Review Article

Migrasomes: From Biogenesis, Release, Uptake, Rupture to Homeostasis and Diseases

Yaxing Zhang,1,2 Wenhai Guo,3,4,5 Mingmin Bi,6 Wei Liu,1,2 Lequan Zhou,1,2 Haimei Liu,1,2 Fuman Yan,1,2 Li Guan,1,2 Jiongshan Zhang,3,4 and Jinwen Xu1,2

1Department of Physiology, School of Basic Medical Sciences, Guangzhou University of Chinese Medicine, Guangzhou, Guangdong 510006, China
2Research Center for Integrative Medicine (Key Laboratory of Chinese Medicine Pathogenesis and Therapy Research), Guangzhou University of Chinese Medicine, Guangzhou, Guangdong 510006, China
3Department of Traditional Chinese Medicine, The Third Affiliated Hospital, Sun Yat-sen University, Guangzhou, Guangdong 510630, China
4Institute of Integrated Traditional Chinese and Western Medicine, Sun Yat-sen University, Guangzhou, Guangdong 510630, China
5Graduate School of Guangzhou University of Chinese Medicine, Guangzhou, Guangdong 510006, China
6Department of Otorhinolaryngology, The Seventh Affiliated Hospital, Sun Yat-sen University, Shenzhen, Guangdong 518107, China

Correspondence should be addressed to Yaxing Zhang; zhangyaxing@gzucm.edu.cn and Jinwen Xu; xujinwen@gzucm.edu.cn

Received 9 October 2021; Revised 27 November 2021; Accepted 10 March 2022; Published 14 April 2022

Academic Editor: Claudio Cabello-Verrugio

Copyright © 2022 Yaxing Zhang et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Migrasomes are migration-dependent membrane-bound vesicular structures that contain cellular contents and small vesicles. Migrasomes grow on the tips or intersections of the retraction fibers after cells migrate away. The process of releasing migrasomes into the extracellular space is named as “migracytosis”. After releasing, they can be taken up by the surrounding cells [1, 2]; or they will rupture/disappear and release their contents into the environment in a migration-dependent release process named “migracytosis” [1–4]. The primary function of PLSs is intercellular communication, similar to the mechanisms such as exocytosis and exosome release [1, 2, 5]. This novel extracellular vesicle (EV) has displayed many biological functions. Migrasomes provide regional cues for organ morphogenesis during zebrafish gastrulation [3]. Damaged mitochondria can be discarded via migrasomes, cells [1, 2]; or they will rupture/disappear and release their contents into the environment in a migration-dependent release process named “migracytosis” [1–4]. The primary function of PLSs is intercellular communication, similar to the mechanisms such as exocytosis and exosome release [1, 2, 5]. This novel extracellular vesicle (EV) has displayed many biological functions. Migrasomes provide regional cues for organ morphogenesis during zebrafish gastrulation [3]. Damaged mitochondria can be discarded via migrasomes,

1. Introduction

During the process of cell migration, large vesicles grow on the tips or at the intersections of the retraction fibers; eventually, the retraction fibers break, and the pomegranate-like structures (PLSs, referred as “migrasomes”), within a single-limiting membrane, are released into the extracellular space from retraction fibers at the rear of migrating cells; the released PLSs can be directly taken up by the surrounding

...
which highlight the essential role of migrasomes in modulating mitochondrial quality control process and redox signaling [6]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) induces platelets to release migrasomes and initiates programmed cell death of platelets in severe coronavirus disease 2019 (COVID-19) [7]. Moreover, tumor necrosis factor α (TNFα) induces the formation of migrasomes in human coronary artery endothelial cells (ECs) [8], parenchymal migrasomes were formed during ischemic brain injury [9], the podocyte-released migrasomes in urine are indicators for early podocyte injury [10], and migrasomes can also modulate cancer cell proliferation via lateral transferring mRNA and protein in vitro [2]. In this review, we will summarize the current understanding of migrasomes from biogenesis, release, uptake, and rupture to its roles in homeostasis and diseases; and discuss the perspective of migrasomes based on the keywords "migrasome" or "migracytosis" according to the official publishing in PubMed and Web of Science before January 22, 2022.

2. The Discovery of Migrasomes/Migracytosis

The long projections from the surface of cells or the retraction fibrils/fibers from the migrating cells have been observed by Porter [11] and by Taylor [12], respectively; however, retraction fibers have received little attention despite their widespread presence in different cell types [1]. Dr. Yu found “a structure closely resembling an opened pomegranate stood outside a cell” by transmission electron microscopy; the particular image was unusual because there were several of these large structures outside the cell: some of them were empty, some of them had a few vesicles inside, and some of them were packed with vesicles [1, 13]. In 2015, the milestone about PLSs was published in Cell Research; Yu’s team isolated PLSs by subcellular fractionation via density gradient centrifugation and confirmed by transmission electron microscopy [1]. They identified PLS proteins by mass spectrometry analysis and identified tetraspanin-4 (TSPAN4) as the clearest PLS marker by using green fluorescent protein (GFP)-tagged candidate proteins [1]. Besides TSPAN4, wheat-germ agglutinin (WGA), a lectin that binds specifically to sialic acid and N-acetyl-d-glucosamine [14], can also label migrasomes in living cells [15]. Time-lapse imaging revealed that the average lifespan of a PLS derived from normal rat kidney (NRK) cell is about 200-400 min [1, 4]. Using the inhibitor or promoter of migration, they confirmed that the formation of PLSs is migration-dependent (see detail in "The current understanding of migrasomes biogenesis") [1]. Migrasomes are not an artifact caused by culturing cells on a highly rigid surface such as glass or plastic; these PLSs were widely existed in many tissues and cells in vivo and in vitro [1]. By overexpressing GFP as a tracer for the cytosolic contents in TSPAN4-mCherry-expressing NRK cells, they discovered that the cytosolic components/material and vesicles of unknown origin can actively enter into migrasomes; then, migrasomes and their contents are released into the extracellular space [1, 4]. To their astonishment, they observed that migrasomes left by one cell can be taken up by the surrounding cells [1, 2]. These indicated that migrasomes might play essential roles in modulating intercellular communication.

3. The Basic Features of Migrasomes

The detail methods for visualizing migrasomes by fluorescence microscopy and electron microscopy have been well established by Dr. Chen in Yu’s lab [16]. As the novel vesicle structure, we have also summarized the basic differences between migrasomes and exosomes in June, 2020 [17]. The number of smaller vesicles in migrasomes varies greatly; some migrasomes contain up to 300 vesicles, while most contain fewer than 10 [1]. What are these smaller vesicles? The diameters of exosomes are 30-200 nm, which are smaller than that of migrasomes (0.5-3 μm in NRK cells and 1.87 ± 0.18 μm in mice brain) [17]. However, it is unclear whether these smaller vesicles in migrasomes contain exosomes and whether the exosomes reported previously in the literature are partially released by migrasomes [1]. The protein types in migrasomes are not always the same, as that these in NRK cells and in the infarcted brain parenchyma of mice have been shown to be different [1, 9]. Although migrasomes from infarcted brain parenchyma of mice or NRK cells contain RNA-binding proteins, co-staining of F4/80 and RNA did not show RNA signalling within the migrasome either in cerebral cortex or white matter tracts [1, 9]. In contrast, Yu et al. found mRNA in migrasomes from L929 cells (the mouse fibrosarcoma cell line [18]) [2]. Liu et al. have found that miRNA exist in human podocyte cell lines (HPCs)-derived migrasomes, and its miRNA expression profile is different from these in exosomes derived from HPCs [10]. In addition, Antje et al. had identified DNA-interacting proteins in migrasomes from the infarcted brain parenchyma of mice; however, they have not investigated the DNA signalling in these migrasomes [9], and whether the migrasomes of a certain type of cell in a particular state contain DNA is unclear.

Migrasomes extensively distribute in normal human, mouse or rat cells in vitro, in cancer cells in vitro, and in human, mouse, rat, and zebrafish in vivo [1, 3, 6, 9, 10, 19–21] (Figure 1). For example, the differentiation of osteoclasts from murine monocyte-macrophage cell line (RAW 264.7 cells) stimulated by receptor activator of nuclear factor κ-B ligand (RANKL) can induce the formation of vesicle resemble “migrasomes” [21]. Therefore, the location of these PLSs seems to confer them with different biological functions and to investigate their expression patterns in different cells or tissues are of great importance.

4. The Current Understanding of Migrasome Biogenesis

Cell migration is a physically integrated multistep process [22, 23]. To migrate, a cell must acquire a spatial asymmetry enabling it to turn intracellularly generated forces into net cell body translocation; one manifestation of this asymmetry is morphological polarization, i.e., a clear distinction between cell front and rear [22]. An important consequence of polarization is that extension of active membrane processes, which takes place primarily around the cell front
Therefore, for migration to occur, extend protrusions in the direction of migration must form and then stabilize by attaching to the surroundings [22]. These protrusions can be broad, flat, sheet-like structures, named “lamellipodia,” or thin, cylindrical, needle-like projections, named “filopodia” et al.; they are usually driven by actin polymerization, by the cortical expansion mechanism, the Brownian ratchet mechanism, or a combination of these [22, 24]. These protrusions are stabilized by adhering to extracellular matrix (ECM) or adjacent cells via the transmembrane migration-promoting receptors, which, as the “feet” of a migrating cell, linked to the actin cytoskeleton via adaptors [22, 23]. These adhesions serve as traction sites for migration as the cell moves forward over them [23]. Once the protrusions have become adherent to the substratum, translocation of the cell body forward may occur by myosin interactions with actin filaments, possibly via relative movement of adhesion complexes across cortical actin filament “tracks,” or the contraction of filaments connecting cell-substratum adhesion complexes with intracellular structures; in either case, the magnitude of traction is greater than the rearward pull on the adhesion complexes [22]. At the rear of the cell, the adhesions are released as the trailing edge detaches from the substratum (here, the magnitude of traction is less than the contraction force), thus allowing net translocation of the cell in the direction of movement and completing a
migratory cycle [22, 25]. Therefore, the polarity is intrinsic to a migrating cell, and the basic cell migration cycle includes extension of a protrusion from cell membrane in the direction of movement, formation of stable attachments near the leading edge of the protrusion, translocation of the cell body forward, release of adhesions, and retraction at the cell rear [22, 23, 25–30].

Time-lapse imaging revealed that formation of migrasomes is likely related to cell migration [1]. Therefore, if migrasome is dependent on migration, modulation events/process involved in migration will influence the formation of migrasomes. Indeed, the number or formation of PLSs was largely reduced when reducing cell migration speed by migration inhibitors [1]: the myosin II inhibitor “blebbistatin” [31, 32], and a cell-permeable dynamin inhibitor “dynasore” [33], which has been shown to suppress lamellipodia formation and cancer cell invasion by destabilizing actin filaments [34]. As we have mentioned above, lamellipodia or filopodia formation is usually driven by actin polymerization. The polymerized actin fibers are closely associated with the membrane of some migrasomes [1]. So, what is the function of actin polymerization in migrasomes? Suppressing actin polymerization with cytochalasin B or latrunculin A, or blocking formation of branched actin networks with CK636 (an inhibitor of the Arp2/3 complex, and Arp2/3 complex is an important actin filament nucleator that creates branched actin filament networks required for formation of lamellipodia and endocytic actin structures [35]), reduces the number of PLSs by preventing forming new migrasomes [1]. Thus, actin polymerization is likely required for migrasome formation, either by affecting cell migration as some of these actin polymerization inhibitors can also inhibit migration or by directly involving in migrasome biogenesis [1]. In contrast, the number of migrasomes was increased when accelerating cell migration by different strategies (see detail in below) [1, 4]. Recently, Lu et al. have identified 507 compounds which had significant inhibitory effect on migrasome generation, and 463 out of these 507 hits showed no or less retraction fibers indicating defect of cell migration; this further confirmed that generating migrasome is dependent on migration [36]. Based on migration-dependent biogenesis of PLSs, these PLSs were named as “migrasomes” [1]. Hu et al. has identified “accessible cholesterol”-rich particles released from the macrophage; they are about 30 nm and represent fragments of the plasma membrane that are pulled away and left behind during the projection and retraction of filopodia and lamellipodia [37]. This particle release was abolished when the movement of filopodia/lamellipodia was blocked by blebbistatin or by actin depolymerization (latrunculin A), and their release was increased if the disassembly of focal adhesions (the macromolecular complexes that tether cells to the underlying substrate) was suppressed by FAK inhibitor (CAS 4506-66-5) [37]. Thus, future study focusing on the biological characteristics of these particles and migrasomes is required.

The functional units of cell adhesion typically include cell adhesion molecules/adhesion receptors, the ECM proteins, and the cytoplasmic plaque/peripheral membrane proteins [24]. Among these above, cell adhesion receptors, including members of the integrin, cadherin, immunoglobulin, selectin, and proteoglycan (e.g., syndecans) superfamilies, are usually transmembrane glycoproteins that mediate binding interactions at the extracellular surface and determine the specificity of cell-cell and cell-ECM recognition [24]. Integrins are αβ heterodimers with a large extracellular domain that binds the ECM and links to the actin cytoskeleton by a short cytoplasmic tail [38]. The extracellular domain of integrins determines the binding specificity and recognizes diverse matrix ligands including fibronectin (e.g., α5β1, αvβ3, and α4β1), collagen (e.g., α1β1 and α2β1), and laminin (e.g., α2β1, α3β1, and α6β1) [38]. Both integrins and TSPAN4 are highly enriched on migrasomes; unlike TSPAN4 that is also abundant on retraction fibers, integrins are only present at very low levels on retraction fibers [1, 4]. Moreover, TSPAN4 was on the upper side, while the endogenous integrin α5 and β1 were enriched on the bottom of migrasomes, and Yu has confirmed that the integrin-enriched regions on migrasomes are not focal adhesions (FAs) [4]. The number of PLSs was increased when accelerating cell migration by knocking down SHARPIN (an endogenous inhibitor of β1-integrin activation), and fibronectin increased migrasomes number per cell in a dose-dependent manner [1, 36, 39]. GLPG0187, the inhibitor of integrin α5β1, inhibited the biogenesis of migrasomes in a concentration-dependent manner without cytotoxicity [36]. The integrin α5 mRNA levels are much higher than other examined integrins (α1, α2, α3, and α6) in TSPAN4-GFP-expressing NRK (NRK-TSPAN4-GFP) cells [4]. Therefore, these cells produced more migrasomes on cover glasses coated with α5-pairing fibronectin than with other integrin-pairing laminin 511 or collagen I, and very few migrasomes formed on noncoated cover glasses [4]. Moreover, knockdown of ITGA5 that encodes α5 impaired the formation of migrasomes on cells cultured on fibronectin, but not on other ECMs [4]. Overexpressed integrin α1 or α3 in different cells enhanced migrasome formation, cell spreading, and migration on their corresponding ECM partner protein, but not on other ECM proteins [4]. Therefore, pairing of integrin with its specific ECM partner is a determinant for migrasome formation.

Recently, using chemical screening and RNAi, Yu’ team identifies ROCK1 (a positive regulator of microfilament bundle and focal adhesion assembly [40]), rather than ROCK2, as a regulator of migrasome formation [36]. ROCK1 contributes to the formation of migrasomes via its role in adhesion to fibronectin to generate a traction force [36]. The role of adhesion on migrasome formation has also been confirmed in vivo. The /B1b−/β−/ (encode integrin β1b) zebrafish embryos formed significantly fewer migrasomes at the gastrulation stages without impaired the speed of cell migration during gastrulation, which implies that integrin β1b in zebrafish gastrulas most probably regulates migrasome formation by providing adhesion [3]. Saito et al. have evaluated the potential of peptide scaffolds on the forming of migrasomes in cell culture; they found that the peptide interface comprising cell-penetrating peptides (pVEC and R9) and virus fusion peptide (SIV) have superior properties for enabling cell migration and migrasome formation than...
fibronectin protein, integrin-binding peptide (RGD), or bare substrate [20]; and these will help us to establish cell model for investigating migrasomes.

The regulatory processes of migrasome biogenesis discussed above were investigated based on migration-dependent characteristics of PLSs. TSPAN4 has been shown as a clearest PLSs marker on migrasomes. However, what is the function of this protein? Indeed, TSPAN4 is a key mediator for migrasome formation [41]: overexpression of 14 (1, 2, 3, 4, 5, 6, 7, 9, 13, 18, 25, 26, 27, and 28) out of the 33 known mammalian TSPANs in NRK cells enhanced migrasome formation, and among these 14 TSPANs, 9 TSPANs (1, 2, 4, 6, 7, 9, 18, 27, and 28) had a strong effect [41]. On the contrary, TSPAN4 deficiency impairs migrasome formation in NRK cells and MGC-803 cells, while knockout of TSPAN4 did not impair migrasome formation in L929 cells [41]. It seems that migrasomes-forming TSPANs have the compensative effect for the loss of TSPAN4, or TSPAN4 totally has no function in migrasome formation in L929 cells. Dynamically, TSPAN4 is recruited to the migrasomes from the retraction fibers during the migrasomal growth phase; in terms of organization, TSPAN4 forms discrete fast-moving puncta that concentrate on the migrasomal surface; and TSPAN4 cannot move from the migrasomes to the retraction fibers once it is recruited to the migrasomes [41]; however, the mechanisms of TSPAN4 nonreturn are not clear. TSPAN4 in migrasomes is about 4 times higher than in retraction fibers [41]. It is easy to think that TSPAN4 alone cannot form a migrasome. The proteins that interact with TSPAN4 might be another breakthrough to answer this question. TSPAN4 belongs to TSPANs family, which includes 33 members in human beings [17]. It has been well known that TSPANs, combined with a set of TSPANs-associated proteins and a high concentration of cholesterol, form a functional unit in cell plasma membranes, named TSPAN-enriched microdomains (TEMs) [17, 41, 42]. Migrasomes were also enriched with other TEMs components, such as integrins and other TSPANs, e.g., TSPAN1, TSPAN2, TSPAN27/CD82, TSPAN28/CD81, and cholesterol molecules; TEMs enrichment causes the stiffening of the plasma membrane, thus facilitating a new migrasome formation [3, 41, 43].

5. The Current Understanding of the Biological Functions of Migrasomes

5.1. Migrasomes Coordinate Organ Morphogenesis via Serving as Chemoattractants. Migrasomes exist in vivo, what are their physiological functions in living organisms? The robust movement of cells during gastrulation of zebrafish embryo, the optical clarity, and out-of-mother development facilitating high-quality imaging make zebrafish embryo as a promising model to visualize, investigate, and characterize endogenous extracellular vesicles (EVs) in real-time and expand our understanding of EVs biology at cellular and systems level [3, 44–47]. The embryonic cells during zebrafish gastrulation generate long projections and migrasomes, which are present in the pockets between the blastodermal margin and the yolk syncytial layer, and in the extracellular pockets of the space between mesendodermal cells [3]. By developing itgb1b−/− embryos, maternal zygotic (MZ) tspan7−/− and MZtspan4a-mutant embryos, TSPAN7 and 4a, and integrin β1b have been confirmed as the key molecules mediating the formation of migrasomes in zebrafish gastrulas [3]. Physiologically, migrasomes act as a source of Cxcl12 during zebrafish gastrulation, and migrasomes are enriched on a large cavity underneath the embryonic shield where they serve as chemoattractants through delivering Cxcl12a for Cxcl12a–Cxcr4b signalling axis to ensure the correct positioning of dorsal forerunner cells vegetally next to the embryonic shield, thereby affecting organ morphogenesis [3].

In addition to zebrafish, migrasome-like structures are also in mouse embryonic stem cells and embryonic fibroblast in vitro [1] (Figure 1), while the function of migrasomes in mouse embryonic development has not been identified. Mammalian fertilization comprises sperm migration via the female reproductive tract, biochemical and morphological changes to sperm, and sperm-egg interaction in the oviduct [48]. Motility is one of the most remarkable characteristics of mammalian spermatozoa, while it is not clear whether sperm can produce or release migrasomes; if can, what are the functions of migrasomes in mammalian fertilization?

5.2. Migrasomes Discard the Damaged Mitochondria: An Essential Role in Oxidative Stress. On 2021 May 27, a study
published in *Cell* by Yu’s lab has showed that migrasomes contain multiple mitochondria [6]. They found that the oxidative phosphorylation uncoupler carbonyl cyanide 3 chlorophenylhydrazone (CCCP) induces loss of mitochondrial membrane potential (MMP), and generation of high reactive oxygen species (ROS) in mitochondria; subsequently, these damaged mitochondria with an average size of 240 nm and swollen cristae signal their status and subsequently move to the cell periphery through their intrinsic avoidance of binding the inward motor protein dynein, and through globally enhancing the recruitment of KIF5B (the outward motor binding the inward motor protein dynein, and through the globular domain) to the cell periphery through their intrinsic avoidance of damaged mitochondria with an average size of 240 nm and swollen cristae [50–52]. The tips of tubular mitochondria bind to cortical actin and undergo fission factor (Drp1) [53]-mediated fission, and then, they are sent into migrasomes; these migrasomes containing damaged mitochondrion were referred as “mitosomes”; finally, damaged mitochondria with deleterious mtDNA mutations are selectively disposed of by migrasomes release, a process named as “mitocytosis” [6].

By genetically manipulating the expression of TSPAN4, TSPAN9, dynein, KIF5B and integrin, and by blocking migration using the myosin II inhibitor “blebbistatin” in L929 cells, Jiao et al. found that blocking mitocytosis causes loss of MMP and reduction of spare respiration capacity in cells that are not exposed to mitochondrial stressors, while enhanced mitocytosis improves the loss of MMP and preserves the spare respiration capacity in cells with or without CCCP treatment [6]. Besides CCCP, other mitochondrial stressors, such as deferiprone (a typical iron chelator [54, 55]), antimycin A (a complex III inhibitor [56]), and oligomycin (a selective F1F0-ATPase inhibitor [57, 58]), and starvation can also induce mitocytosis in L929 cells [6]. CCCP treatment also induces mitocytosis in mouse bone marrow-derived macrophages, human pancreatic cancer cells (MIACaPa-2 [59]), and human umbilical vein ECs [6]. Therefore, mitocytosis is a general mechanism that is activated by various mitochondrial stresses in a variety of cells [6].

5.3. Migrasomes in Innate Immunity and COVID-19: Still Long Way to Go. The classical EVs, including exosomes (30–200 nm), microvesicles (approximately 200 nm), and apoptotic bodies (1–2 μm) [17, 60, 61], can convey pathogen molecules that serve as antigens or agonists of innate immune receptors to induce host defence and immunity, or that serve as regulators of host defence and mediators of immune evasion [60]. The functions of EVs on innate immunity are conferred partially by transferring pro- or anti-inflammatory mediators, membrane receptors, enzymes, mRNAs, and noncoding RNAs to the targeting cells and by the interaction of EVs with the complement and coagulation systems [61–65]. Migrasomes are newly discovered EVs and also contain proteins and nucleic acids; what are the functions of migrasomes in regulating longevity?

Two studies have shown that macrophages are capable of generating migrasomes [1, 6]. The bone marrow-derived macrophages (BMDMs) derived from TSPAN9−/− mice have significant reduced migrasome numbers and loss of MMP compared to those from wild-type (WT) mice; re-expressing TSPAN9 in TSPAN9−/− macrophages will partially restore the impaired migrasome formation and improve the loss of MMP in cells grown on the untreated migrasome-forming surface, rather than on a hydrophilic surface, which significantly reduces the migration and does not support migrasome formation [6]. These indicated that loss of membrane potential is possibly caused by reduced mitocytosis, rather than by a function of TSPAN9 independent of mitocytosis.

There are migrasomes in human blood, although their origin is not clear [19]. Jiao et al. found that migrasomes were extensively generated by circulating neutrophils in mice, as that around 87% of migrasomes from blood originated from neutrophils [6]. Some neutrophil-derived migrasomes can adhere to vessels in the circulation for a long time, while some are detached quickly after generation [66, 67]. Most importantly, the migrasomes generated by neutrophils contain damaged mitochondria [6]. Migrasome formation by neutrophils from TSPAN9−/− mice is significantly reduced, and the percentage of spleen neutrophils with higher MMP is greatly reduced in TSPAN9−/− mice when compared with the WT, while there is almost no difference in MMP between WT and TSPAN9−/− bone marrow neutrophils, as that bone marrow neutrophils have not yet undergone their long-distance migration; therefore, migrasome/mitocytosis has not yet kicked in; thus, this confirmed that it is migrasome, but not TSPAN9, that contribute to mitochondrial quality control [6].

So, what is the consequence of controlling mitochondrial quality by mitocytosis in immune cells? Jiao et al. showed that the generation and maturation of neutrophils are normal in TSPAN9−/− mice; in contrast, the number of neutrophils is reduced in the spleen from TSPAN9−/− mice compared with WT [6]. When injecting TSPAN9−/− or WT bone marrow neutrophils to WT mice, WT neutrophils significantly outnumber TSPAN9−/− neutrophils after one day’s circulation; thus, mitocytosis physiologically contributes to the viability of neutrophils in the circulation [6]. Therefore, disposal of damaged mitochondria via releasing migrasomes is essential for keeping circulating neutrophils alive; however, these are limited to the mice in the steady state [6, 67], and using the infectious animal models or patients to explore the functions of migrasomes in other migratory immune cell development and in antiviral innate immunity will be more excited.

With almost two years into the severe coronavirus disease 2019 (COVID-19) pandemic, the impacts of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) go far beyond the suffering and death caused by COVID-19 itself. Scientists around the world are actively investigating SARS-CoV-2 and looking for the effective prevention and control strategies both in modern medicine and in...
leading to monocyte tissue factor release and thus contribut-

In these patients, platelets become activated and COVID-19 present with hypercoagulation and thrombosis [68]. Moreover, many patients with COVID-19 are characterized by cytokine storm [68]. In pneumonia, lymphopenia, exhausted lymphocytes, and a particular type of signalling vesicles in atherosclerosis due to the high rate of immune cell migration [83].

TSPAN8, the key organizers of migrasomes and exosomes, are extensively expressed in hematopoietic and vascular cells and are involved in both physiological and pathological processes related to thrombosis, hemostasis, angiogenesis, and vascular injuries [17, 84]. TSPAN8 expressed in the membrane of exosomes from cancer cells contributed to a selective recruitment of mRNA and proteins into exosomes, including CD106 and CD49d, which were implicated in exosomes-ECs binding and ECs internalization [85]. Subsequently, the exosomal mRNA and/or proteins induce gene expression that suffices for activation of the quiescent ECs, and these exosomes also allow for the survival of EC progenitors (ECP) [85]. We are unclear whether TSPANs in migrasomes have the same influence on vascular homeostasis, or whether the TSPANs-independent effects of migrasomes have the vascular effects.

Migrasomes were formed in F4/80^-microglia/macrophages of ischemic hemispheres of mice that received a standard diet, whereas high salt diet (sodium chloride) enhanced migrasome formation in vivo. Sodium chloride can also induce microglial migrasome formation directly in vitro, and migrasomes were also detected in postmortem brain tissue of stroke patients [9]. F4/80^-migrasomes are co-localized with NeuN, which is expressed in nuclei and cytoplasm of neurons; this suggests that the two different scenarios are possible: migrasomes might carry off fragments of damaged neurons, thus, fulfilling a "cleavage function"; or migrasomes might incorporate the cytosol of intact neurons, thereby, inducing neuronal death and aggravating ischemic cell damage [9]. It is urgent to know whether migrasome is the consequence or the contributor during ischemic stroke.

5.5. Migrasomes: the Sensitive Indicators for Early Podocyte Stress and/or Damage. Podocyte-derived EVs have received much more attention for nephrologists and others [86–95], and the urinary podocyte-derived EVs are associated with renal injury in systemic lupus erythematosus [95], preeclampsia [91], and metabolic syndrome [90]. Podocytes control glomerular permeability; they have a higher capacity of motility than other renal cells and can release exosomes and migrasomes, while renal tubular cells secrete less migrasomes; these released migrasomes can be detected in human and mouse urine [10]. It should be noticed that migrasomes and exosomes released from podocyte possess different protein and miRNA profiles; for example, the migrasomes contain more PIGK, miR-1303, miR-490-5p, miR-548a, miR-611, and miR-661 than exosomes isolated from the same cultured podocytes [10]. However, it remains unknown the physiological or pathophysiological functions of these migrasomal miRNA and proteins in podocytes.

The secretion of migrasomes in podocytes was strongly enhanced by puromycin amino nucleoside (PAN), lipopolysaccharide (LPS), or a high concentration of glucose (HG) in vitro [10]. Release of migrasomes from podocytes is dependent on Rac-1 (Ras-related C3 botulinum toxin substrate1), a member of Rho family of small molecular weight guanosine triphosphate (GTP)-binding proteins/GTPases, as that Rac-1 inhibitor (EHT 1864) dose dependently inhibited LPS-, PAN-, or HG-induced migrasome formation [10,
Urinary migrasomes released from podocyte may serve as a more sensitive indicator than proteinuria for podocyte injury, because that increased urinary migrasome number was detected earlier than elevated proteinuria during PAN-induced nephropathy in mice [10, 99]. Furthermore, it is interesting to know whether the migrasomes in urine have the indicative roles for other renal disorders.

5.6. Migrasomes Modulate Cell Proliferation via Lateral Transfer of mRNA and Protein. The intact migrasomes can be engulfed by the surrounding cells; what will happen to the recipient cells after the lateral transfer of cellular contents by migrasomes? In addition to protein, migrasomes also enrich in mRNA [2]. So, when migrasomal proteins and mRNA enter the recipient cells with migrasomes, do the laterally transferred mRNA and proteins have any functional consequence in the recipient cells?

Yu’s team chose tumor suppressor PTEN (phosphatase and tensin homolog on chromosome 10) as an example, as it was among the most abundant group of mRNAs in migrasomes from L929 cells [2]. PTEN was firstly identified as a putative protein tyrosine phosphatase gene mutated in human brain, breast, and prostate cancer in 1997 [100]. The SUMO1 modification of PTEN modulates tumorigenesis by controlling its association with the plasma membrane; subsequently, PTEN dephosphorylates and converts phosphatidylinositol 3,4,5-triphosphate (PIP3) into phosphatidylinositol 4,5-biphosphate (PIP2) and, thus, antagonizes the cations from the philosophy of traditional Chinese Medicine (also known as “The Yellow Emperor’s Canon of Medicine”) and in “five-viscus (also known as “five-zang” or “five-organ”) correlation theory”, and from the philosophy of Western medicine based on modern anatomy, physiology, molecular genetics, and immunology [111]. Similar to other kinds of EVs, migrasomes have a single layer of membrane (phospholipid bilayer structure), which can protect the contents carried by them from being damaged by digestive enzymes in the environment, while their surface have specific adhesion molecules, which can guide them to the correct recipient cells [1, 112]. Migrasomes exist in urine and blood in vivo [6, 10, 19], and they have relative long lifespan [1]; there is no doubt that they can travel into the remote organs via blood circulation [113]. Considered that migrasomes can be engulfed by the recipient cells or rupture to release their contents into the environment [1–3], hence, they might act as the essential modulators of interorgan communication in vivo.

Migrasomes derived from cells can also rupture and release their luminal contents into the environment in a process named “migracytosis” [1–3, 6, 41] (Figure 1). In zebrafish, it is possible that migrasomes have been generated elsewhere by migrating cells, and after breaking from the retraction fibers, they were “washed” to the embryonic shield cavity by moving cells, thus coordinating organ morphogenesis [3]; yet, these still need further investigation. Migrating cells expel dysfunctional mitochondria by releasing migrasomes (a process referred as “mitocytosis”) to protect cells against mitochondrial stressor-induced oxidative damage and maintain mitochondrial homeostasis [6, 114–117]. It is interesting to know what will happen to the damaged mitochondria once transporting into migrasomes and leaving behind the migrating cells. It remains unknown whether mitosomes contain normal mitochondria, and whether mitosomes can be engulfed by the surrounding cells, thus transferring mitochondrial information between cells [6].

6. Discussion

Migrasome is a novel vesicular structure discovered in migrating cells: during cell migration, projections named “retraction fibers” are pulled from the rear end of cells, and large vesicular structures named “migrasomes” grow on the retraction fibers; when the cell migrates away, the retraction fibers break, and migrasomes are left behind [1] (Figure 1). Migrasomes contain many small vesicles, proteins, mRNA, miRNA, and the damaged mitochondria with low MMP and high ROS [2, 6, 10]. The transporting mechanisms of damaged mitochondria to migrasomes are relatively clear [6]. Nevertheless, the origin of small vesicles inside migrasomes and the sorting and transporting mechanisms of these small vesicles, nucleic acids, and proteins into migrasomes remain to be identified [1, 4, 67, 109].

Once detached from cells, migrasomes can be directly taken up by the surrounding cells and transfer their contents into the surrounding cells (Figure 1); according to these, the physiological and pathophysiological functions of migrasomes partially depend on their interaction with the recipient cells [2, 109], although the mechanisms of this interaction and transfer are unclear. It should be considered that the exchange of information between migrasomes and other membranous organelles, such as exosomes, might also influence the functions of migrasomes [110]. There exist essential interorgan communications from the philosophy of traditional Chinese Medicine based on the record in Huang-Di-Nei-Jing (also known as “The Yellow Emperor’s Canon of Medicine”) and in “five-viscus (also known as “five-zang” or “five-organ”) correlation theory”, and from the philosophy of Western medicine based on modern anatomy, physiology, molecular genetics, and immunology [111]. Similar to other kinds of EVs, migrasomes have a single layer of membrane (phospholipid bilayer structure), which can protect the contents carried by them from being damaged by digestive enzymes in the environment, while their surface have specific adhesion molecules, which can guide them to the correct recipient cells [1, 112]. Migrasomes exist in urine and blood in vivo [6, 10, 19], and they have relative long lifespan [1]; there is no doubt that they can travel into the remote organs via blood circulation [113]. Considered that migrasomes can be engulfed by the recipient cells or rupture to release their contents into the environment [1–3], hence, they might act as the essential modulators of interorgan communication in vivo.

Migrasomes derived from cells can also rupture and release their luminal contents into the environment in a process named “migracytosis” [1–3, 6, 41] (Figure 1). In zebrafish, it is possible that migrasomes have been generated elsewhere by migrating cells, and after breaking from the retraction fibers, they were “washed” to the embryonic shield cavity by moving cells, thus coordinating organ morphogenesis [3]; yet, these still need further investigation. Migrating cells expel dysfunctional mitochondria by releasing migrasomes (a process referred as “mitocytosis”) to protect cells against mitochondrial stressor-induced oxidative damage and maintain mitochondrial homeostasis [6, 114–117]. It is interesting to know what will happen to the damaged mitochondria once transporting into migrasomes and leaving behind the migrating cells. It remains unknown whether mitosomes contain normal mitochondria, and whether mitosomes can be engulfed by the surrounding cells, thus transferring mitochondrial information between cells [6].
Mitochondrial ROS is a key regulator of ECM-degrading metalloproteinases transcription and activation [118]; the pairing of integrins with ECM partner protein is essential for the formation of migrasomes [4], which will release into the ECM after formation [1, 119]; and the released migrasomes can discard the damaged mitochondria with high ROS via the process of mitocytosis [6]; hence, the influences of mitocytosis or migrasomes on the status of ECM should also be taken into consideration.

Cell migration is the basic phenomena and fundamental mechanisms of modulating body homeostasis and involved in some human diseases, for example, embryogenesis, wound healing, immune defense, cardio-cerebrovascular diseases, eye diseases, cancer biology, osteoporosis, and the chronic inflammatory diseases, e.g., rheumatoid arthritis and multiple sclerosis [17, 22, 23, 120]. Migrasomes are intrinsically associated with cell migration [6]. Until now, the physiological and pathological functions of migrasomes or its related events have not been determined [7]. Considering the universality of these charming vesicles.

Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Acknowledgments

This work was supported by the National Natural Science Foundation of China [grant number 81900376 and 81673772], the Natural Science Foundation of Guangdong Province [grant number 2018A030313657 and 2017A030313738], the Project of Administration of Traditional Chinese Medicine of Guangdong Province (20221116), and Project from Guangzhou University of Chinese Medicine for the key members of young teacher [grant number A1-2601-21-414-001263]. We apologize to all of authors whose invaluable work we could not discuss or cite in this review due to space constraints.

References

[1] L. Ma, Y. Li, J. Peng et al., "Discovery of the migrasome, an organelle mediating release of cytoplasmic contents during cell migration," Cell Research, vol. 25, no. 1, pp. 24–38, 2015.

[2] M. Zhu, Q. Zou, R. Huang et al., "Lateral transfer of mRNA and protein by migrasomes modifies the recipient cells," Cell Research, vol. 31, no. 2, pp. 237–240, 2021.

[3] D. Jiang, Z. Jiang, D. Lu et al., "Migrasomes provide regional cues for organ morphogenesis during zebrafish gastrulation," Nature Cell Biology, vol. 21, no. 8, pp. 966–977, 2019.

[4] D. Wu, Y. Xu, T. Ding, Y. Zuo, C. Yang, and L. Yu, "Pairing of integrins with ECM proteins determines migrasome formation," Cell Research, vol. 27, no. 11, pp. 1397–1400, 2017.

[5] B. da Rocha-Azevedo and S. L. Schmid, "Migrasomes: a new organelle of migrating cells," Cell Research, vol. 25, no. 1, pp. 1-2, 2015.

[6] H. Jiao, D. Jiang, X. Hu et al., "Mitocytosis, a migrasome-mediated mitochondrial quality-control process," Cell, vol. 184, no. 11, pp. 2896–2910.e13, 2021.

[7] M. Koupenova, H. A. Corkrey, O. Vitseva et al., "SARS-CoV-2 initiates programmed cell death in platelets," Circulation Research, vol. 129, no. 6, pp. 631–646, 2021.

[8] M. Gagat, W. Zielinska, K. Mikolajczyk et al., "CRISPR-based activation of endogenous expression of TPM1 inhibits inflammatory response of primary human coronary artery endothelial and smooth muscle cells induced by recombinant human tumor necrosis factor α," Frontiers in Cell and Developmental Biology, vol. 9, article 668032, 2021.

[9] A. Schmidt-Pogoda, J. K. Strecker, M. Liebmann et al., " Dietary salt promotes ischemic brain injury and is associated with parenchymal migrasome formation," PLoS One, vol. 13, no. 12, article e0209871, 2018.

[10] Y. Liu, S. Li, W. Rong et al., "Podocyte-released migrasomes in urine serve as an indicator for early podocyte injury," Kidney diseases (Basel, Switzerland), vol. 6, no. 6, pp. 422–433, 2020.

[11] K. R. Porter, A. Claude, and E. F. Fullam, "A study of tissue culture cells by electron microscopy: methods and preliminary observations," The Journal of Experimental Medicine, vol. 81, no. 3, pp. 233–246, 1945.

[12] A. C. Taylor and E. Robbins, "Observations on microextensions from the surface of isolated vertebrate cells," Developmental Biology, vol. 6, pp. 660–673, 1963.

[13] L. Yu, "Migrasomes: the knowns, the known unknowns and the unknown unknowns: a personal perspective," Science China. Life Sciences, vol. 64, no. 1, pp. 162–166, 2021.

[14] M. Monsigny, A. C. Roche, C. Sene, R. Maget-Dana, and F. Delmotte, "Sugar-lectin interactions: how does wheat-germ agglutinin bind sialoglycoconjugates?", European Journal of Biochemistry, vol. 104, no. 1, pp. 147–153, 1980.

[15] L. Chen, L. Ma, and L. Yu, "WGA is a probe for migrasomes," Cell discovery, vol. 5, no. 1, p. 13, 2019.

[16] Y. Chen, Y. Li, L. Ma, and L. Yu, "Detection of migrasomes," Methods in molecular biology (Clifton, NJ), vol. 1749, pp. 43–49, 2018.

[17] Y. Zhang, J. Wang, Y. Ding et al., "Migrasome and tetraspanins in vascular homeostasis: concept, present, and future," Frontiers in Cell and Developmental Biology, vol. 8, p. 438, 2020.

[18] W. Vanden Berge, S. Plaisance, E. Boone et al., "p38 and extracellular signal-regulated kinase mitogen-activated protein kinase pathways are required for nuclear factor-κB p65 transactivation mediated by tumor necrosis factor," The Journal of Biological Chemistry, vol. 273, no. 6, pp. 3285–3290, 1998.
[19] X. Zhao, Y. Lei, J. Zheng et al., “Identification of markers for migrasome detection,” Cell discovery, vol. 5, no. 1, p. 27, 2019.

[20] S. Saito, M. Tanaka, S. Tatematsu, and M. Okochi, “Peptide-modified substrate enhances cell migration and migrasome formation,” Materials Science & Engineering: C, Materials for Biological Applications, vol. 131, article 112495, 2021.

[21] N. Lampiasi, R. Russo, I. Kireev, O. Strelkova, O. Zhironkina, and F. Zito, “Osteoclasts differentiates from murine RAW 264.7 cells stimulated by RANKL: timing and behavior,” Biology, vol. 10, no. 2, p. 117, 2021.

[22] D. A. Lauffenburger and A. F. Horwitz, “Cell migration: a physically integrated molecular process,” Cell, vol. 84, no. 3, pp. 359–369, 1996.

[23] A. J. Ridley, M. A. Schwartz, K. Burridge et al., “Cell migration: integrating signals from front to back,” Science, vol. 302, no. 5651, pp. 1704–1709, 2003.

[24] B. M. Gumbiner, “Cell adhesion: the molecular basis of tissue architecture and morphogenesis,” Cell, vol. 84, no. 3, pp. 345–357, 1996.

[25] D. J. Webb, J. T. Parsons, and A. F. Horwitz, “Adhesion assembly, disassembly and turnover in migrating cells – over and over and over again,” Nature Cell Biology, vol. 4, no. 4, pp. E97–100, 2002.

[26] S. Chien, S. Li, Y. T. Shiu, and Y. S. Li, “Molecular basis of mechanical modulation of endothelial cell migration,” Frontiers in Bioscience, vol. 10, no. 1-3, pp. 1985–2000, 2005.

[27] S. S. Seetharaman and S. Etienne-Manneville, “Cytoskeletal crosstalk in cell migration,” Trends in Cell Biology, vol. 30, no. 9, pp. 720–735, 2020.

[28] S. Li, J. L. Guan, and S. Chien, “Biochemistry and biomechanics of cell motility,” Annual Review of Biomedical Engineering, vol. 7, no. 1, pp. 105–150, 2005.

[29] M. P. Sheetz, D. P. Felsenfeld, and C. G. Galbraith, “Cell migration: regulation of force on extracellular-matrix-integrin complexes,” Trends in Cell Biology, vol. 8, no. 2, pp. 51–54, 1998.

[30] D. J. Webb, C. M. Brown, and A. F. Horwitz, “Illuminating adhesion complexes in migrating cells: moving toward a bright future,” Current Opinion in Cell Biology, vol. 15, no. 5, pp. 614–620, 2003.

[31] M. S. Duxbury, S. W. Ashley, and E. E. Whang, “Inhibition of pancreatic adenocarcinoma cellular invasiveness by blebbistatin: a novel myosin II inhibitor,” Biochemical and Biophysical Research Communications, vol. 313, no. 4, pp. 992–997, 2004.

[32] D. Li and Y. L. Wang, “Coordination of cell migration mediated by site-dependent cell-cell contact,” Proceedings of the National Academy of Sciences of the United States of America, vol. 115, no. 42, pp. 10678–10683, 2018.

[33] E. Macia, M. Ehrlich, R. Massol, E. Boucrot, C. Brunner, and T. Kirchhausen, “Dynasore, a cell-permeable inhibitor of dynamin,” Developmental Cell, vol. 10, no. 6, pp. 839–850, 2006.

[34] H. Yamada, T. Abe, S. A. Li et al., “Dynasore, a dynamin inhibitor, suppresses lamellipodia formation and cancer cell invasion by destabilizing actin filaments,” Biochemical and Biophysical Research Communications, vol. 390, no. 4, pp. 1142–1148, 2009.

[35] L. A. Helgeson, J. G. Prendergast, A. R. Wagner, M. Rodnick-Smith, and B. J. Nolen, “Interactions with actin monomers, actin filaments, and Arp2/3 complex define the roles of WASP family proteins and cortactin in coordinately regulating branched actin networks,” The Journal of Biological Chemistry, vol. 289, no. 42, pp. 28856–28869, 2014.

[36] P. Lu, R. Liu, D. Lu et al., “Chemical screening identifies ROCK1 as a regulator of migrasome formation,” Cell discovery, vol. 6, no. 1, p. 51, 2020.

[37] X. Hu, T. A. Weston, C. He et al., “Release of cholesterol-rich particles from the macrophage plasma membrane during movement of filopodia and lamellipodia,” eLife, vol. 8, article e05231, 2019.

[38] A. Huttenlocher and A. R. Horwitz, “Integrins in cell migration,” Cold Spring Harbor Perspectives in Biology, vol. 3, no. 9, article a005074, 2011.

[39] J. K. Rantala, J. Pouwels, T. Pellinen et al., “SHARPIN is an endogenous inhibitor of beta1-integrin activation,” Nature Cell Biology, vol. 13, no. 11, pp. 1315–1324, 2011.

[40] A. Yoneda, D. Ushakov, H. A. Multhaupt, and J. R. Couchman, “Fibronectin matrix assembly requires distinct contributions from rho kinases I and -II,” Molecular Biology of the Cell, vol. 18, no. 1, pp. 66–75, 2007.

[41] Y. Huang, B. Zucker, S. Zhang et al., “Migrasome formation is mediated by assembly of micron-scale tetraspanin macrodomains,” Nature Cell Biology, vol. 21, no. 8, pp. 991–1002, 2019.

[42] M. Yanex-Mo, O. Barreiro, M. Gordon-Alonso, M. Sala-Valdes, and F. Sanchez-Madrid, “Tetraspanin-enriched microdomains: a functional unit in cell plasma membranes,” Trends in Cell Biology, vol. 19, no. 9, pp. 434–446, 2009.

[43] S. Tanovo and C. P. Heisenberg, “Migrasomes take center stage,” Nature Cell Biology, vol. 21, no. 8, pp. 918–920, 2019.

[44] P. J. Keller, A. D. Schmidt, J. Wittbrodt, and E. H. Stelzer, “Reconstruction of zebrafish early embryonic development by scanned light sheet microscopy,” Science, vol. 322, no. 5904, pp. 1065–1069, 2008.

[45] G. J. Lieschke and P. D. Currie, “Animal models of human disease: zebrafish swim into view,” Nature Reviews. Genetics, vol. 8, no. 5, pp. 353–367, 2007.

[46] D. J. Grunwald and J. S. Eisen, “_headwaters of the zebrafish – emergence of a new model vertebrate,” Nature Reviews. Genetics, vol. 3, no. 9, pp. 717–724, 2002.

[47] V. Verdi, A. Becot, G. van Niel, and F. J. Verweij, “_in vivo imaging of EVs in zebrafish: new perspectives from _the waterside,”_ FASEB Bioadv, vol. 3, no. 11, pp. 918–929, 2021.

[48] M. Ikawa, N. Inoue, A. M. Benham, and M. Okabe, “Fertilization: a sperm’s journey to and interaction with the oocyte,” The Journal of Clinical Investigation, vol. 120, no. 4, pp. 984–994, 2010.

[49] Y. Tanaka, Y. Kanai, Y. Okada et al., “_Targeted disruption of mouse conventional kinesin heavy chain, kif5B, results in abnormal perinuclear clustering of mitochondria,”_ Cell, vol. 93, no. 7, pp. 1147–1158, 1998.

[50] B. I. Shneyer, M. Usaj, N. Wiesel-Motiuk, R. Regev, and A. Henn, “_ROS induced distribution of mitochondria to the cell discov__ertion: a novel myosin II inhibitor,”_ Biochemical and Biophysical Research Communications, vol. 313, no. 4, pp. 992–997, 2004.

[51] H. Yamada, T. Abe, S. A. Li et al., “Dynasore, a dynamin inhibitor, suppresses lamellipodia formation and cancer cell invasion by destabilizing actin filaments,” Biochemical and Biophysical Research Communications, vol. 390, no. 4, pp. 1142–1148, 2009.

[52] L. A. Helgeson, J. G. Prendergast, A. R. Wagner, M. Rodnick-Smith, and B. J. Nolen, “Interactions with actin monomers, actin filaments, and Arp2/3 complex define the roles of WASP family proteins and cortactin in coordinately regulating branched actin networks,” The Journal of Biological Chemistry, vol. 289, no. 42, pp. 28856–28869, 2014.
[84] F. Zhang, J. Kotha, L. K. Jennings, and X. A. Zhang, “Tetraspansins and vascular functions,” Cardiovascular Research, vol. 83, no. 1, pp. 7–15, 2009.

[85] I. Nazarenko, S. Rana, A. Baumann et al., “Cell surface tetraspanin Tspan8 contributes to molecular pathways of exosome-induced endothelial cell activation,” Cancer Research, vol. 70, no. 4, pp. 1668–1678, 2010.

[86] Y. Huang, R. Li, L. Zhang et al., “Extracellular vesicles from high glucose-treated podocytes induce apoptosis of proximal tubular epithelial cells,” Frontiers in Physiology, vol. 11, article 579296, 2020.

[87] H. Su, J. Qiao, J. Hu et al., “Podocyte-derived extracellular vesicles mediate renal proximal tubule cells dedifferentiation via microRNA-221 in diabetic nephropathy,” Molecular and Cellular Endocrinology, vol. 518, article 111034, 2020.

[88] I. O. Sun and S. H. Kwon, “Extracellular vesicles: a novel window into kidney function and disease,” Current Opinion in Nephrology and Hypertension, vol. 29, no. 6, pp. 613–619, 2020.

[89] J. S. Jeon, E. Kim, Y. U. Bae et al., “microRNA in Extracellular Vesicles Released by Damaged Podocytes Promote Apoptosis of Renal Tubular Epithelial Cells,” Cell, vol. 9, no. 6, p. 1409, 2020.

[90] L. H. Zhang, X. Y. Zhu, A. Eirin et al., “Early podocyte injury and elevated levels of urinary podocyte-derived extracellular vesicles in swine with metabolic syndrome: role of podocyte mitochondria,” American Journal of Physiology. Renal Physiology, vol. 317, no. 1, pp. F12–F22, 2019.

[91] S. I. Gilani, U. D. Anderson, M. Jayachandran et al., “Urinary Extracellular Vesicles of Podocyte Origin and Renal Injury in Preeclampsia,” J Am Soc Nephrol, vol. 28, no. 11, pp. 3363–3372, 2017.

[92] S. H. Kwon, J. R. Woollard, A. Saad et al., “Elevated urinary podocyte-derived extracellular microvesicles in renovascular hypertensive patients,” Nephrology, Dialysis, Transplantation, vol. 32, no. 5, pp. 800–807, 2016.

[93] U. Erdbrügger and T. H. Le, “Extracellular vesicles in renal diseases: more than novel biomarkers?,” J Am Soc Nephrol, vol. 27, no. 1, pp. 12–26, 2016.

[94] D. Burger, J. F. Thibodeau, C. E. Holterman, K. D. Burns, R. M. Touyz, and C. R. Kenney, “Urinary podocyte microparticles identify prealbuminuric diabetic glomerular injury,” J Am Soc Nephrol, 25, no. 7, pp. 1401–1407, 2014.

[95] J. Lu, Z. B. Hu, P. P. Chen et al., “Urinary podocyte microparticles are associated with disease activity and renal injury in systemic lupus erythematosus,” BMC Nephrology, vol. 20, no. 1, p. 303, 2019.

[96] E. E. Bosco, J. C. Mulloy, and Y. Zheng, “Rac1 GTPase: a "Rac" of all trades,” Cellular and Molecular Life Sciences, vol. 66, no. 3, pp. 370–374, 2009.

[97] L. M. Chen, S. Hobbie, and J. E. Galan, “Requirement of CDC42 for salmonella-induced cytoskeletal and nuclear responses,” Science, vol. 274, no. 5295, pp. 2115–2118, 1996.

[98] W. D. Hardt, L. M. Chen, K. E. Schuebel, X. R. Bustelo, and J. E. Galan, “S. typhimurium encodes an activator of Rho GTPases that induces membrane ruffling and nuclear responses in host cells,” Cell, vol. 93, no. 5, pp. 815–826, 1998.

[99] M. Ardalan, S. M. Hosseinian Khatibi, Y. Rabbar Saadat et al., “Migrasomes and exosomes; different types of messaging vesicles in podocytes,” Cell Biology International, vol. 46, no. 1, pp. 52–62, 2022.

[100] J. Li, C. Yen, D. Liaw et al., “PTEN, a putative protein tyrosine phosphatase gene mutated in human brain, breast, and prostate cancer,” Science, vol. 275, no. 5308, pp. 1943–1947, 1997.

[101] S. Das, J. E. Dixon, and W. Cho, “Membrane-binding and activation mechanism of PTEN,” Proceedings of the National Academy of Sciences of the United States of America, vol. 100, no. 13, pp. 7491–7496, 2003.

[102] G. R. Masson and R. L. Williams, “Structural mechanisms of PTEN regulation,” Cold Spring Harbor Perspectives in Medicine, vol. 10, no. 3, article a036152, 2020.

[103] J. Huang, J. Yan, J. Zhang et al., “SUMO1 modification of PTEN regulates tumorigenesis by controlling its association with the plasma membrane,” Nature Communications, vol. 3, no. 1, p. 911, 2012.

[104] F. Vazquez, S. Matsuoka, W. R. Sellers, T. Yanagida, M. Ueda, and P. N. Devreotes, “Tumor suppressor PTEN acts through dynamic interaction with the plasma membrane,” Proceedings of the National Academy of Sciences of the United States of America, vol. 103, no. 10, pp. 3633–3638, 2006.

[105] A. Savukaityte, G. Gudoitkyte, A. Bartnykaitė, R. Ugenkienė, and E. Juzoaitiūtė, “siRNA knockdown of REDD1 facilitates aspirin-mediated dephosphorylation of mTORC1 target 4EBP1 in MDA-MB-468 human breast cancer cell line,” Cancer Management and Research, vol. Volume 13, pp. 1123–1133, 2021.

[106] P. Flynn, M. Wongdagger, M. Zavar, N. M. Dean, and D. Stokoe, “Inhibition of PDK-1 activity causes a reduction in cell proliferation and survival,” Current Biology, vol. 10, no. 22, pp. 1439–1442, 2000.

[107] C. Mehra and L. Pernas, “Frequent inactivation of PTEN in paraaffin-embedded primary prostate cancer correlates with high Gleason score and advanced stage,” Cancer Research, vol. 60, no. 17, pp. 4291–4296, 1999.

[108] R. J. Vlietstra, D. C. van Alewijk, K. G. Hermans, G. J. van Steenbrugge, and J. Trapman, “Frequent inactivation of PTEN in prostate cancer cell lines and xenografts,” Cancer Research, vol. 58, no. 13, pp. 2720–2723, 1998.

[109] Y. Chen, “Research progress of extracellular vesicles,” Chinese Journal of Cell Biology, vol. 41, no. 2, pp. 202–210, 2019.

[110] Y. Chen and L. Yu, “Research progress of membranous organelles and their subcellular structures in China,” Chinese Science Bulletin, vol. 62, no. 19, pp. 2055–2062, 2017.

[111] Y. Zhang and X. M. Fang, “Hepatocardiac or cardiohepatic interaction: from traditional Chinese medicine to Western medicine,” Evidence-based complementary and alternative medicine : eCAM, vol. 2021, article 6655335, 14 pages, 2021.

[112] W. Zhang, L. Yu, and Y. Chen, “Research progress in extracellular vesicles detection and analysis,” Chinese Journal of Cell Biology, vol. 42, no. 1, pp. 159–165, 2020.

[113] Y. Chen, “Migrasome: a new cellular organelle,” Zhongguo Shengwu Xuebao Yu Fenzi Shengwuxue Xuebao, vol. 37, no. 5, pp. 551–555, 2021.

[114] C. Mehra and L. Pernas, “Move it to lose it: mitocytosis expels damaged mitochondria,” Developmental Cell, vol. 56, no. 14, pp. 2014–2015, 2021.

[115] K. Baumann, “Damaged mitochondria are discarded via migrasomes,” Nature Reviews Molecular Cell Biology, vol. 22, no. 7, pp. 442–442, 2021.

[116] D. R. Green, “Mitochondrial quality control: just walk away,” Cell Metabolism, vol. 33, no. 6, pp. 1069–1071, 2021.
[117] C.-S. Lee and J. Song, “Migrating cells dispose of damaged mitochondria into the surrounding environment,” *Molecules and Cells*, vol. 44, no. 11, pp. 781–783, 2021.

[118] K. K. Nelson and J. A. Melendez, “Mitochondrial redox control of matrix metalloproteinases,” *Free Radical Biology & Medicine*, vol. 37, no. 6, pp. 768–784, 2004.

[119] T. Kang, I. Atukorala, and S. Mathivanan, “Biogenesis of extracellular vesicles,” *Sub-Cellular Biochemistry*, vol. 97, pp. 19–43, 2021.

[120] M. Potente, H. Gerhardt, and P. Carmeliet, “Basic and therapeutic aspects of angiogenesis,” *Cell*, vol. 146, no. 6, pp. 873–887, 2011.