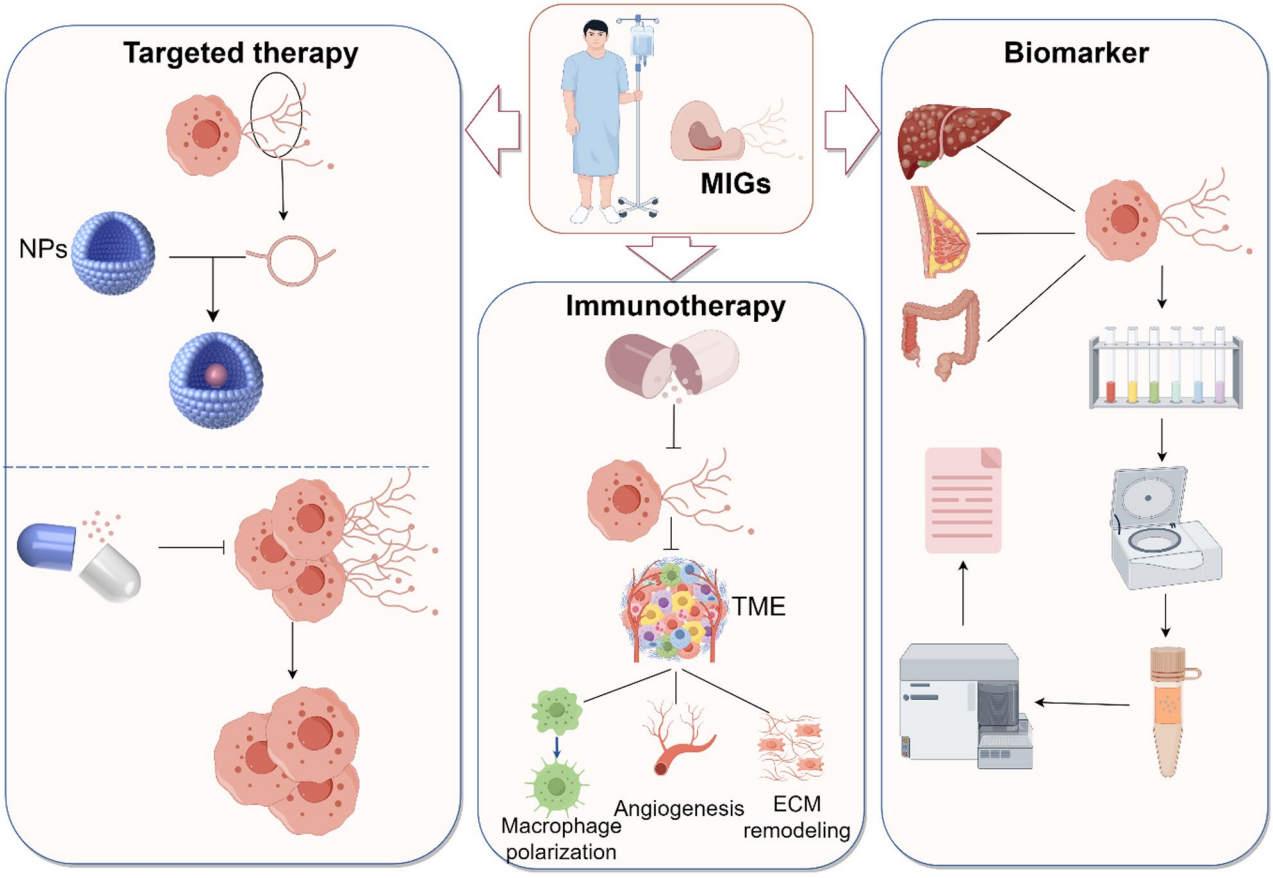

Fig. 4 Clinical application of migrasomes

obstacle is understanding the underlying mechanisms, as the functional role of migrasomes in cancer progression and metastasis remains poorly understood. Although studies suggest that migrasomes are involved in metastatic carcinogenesis, the mechanisms of cargo sorting—specifically, how mRNAs or proteins are selected for incorporation into migrasomes—and the precise effects of these cargoes on recipient cells and the tumor microenvironment require further investigation. This knowledge is essential for developing novel therapeutic strategies targeting migrasomes. A major barrier to clinical translation is the technical difficulty in isolating and quantifying migrasomes from body fluids, particularly blood. Due to their scarcity and high morphological similarity to exosomes, traditional methods often suffer from low specificity. For instance, while ultracentrifugation is widely used, it frequently co-isolates other vesicular structures, leading to contamination rates exceeding 30%. Recent advances in microfluidic chips and specific surface markers (e.g., Rab27a) have improved detection, but standardized protocols for high-throughput analysis are still lacking. Moreover, the transition from animal models to human clinical data requires rigorous validation. [141–143]. Regarding translational potential, a comprehensive search of clinical trial databases, including ClinicalTrials.gov (queried as of December 2025), yields no registered trials involving migrasomes for cancer or any other condition, indicating that the research is still preclinical and that therapeutic applications remain hypothetical without human data. Current studies often rely on small sample sizes, resulting in insufficient statistical power to determine key biomarker metrics such as sensitivity and specificity in diverse cancer types. Without robust multi-group clinical cohorts, the reproducibility of migrasome-based diagnostics across different laboratories remains questionable. Further standardization in clinical practice is needed to ensure reliability and reproducibility across diverse settings.

As a novel organelle, the full therapeutic potential of migrasomes in cancer remains unexplored. Due to their ability to transport various substances, migrasomes hold promise as carriers for anticancer drugs. Efficient loading of chemotherapeutic or immunotherapeutic agents onto migrasomes for targeted delivery could enable precise action on specific cancer cells, enhancing therapeutic efficacy while minimizing toxicity and side effects on normal tissues [144]. As carriers capable of transporting mRNA, migrasomes also show potential in delivering

gene-editing tools for precise regulation of gene expression in cancer cells. Thus, migrasomes serve not only as a standalone therapeutic target but also as a potential synergistic partner in combination with other cancer therapies [16]. Given the complexity of migrasome research, interdisciplinary collaboration is essential for advancing translational research. Bioinformaticians can support the analysis of high-throughput data, while clinicians can guide research by providing insights into clinical challenges. Together, these efforts can help integrate migrasomes into clinical cancer prevention and treatment strategies [108].

To advance migrasome-based diagnostics and therapeutics toward clinical implementation, several regulatory and technical hurdles must be addressed. Regulatory pathways for novel biomarkers like migrasomes typically involve qualification processes established by agencies such as the FDA and EMA [64]. Challenges arise from migrasomes' novelty, with limited precedents; for instance, no migrasome-specific products have yet received approval, mirroring delays in extracellular vesicle therapies [145]. Therefore, technical requirements for clinical implementation demand rigorous standardization to ensure reproducibility and reliability. Isolation and quantification protocols must be optimized to distinguish migrasomes from similar structures like exosomes, incorporating GMP-compliant environments, traceable sources (e.g., engineered cell lines for scalability), and standardized reagents to minimize contamination and variability. Pre-analytical standardization, including sample handling (e.g., anticoagulants, storage at -80 °C), is critical to prevent artifactual EV generation and ensure assay precision, trueness, and linearity, as guided by MISEV guidelines adapted for migrasomes. Validation cohorts are essential, involving large, multi-center studies with diverse populations to establish reference ranges, cut-offs via ROC analysis, and metrics like clinical sensitivity/specificity, overcoming current limitations in small-sample animal data [146, 147].

Conclusions

Migrasomes represent a novel and critical organelle that bridges cell migration with tumor progression and immune evasion. Their unique biogenesis on retraction fibers and distinct cargo composition distinguish them from exosomes, positioning them as pivotal players in cancer metastasis and drug resistance. Recent studies have established that migrasomes are crucial in tumor development, making them a prominent focus of cancer research. They contribute to tumor proliferation and metastasis by promoting tumor cell migration, invasion, and dissemination. Additionally, migrasomes are involved in cytokine release and intercellular substance transfer, further facilitating cancer progression. Moreover, migrasomes interact with the tumor immune microenvironment by engaging with immune cells, thereby influencing immune escape mechanisms within tumors. Migrasomes also contribute to tumor drug resistance by inducing genetic modifications or adaptive changes in tumor cells, affecting the efficacy of chemotherapy and targeted therapies. These findings underscore the importance of migrasomes in cancer biology and highlight their potential as novel therapeutic targets. Clinically, with advances in detection technologies, migrasomes are poised to become valuable biomarkers for early cancer diagnosis. By analyzing migrasomes and their components in body fluids such as blood and urine, early cancer screening and real-time monitoring could be achieved [139]. Migrasome-based therapeutic strategies, including drug development targeting migrasomes and associated pathways, have the potential to revolutionize cancer treatment [114]. Furthermore, the development of nanotechnology and single-cell analysis techniques may provide new ways to precisely regulate migrasome function, thereby enhancing anticancer efficacy [97]. In particular, single-cell RNA sequencing offers a more detailed molecular-level understanding of the complex relationship between migrasomes and tumor cells, potentially uncovering new cancer therapeutic targets [148].

As a recently discovered cellular structure, research on migrasome has been making rapid progress. However, it remains heavily reliant on foundational studies from a limited number of research groups, which may introduce potential biases in interpretation and reproducibility. Contradictory or negative findings are notably scarce, possibly due to the field's novelty and the predominance of positive results; for example, while migrasomes are often portrayed as pro-oncogenic, while certain contexts suggest it exhibits context-dependent effects—for example, in some cold TME, the transplanted tissue may exert a protective role as an immune target. Nevertheless, no direct negative data currently exists to refute its pro-cancer function. Besides, as highlighted by the numerous unresolved questions discussed earlier, the complexity of cancer means that the relationship between migrasomes and biological processes such as cancer progression and metastasis has yet to be fully elucidated, thus independent validation across diverse models and laboratories is needed to address these gaps and potential controversies. Their potential applications in clinical cancer monitoring and treatment also require further investigation. Future research on migrasomes should focus on several key directions that promise significant breakthroughs. In the short term, priorities should emphasize methodological advancements to overcome current challenges in migrasome research. This includes developing standardized isolation and detection techniques, such as optimized ultracentrifugation combined with flow cytometry for

distinguishing migrasomes from other extracellular vesicles, to improve reproducibility across laboratories. Additionally, conducting genome-wide screenings to identify novel genes involved in migrasome biogenesis (e.g., beyond TSPAN4 and integrins) and establishing universal markers distinct from exosomes will facilitate broader studies. In the medium term, research should delve into mechanistic insights and disease-specific roles. Key areas include elucidating the molecular mechanisms of migrasome formation in tumor cells, such as the recruitment dynamics of PIP5K1A and Rab35-integrin α5 interactions, and their interplay with cancer signaling pathways like PI3K/AKT. Exploring migrasome heterogeneity across cell types and tissues, using single-cell sequencing to map gene expression patterns (e.g., correlations with tumor senescence or immune infiltration), will reveal how migrasomes contribute to the TME, including immune cell modulation and metastatic niche formation in cancers like pancreatic and liver. Furthermore, investigating migrasomes' role in drug resistance, such as through intercellular transfer of oncogenic cargo, and testing targeted interventions (e.g., small-molecule inhibitors of biogenesis enzymes) in preclinical animal models will provide proof-of-concept for therapeutic strategies. In the long term, the focus should shift toward translational and clinical applications. This involves large-scale clinical cohorts to validate migrasome-related biomarkers (e.g., urinary migrasomes for early detection in renal-associated cancers) and develop non-invasive diagnostic tools for real-time monitoring of treatment responses. Advancing migrasome-targeted therapies, such as nanoparticle-based drug delivery systems to block migrasome-mediated metastasis or enhance immunotherapy by targeting PD-L1-enriched migrasomes, could enter phase I/II trials. Integrating emerging technologies like in vitro reconstitution of migrasomes for high-throughput screening will support precision medicine approaches, ultimately establishing migrasomes as routine clinical targets in oncology. By addressing these challenges through phased priorities, migrasomes offer exciting opportunities to advance cancer research and improve patient outcomes.

Abbreviations

CAFs	Cancer-associated fibroblasts
CPQ	Carboxypeptidase Q
CTCs	Circulating tumor cells
DCs	Dendritic cells
ECM	Extracellular matrix
EMT	Epithelial-mesenchymal transition
EOGT	EGF domain-specific O-linked N-acetylglucosamine transferase
HDAC	Histone deacetylase
MDSCs	Myeloid-derived suppressor cells
MMPs	Matrix metalloproteinases
MSCs	Mesenchymal stromal cells
MSI	Microsatellite instability
NDST1	Bifunctional heparan sulfate N-deacetylase/N-sulfotransferase 1
NPs	Nanoparticles
PIGK	Phosphatidylinositol glycan anchor biosynthesis class K
ROCK1	Rho-associated coiled-coil containing protein kinase 1

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Data availability
No datasets were generated or analyzed in this study; therefore, data sharing is not applicable.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
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Competing interests
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