Nano Research

Open Access

Review Article

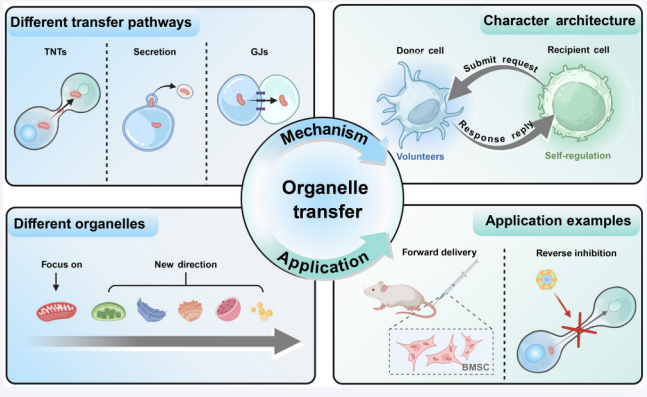
Mechanisms and prospects of multifunctional organelles in intercellular communication

Kexin Yin[1,§], Zuoxi Zhang[1,§], Feiyu Zhao[3], Niansong Qian[4] ✉, Huining He[2] ✉, and Bin Zheng[1,2] ✉

[1] *Academy of Medical Engineering and Translational Medicine, Department of Medicine, Tianjin University, Tianjin 300072, China*
[2] *School of Biomedical Engineering and Technology, Tianjin Medical University, Tianjin 300070, China*
[3] *Department of Radiation Therapy, Oncology Medical Department, the Fifth Medical Center of Chinese People's Liberation Army General Hospital, No. 8 East Main Street, Fengtai District, Beijing 100071, China*
[4] *Department of Respiratory, the Eighth Medical Center of Chinese PLA General Hospital, Beijing 100853, China*
[§] *Kexin Yin and Zuoxi Zhang contributed equally to this work.*

Cite this article: *Nano Research*, **2026**, *19*, 94908422. https://doi.org/10.26599/NR.2026.94908422

ABSTRACT: Organelles function as the primary units of cellular activity and also play a crucial role in intercellular communication. In recent years, there has been a notable increase in the level of interest among researchers in the field of organelle transfer and exchange. A mounting body of evidence suggests that a variety of organelles—including, but not limited to, mitochondria, chloroplasts and lysosomes—can be transferred between cells via multiple mechanisms, thereby impacting cellular destiny. It is evident that the absence of a consolidated logical framework is due to the heterogeneity of the disease models and perspectives that underpin the extant discoveries. Consequently, there is an absence of a unifying logical framework that can summarize the mechanisms of intracellular and extracellular environment remodeling before and after multi-organelle transfer for targeted investigation and clinical application. This review systematically examines extant research on intercellular organelle transfer, encompassing transferable organelle types, triggering factors, effects on donor/recipient cells, and mechanistic analyses/intervention strategies from physiological and pathological perspectives. The objective of this review is to gain a more profound comprehension of the mechanisms that regulate fundamental life processes by meticulously analyzing the transfer processes of diverse organelles. In this review, we discuss the critical challenges in organelle transfer research and emphasize its significance for innovative therapeutic strategies and the elucidation of universal biological mechanisms.



KEYWORDS: organelle transfer, intercellular communication, engineered organelle applications, organelle biology

1 Introduction

In the realm of research concerning the origins of cellular life, a multitude of hypotheses have been advanced in an attempt to elucidate the genesis of eukaryotic cells. The mainstream transitional model combines symbiotic origin theory with gradualism [1–3]. Despite significant differences between these two academic theories, both agree that organelles originated when prokaryotic cells entered another cell during symbiosis and gradually differentiated into functional microstructures [4]. It is therefore comprehensible that a fundamental principle underlying cellular evolution from Last Universal Common Ancestor (LUCA) to eukaryotic multicellular organisms is the utilisation of cargo transfer for the purpose of rectifying deficiencies and ensuring self-protection [5, 6]. In a multitude of extant multicellular organisms, it is evident that following extended symbiotic relationships, intracellular algae metamorphose into energy-generating entities that bear a resemblance to chloroplasts [7]. It has been demonstrated that certain species of slug, for example, have been observed to incorporate chloroplasts from plant cells into their own,

Received: November 29, 2025; **Revised:** January 3, 2026
Accepted: January 8, 2026

✉Address correspondence to Niansong Qian, qianniansong1@163.com; Huining He, hehuining@tmu.edu.cn; Bin Zheng, binzheng@tju.edu.cn

thereby achieving photosynthetic autotrophy [8–10]. It is therefore not difficult to understand that organelle transfer between cells represents a form of simple "appropriation". Cells transfer and acquire organelles as "asset-light", ultimately achieving their predetermined goals. In recent years, the field of research has seen a surge of interest in the phenomenon of organelle transfer within animal bodies, and the potential ramifications this transfer may have on animal cells [11, 12].

Since the advent of organelle transfer research, a plethora of structural units and potentially transferable organelles have been the subjects of study and deconstruction [13–15]. Researchers have discovered that organelle transfer between cells resembles a unique communication strategy, whereby cells transport organelles as cargo, physiological structures, and initiation components. Consequently, intercellular organelle transfer frequently utilizes the same types of transport structures and tools employed for signal transfer. In a manner analogous to secreted proteins, cells possess the capacity to employ secretory vesicles to facilitate the long-distance transfer or targeted delivery of organelles, such as mitochondria, to the extracellular environment [16–19]. In a manner analogous to tunneling for fundamental material transfer between cells, cells have been observed to form tunneling nanotubes (TNTs) to deliver organelles such as mitochondria [20–22]. In a similar manner, plasmodesmata facilitate signal communication in plant cells, and these cells create complex protein pores through cell wall openings to exchange chloroplasts [23, 24]. Following the classification and investigation of the fundamental structures implicated in organelle transfer, researchers conducted extensive studies on the categories of organelles capable of migration [25]. The extant literature suggests that, in addition to the prevalent phenomenon of mitochondrial transfer [26–29], organelles such as chloroplasts [24, 30, 31], lysosomes [15, 32–36], endoplasmic reticulum [37, 38], and lipid droplets [39, 40] have also been observed to undergo transfer and exchange. These organelle transfers occur during both normal tissue life processes and in the context of disease or cellular damage. These biological activities are influenced by functional changes resulting from intracellular organelle transfers, altering the internal stable environment and ultimately acting as a double-edged sword.

In this review, we methodically categorize the roles played during organelle transfer and exchange into three distinct domains: effects on the donor cell's internal environment, effects on the recipient cell's internal environment, and effects on the extracellular environment within multicellular spaces. This classification strategy facilitates the delineation of research areas in organelle transfer. In the context of malignant diseases, for instance, inhibitory effects can be achieved by impeding the acquisition of exogenous organelles by tumor cells or necrotic cells. In the context of autoimmune systems or existing necrotic regions, exogenous organelle delivery can be achieved by introducing pluripotent stem cells or direct artificial transplantation to facilitate tissue repair and regeneration. However, challenges such as cross-staining and false positives in visualizing organelle transfer and exchange may lead to misinterpretation of biological pathways considered in articles or studies. These research obstacles urgently require the development of novel high-precision visualization techniques to facilitate imaging and analysis. Concurrently, this paper proposes the development of activator drugs that promote organelle transfer to address the low probability of organelle transfer *in vitro* cultures. In this study, we provide a comprehensive overview of the structural underpinnings that govern organelle transfer, the various categories of transferable organelles, and the specific organelle groups that are capable of transfer. A subsequent discussion will address the series of effects on donor and recipient cells before and after organelle transfer. The integration of existing applications is a key aspect of this work, as it provides novel perspectives for the development of future targeted therapies.

2 Triggers and mechanisms of organelle transfer

During the evolution of organisms from unicellular to multicellular states, the establishment of intercellular interactions and material transport led to the formation of intricate networks that interconnected cells of similar or distinct types [41, 42]. In this process, functional differences arising from cellular differentiation or disease led to significant alterations in the internal substances or organelles of cells. A substantial body of research has demonstrated that in organelles containing deoxyribonucleic acid (DNA), including mitochondria and chloroplasts, gene expression is closely associated with cellular function [43, 44]. Consequently, organelles of the same type within different cells may exhibit substantial functional variations [45]. In such conditions, cells — as fundamental units of life capable of independently completing life processes and regulating themselves — have the capacity to acquire or appropriate organelles with functions they originally lacked through multiple mechanisms [46]. The advent of sophisticated imaging techniques and labeling methodologies has engendered a paradigm shift in the precision with which trajectory tracing can be achieved. In recent years, there has been an extensive examination of the mechanisms and triggers that regulate organelle transfer [47–50]. This chapter will introduce the fundamental mechanisms and structural bases of organelle transfer by analyzing existing literature.

2.1 The structural basis of organelle transfer

The simplification of intracellular compartments enabled cells to form localized functional units, which ultimately evolved into membrane-bound or membrane-less organelles [51, 52]. A plethora of research has indicated that cells underwent a minimum of two symbiotic or mutualistic events related to prokaryotic cells during the course of evolution. These events were categorized as independent events which were responsible for the emergence of primary and complex organelles. In high concentrations of reducing gases, early life evolved a metabolic pathway that utilized light energy. These bacteria were found to eventually release substantial amounts of oxygen and synthesize organic compounds. The increase in oxygen concentration resulted in accelerated growth among archaeal bacterial groups that utilized oxygen for the consumption of organic matter. This metabolic trait underwent horizontal transfer and refinement, forming a precursor resembling cellular aerobic respiration. In conclusion, the production and demand for oxygen within specific bacterial symbiosis led to the formation of localized endosymbiotic structures. It has been observed that some archaea have invaginated their inner membranes to enclose genetic material, forming nuclei, and created numerous internal cavities within their cells. These spaces were subsequently colonized by oxygen-producing and oxygen-consuming bacteria, which underwent a process of evolution, ultimately resulting in the formation of organelles such as chloroplasts and mitochondria. This symbiotic mutualism

underwent a transformation into a state of dependency, ultimately resulting in its indispensability [53]. This evolutionary mechanism provides a theoretical framework for understanding the utilization of organelles within cells. Cells are in a constant state of renewal, transfer, and release of organelles in order to maintain internal homeostasis. Horizontal organelle transfer provides information to enhance cellular functions. More crucially, given that the internalization of bacteria and the formation of organelle precursors transpired during a period of frequent gene transfer between bacteria, the genes and structures of organelles across cells remain strikingly similar. It has been demonstrated that these organelles retain significant bacterial signaling structures, thereby providing a substantial structural foundation and universal biological mechanism for organelles to function as signaling molecules [54]. This foundation enables researchers to study organelles as localized functional units [55, 56]. Conversely, researchers have thoroughly elucidated multiple critical forms of transport and transfer when discussing material transfer and intercellular communication (Fig. 1). These transport mechanisms depend on intracellular ion levels, redox states, cytoskeletal localization, and other factors [57–59]. Building upon this foundation, cells gradually formed structures by arranging and combining these units. Examples include exosome or vesicle structures, which are constructed via membrane fusion, and filamentous structures on the membrane surface, which are formed through the coupling of membranes with the cytoskeleton [60–63]. Transport mechanisms such as proximity-mediated fusion and the assembly of small molecule monomers after transfer were also established using ion channels or transmembrane proteins [64].

Similar to intercellular material transfer, organelles rely on pore structures formed between adjacent cells for transport. Based on this theory, TNTs have been reported to exist between heterologous or homologous cells [65]. These spontaneously formed, membrane-bound tubular protrusions originate from the plasma membrane and function by forming internal cytoskeletal networks that ultimately achieve intercellular fine structures ranging from 20 to 2000 nm [14, 61, 66]. The stable tubular architecture within these structures enables the transport of macromolecules and even fully formed organelles [65, 66]. Since their discovery, it has been demonstrated that mitochondrial membrane vesicles, dysfunctional mitochondria, and even entire mitochondria traverse these channels for intercellular transfer (Fig. 2) [67–72]. Furthermore, due to the expandability of the tubular network, cells can exchange secondary organelle structures, transporting them from donor to recipient cells. Once initiated, the transport process enables rapid intercellular organelle transfer between donor and recipient cells, ultimately facilitating parallel genomic exchange [24, 73]. Concurrently, the formation of intercellular canal networks

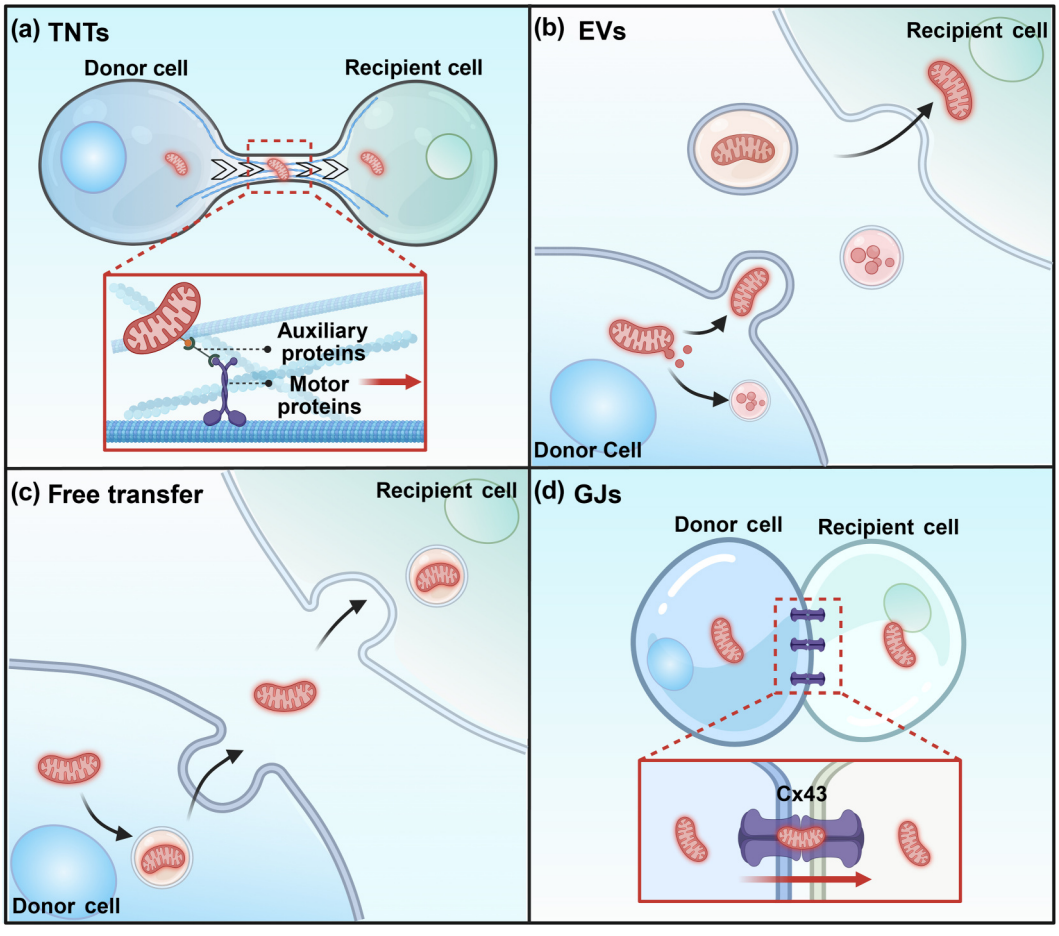


Figure 1 Pathways for mitochondrial transfer from donor to recipient cells. (a) TNTs, the most prevalent intercellular transfer pathway, are membrane-bound tubular tunnels extending from the plasma membrane. (b) Extracellular vesicles (EVs) formed from the cell membrane represent another pathway for organelle transfer. (c) Certain organelles, such as mitochondria, can be secreted into the extracellular environment and internalized by neighboring cells. (d) Numerous gap junctions exist between cells, particularly in plants, where some protein complexes can facilitate organelle transfer by forming assemblies.

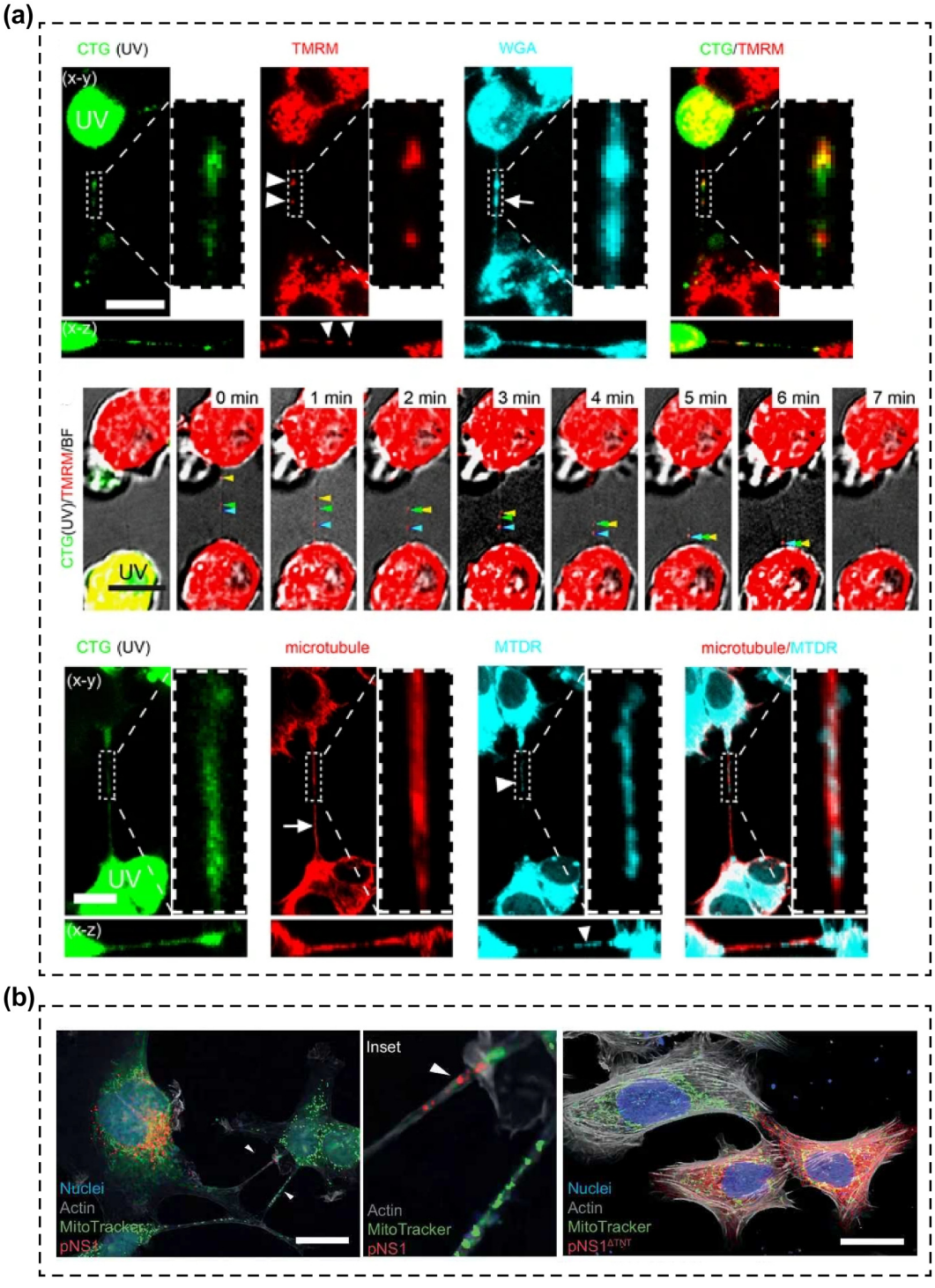


Figure 2 TNTs serve as the primary bridge for intercellular organelle transfer. (a) Researchers discovered that mitochondria can be transferred between cells via tunneling nanotubes to rescue apoptotic PC12 cells. Using fluorescence labeling of mitochondria, microtubulin, and cytoplasm, time-lapse confocal microscopy imaging confirmed that mitochondria colocalize with microtubules within TNTs and are transported along TNTs from healthy cells to stressed cells [69]. Reproduced with permission from Ref. [69], © Wang, X. et al. 2015. (b) Researchers discovered that the virus induces TNT formation in multiple cell types, including placental trophoblasts. By fluorescently labeling cell nuclei, mitochondria, actin, and viral particles, confocal microscopy captured the generation of intercellular TNTs and mitochondrial transfer. They observed that TNT-mediated mitochondrial transfer serves both as a bridge for infecting neighboring cells and as an energy boost for infected cells [70]. Reproduced with permission from Ref. [70], © Michita, R. T. et al. 2025.

represents a conserved transport mechanism across diverse multicellular organisms [61, 74]. Recent studies indicate that plant cells can transfer chloroplasts through intercellular conduits or plasmodesmata-like structures, facilitating genomic dissemination [24]. Researchers have observed significant horizontal gene transfer phenomena within certain grafted or symbiotic plants. These processes allow different cell types to select suitable phenotypes and respond to external environmental stimuli.

Mounting evidence indicates that cells can internalize extracellular debris and minute cellular structures through endocytosis (Fig. 3) [75–77]. Researchers discovered that sea slugs can perform photosynthesis by isolating chloroplasts from algae and completing their internalization [30, 31]. Furthermore, in various cell types, it has been observed that cells can process and ingest internalized dysfunctional or intact organelles through vesicles or exosome structures formed by endocytosis and exocytosis [78–85]. These experiments confirm that this extracellular environment-dependent uptake mechanism enables organelles to migrate long distances within multicellular organisms [82, 86].

Another method of intercellular organelle transfer relies on gap junctions, which are formed by transmembrane proteins that create pores in the cell membrane (Fig. 4) [23, 87, 88]. When donor and recipient cells dock, these channels polymerize to create openings between cells, facilitating the transfer of substances and organelles [89, 90]. Due to the distinct nature of this coupling mechanism, different studies have employed vastly divergent terminology to describe it. This paper adopts the simplest designation, gap junctions (GJs), to ensure this gap junction protein-based pathway can be applied across cells and species. Recent studies indicate that cells can exchange information directly through gap junctions when participating in the transfer of mitochondria and chloroplasts [24, 91, 92]. This article demonstrates that organelles can undergo connection, internalization, and release processes via the Cx43 protein between human mesenchymal stem cells and certain cells [92–94]. In plants, openings in cell walls and membranes enable intercellular tissue fusion, forming a cytoplasmic connection that spans the cell wall [24]. This connection increases the likelihood that plastids will move from one cell to another through these pores.

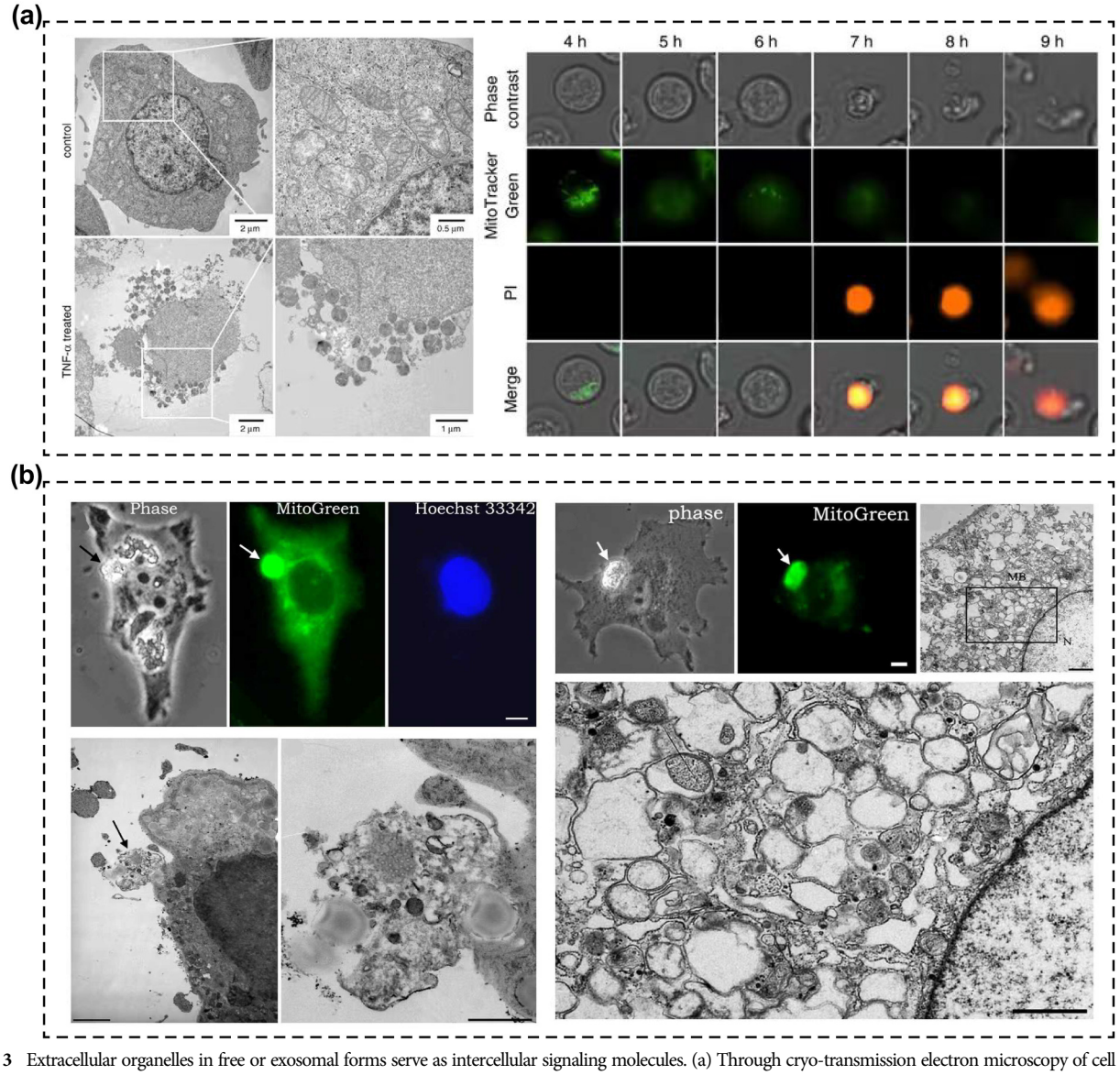


Figure 3 Extracellular organelles in free or exosomal forms serve as intercellular signaling molecules. (a) Through cryo-transmission electron microscopy of cell sections stained with actin, research has found that intact mitochondria are released from dead cells and serve as danger signals between cells. Simultaneously, primary human macrophages and dendritic cells phagocytose mitochondria derived from dead cells, regulating cytokine secretion by macrophages and inducing dendritic cell maturation [75]. Reproduced with permission from Ref. [75], © Maeda, A. et al. 2014. (b) When stimulated, cells release vesicles containing organelles. For example, researchers have discovered that cells release mitochondrial apoptosomes, discharging them outside the cell via "vesicular protrusions" using fluorescence staining and cryo-transmission electron microscopy [77]. Reproduced with permission from Ref. [77], © Elsevier B.V. All rights reserved 2008.

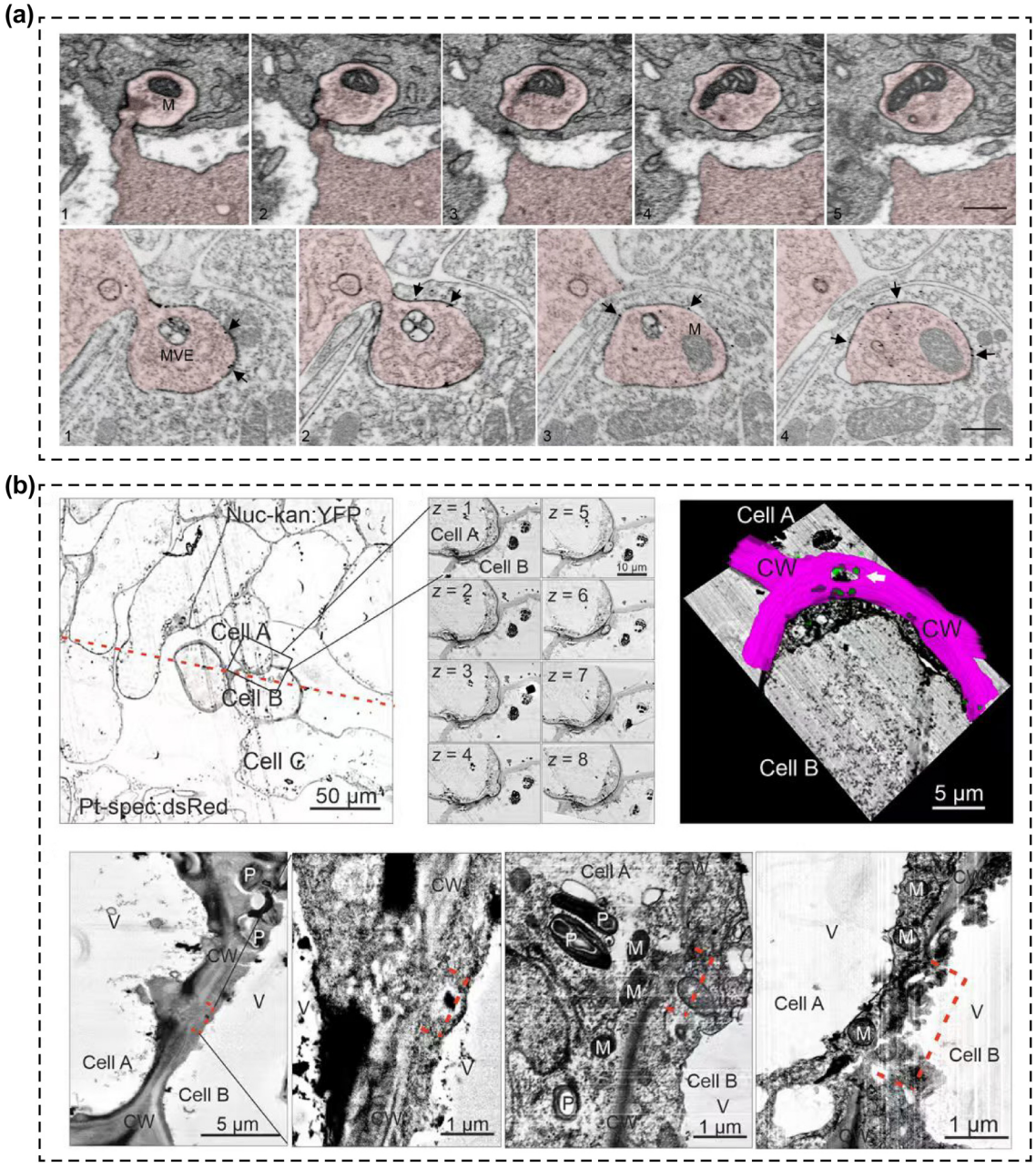


Figure 4 Intercellular organelle transfer occurs through the formation of gap junctions. (a) Existing research has revealed that the gap junctions protein connexin 43 (Cx43) is essential for mitochondrial transfer. Transmission electron microscopy (TEM) revealed that intercellular junctions or ring-shaped gap junctions form, ultimately integrating the entire organelle into a double-membrane vesicle to achieve organelle transfer [23]. Reproduced with permission from Ref. [23], © John Wiley & Sons A/S. Published by John Wiley & Sons Ltd. 2021. (b) Using TEM for 3D layer-by-layer scanning, it was discovered that protein polymer channels spanning cell walls form between plant cells (such as within callus complexes formed after grafting), mediating intercellular chloroplast transfer and ultimately enabling gene-level transfer [24]. Reproduced with permission from Ref. [24], © Hertle, A. P. et al. some rights reserved; exclusive licensee American Association for the Advancement of Science 2021.

Overall, existing research has elucidated multiple pathways and structural foundations for intercellular organelle transfer [86]. These include TNTs [95, 96], EVs [26, 97–101], endocytosis [24, 91, 92], as well as gap junction intercellular communication (GJIC) structures [23, 87, 88]. These pathways help researchers better decipher cellular life activities and deepen their understanding of intercellular interactions and communication within multicellular organisms.

2.2 Factors inducing organelle transfer

In recent years, significant attention has been given to the spontaneous secretion and transfer of organelles within cells, as well as their horizontal transport [20]. Analysis of the underlying mechanisms has revealed that cells can respond to diverse external signals, recognize ionic conditions within their microenvironment, comprehend their own cellular requirements, and ultimately initiate intracellular transport processes [15, 38, 102, 103]. As pathways involving extracellular vesicles, nanotubes, and gap junction intercellular communication structures have been elucidated, mounting evidence suggests that this localized or long-distance organelle transfer is a spontaneous, self-protective, or defensive process for cells (Fig. 5, Table 1).

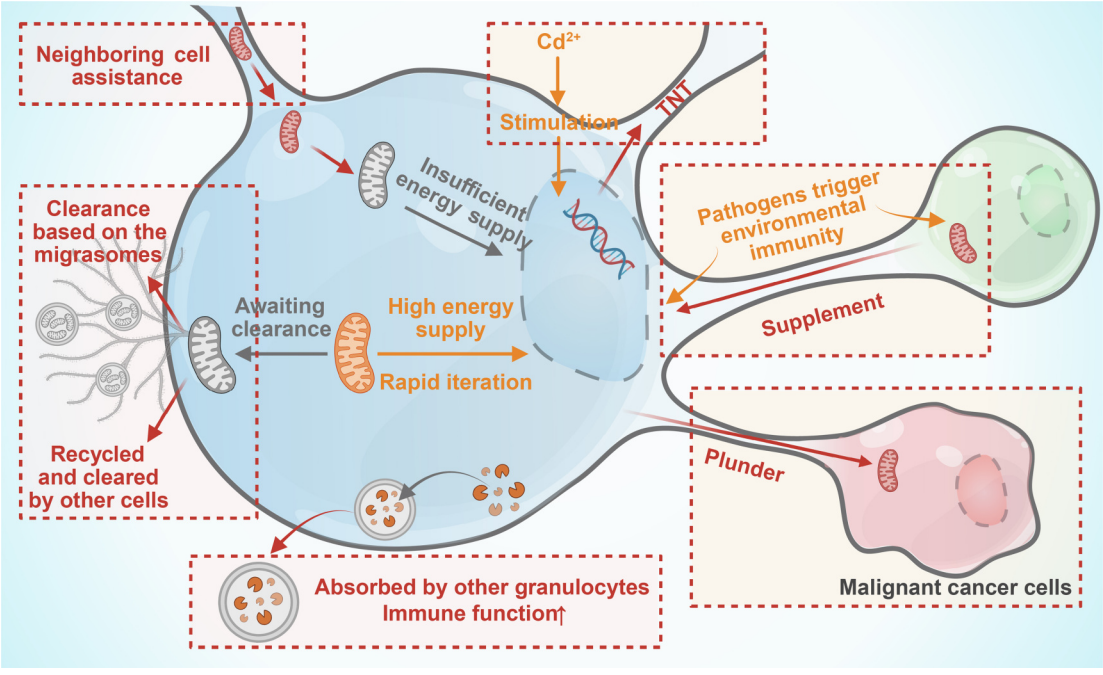


Figure 5 Intrinsic and extrinsic factors regulating organelle transfer and exchange. During life processes, cells respond to intrinsic and extrinsic stimuli to complete organelle transfer. When energy is depleted or urgent functions arise, cells actively form nanotubes to replenish mitochondria. During rapid migration or high-power cell proliferation, mitochondrial structures may become damaged, prompting cells to spontaneously expel organelles for processing and clearance by other cells. During endotoxin stress, cells utilize lysosomes to encapsulate waste and actively deliver it to immune cells for immune responses. Under external stress, organelle transfer often occurs passively—for instance, heavy metal stress triggers nanotube formation and prepares for organelle transfer. Stronger external stimuli like hyperimmunity simultaneously affect multiple cells, forming cellular networks that enable organelle sharing and assist immune functions. Within the tumor microenvironment, immune cells and neural cells can be hijacked by cancer cells, with organelles being appropriated by the tumor.

Cells possess multiple rapid and efficient regulatory mechanisms to assist in fulfilling their predetermined life processes [97, 104, 105]. Once a cell detects deficiencies or surpluses of functional components, it initiates organelle transfer processes [97, 101]. For example, when a cell identifies insufficient foundational proteins in its internal energy supply or drug resistance mechanisms, it releases microtubule structures into the surrounding environment and forms connections with donor cells [106–108]. High-energy-consuming tumor cells within a cellular population have been considered, as their internal energy supply is often insufficient to sustain their relentless migration and proliferation [109, 110]. Consequently, tumor cells establish organelle transfer networks with immune cells [110], neurons [27], epithelial cells [111], and others [109, 112, 113]. Through this process, tumor cells absorb appropriate mitochondria from neighboring cells, thereby aiding their own migration, infiltration, and metastasis. Conversely, when a cell detects dysfunction in its organelles, it expels the impaired organelles into the extracellular environment through exocytosis or the formation of exosomes. Studies have also shown that cells eliminate impaired mitochondria through mitocytosis when they undergo stress or experience mitochondrial mutations or damage due to high-intensity energy metabolism. Mitocytosis is a process mediated by exocytosis, exosomes, and migrasomes. This self-regulatory function, in which cells autonomously remove dysfunctional components to maintain organelle quality control and renewal, contributes to an extended cellular lifespan [26, 114, 115].

In addition to initiating pathways for spontaneous organelle migration within cells in response to sudden environmental changes or stress, cells form communication structures with neighboring cells to seek external assistance and collectively defend against environmental threats [116–118]. In the field of tissue repair, stem cells can rapidly prepare for differentiation by transferring organelles to cells with specific differentiation pathways [86, 119, 120]. Furthermore, cell types susceptible to external stimuli, such as epithelial and muscle cells, often form long-lasting, stable organelle transfer networks [121–124]. These networks allow damaged cells to repair themselves before necrosis occurs, thus minimizing the impact on surrounding cells. However, this organelle transfer in response to external threats is equally prevalent in infections [125, 126] and tumor microenvironments [127, 128], which exacerbates the development of drug resistance. Nevertheless, this process is not insurmountable; immune cells in multicellular organisms also use intercellular organelle transfer to enhance their functions [129, 130]. Research shows that immune cells can restore or enhance their immune activation and phagocytic capabilities by acquiring exogenous or free organelles, such as mitochondria or lysosomes [127, 131, 132]. This allows for the rapid infiltration of affected areas and the successful completion of immune functions.

In general, intercellular organelle migration depends on a cell's signaling responses. It is initiated by internal physiological regulation and survival needs, as well as by responding to extracellular environmental stresses and adapting to external conditions [26, 29, 37, 101, 114, 127, 133]. This process not only helps cells perform their functions efficiently, supports internal quality control, and extends cell lifespan, but also plays a dual role in disease progression, drug resistance development, and immune failure.

2.3 Research on types of intercellular organelle transfer

As early as the beginning of the 21st century, American Physiological Society collaborative research had estimated and

Table 1 Intrinsic and extrinsic factors regulating organelle transfer and exchange[a]

Classification of transfer causes	Transfer of causation	Types of organelles	Biological mechanism	Ref.
Internal factors	Insufficient energy supply	Mitochondria	Donor mitochondrial transfer provides a potential mechanism for exogenous replacement of dysfunctional mitochondria in stressed recipient osteoblasts, thereby rescuing the recipient osteoblasts.	[133]
	Endotoxin injury	Mitochondria	When mitochondria are damaged by endotoxin, mesenchymal stem cells injected into the trachea successfully transfer mitochondria to pulmonary alveolar epithelial cells in the lungs.	[101]
	Mitochondrial dysfunction	Mitochondria	Acquiring functional mitochondria increases mitochondrial mass and enhances metabolic health in T cells.	[127]
	Organelle quality control	Mitochondria	Neurons can release damaged mitochondria and transfer them to astrocytes for processing and recycling.	[26]
	Organelle quality control	Mitochondria	The crucial role of intercellular mitochondrial transfer in mitochondrial quality control	[115]
	Organelle quality control	Mitochondria	Mitochondrial quality control processes mediated by migrans	[114]
	Removal of intracellular debris	Lysosomes/ endosomes	Nanoplastics (NPs) are internalized by granulocytes in green mussels (Perna viridis), transferred to new blood cells (primarily granulocytes) via lysosomes and endosomes, respectively, subsequently enhancing phagocytic activity and promoting immune responses.	[132]
	Genome-level transmission	Chloroplasts	Plant genomes undergo horizontal transfer via intercellular transfer through chloroplasts.	[24]
Exogenous stimulus	Synergistic completion of angiogenesis	Mitochondria	Under cellular stress, MSCs transfer mitochondria to ECs via tunnel nanotubes, and blocking this transfer impairs EC implantation.	[29]
	Toxin stress or heavy metal stimulation	Mitochondria	When cells are under stress, TNTs serve as critical structures for transferring cellular contents or energy from damaged cells to others.	[37]
	Acute injury	Mitochondria	BMSCs prevent ALI by restoring alveolar bioenergetics through Cx43-dependent alveolar adhesion and mitochondrial transfer.	[101]
	Inflammatory cascade stress	Mitochondria	Mesenchymal stem cells support macrophage immune homeostasis via mitochondrial transfer, restoring male fertility and testosterone production in an ischemic-reperfusion injury mouse model.	[230]
	Stem cell responsive differentiation	Mitochondria	Macrophages promote MSC osteogenic differentiation by transferring mitochondria to MSCs.	[231]
	Tissue injury/tissue regeneration requirements	Mitochondria	Intercellular mitochondrial transfer as a means of tissue revitalization	[86]
	Tumor cell hijacking	Mitochondria	Cancer cells receiving mitochondria from primary tumor neurons exhibit enhanced metastatic capacity; the nervous system supports cancer metabolism and metastatic dissemination.	[27]

[a]BMSCs: bone marrow-derived mesenchymal stem cells; ALI: acute lung injury.

categorized the potential types of organelles that could be transferred [25]. Building on nearly two decades of advances in organelle transfers, like migration, uptake, and secretion, this subsection aims to provide a comprehensive classification of organelles capable of intercellular transfer. Of the various models and variants of intercellular organelle transfer that have been described, researchers have determined that organelles that supply energy (e.g., mitochondria and chloroplasts) [28–31], endomembrane organelles (e.g., the endoplasmic reticulum and the Golgi apparatus) [37, 38, 134], and organelles that degrade or digest (e.g., lysosomes and melanosomes) [34, 35] can all undergo cross-cell transfer (Table 2).

2.3.1 *Energy-supplying organelles*

Mitochondria are the most thoroughly characterized organelles in terms of mechanism elucidation, application, and medical translation because they are a hotspot in intercellular organelle transfer research [21, 86, 127, 135, 136]. In living organisms, they perform several functions, including supplying energy and regulating intracellular redox processes [86, 137–139]. Consequently, this highly metabolic organelle is particularly susceptible to damage. Research indicates that significant mitochondrial transfer occurs between co-incubated cells when cells experience mitochondrial dysfunction [29]. This migration has been widely observed in stem cells, cardiovascular cells, and neurons [27, 29, 137]. Previous studies have demonstrated unidirectional mitochondrial transfer between cardiomyocytes and adipose-derived pluripotent stem cells [124, 138, 140, 141]. Conversely, mitochondrial transfer between renal tubular cells and mesenchymal stem cells is bidirectional [142, 143]. Through co-culture experiments with various cell types, researchers have observed that, under physiological conditions, mitochondrial transfer helps maintain tissue stability while promoting development and repair [86]. Meanwhile, mitochondrial transfer can also serve as an indicator of disease progression or diagnosis. Within the nervous system, fluctuating levels of mitochondrial transfer may contribute to the development of Alzheimer's and Parkinson's diseases [144–146]. In cardiovascular and cerebrovascular contexts, the presence of mitochondrial transfer can serve as an indicator of myocardial injury, myocardial

infarction, hypertension, and hypoxia-induced damage [93, 147–151]. In respiratory infections, skeletal muscle conditions such as chondrodystrophy and rheumatoid arthritis, and atypical disease models like myoclonic epilepsy and respiratory alkalosis, mitochondrial vitality indicators and transfer probabilities are being extensively explored as potential therapeutic strategies [86, 152, 153].

Another type of intracellular energy organelle that is unique to plants is the chloroplast and its derived vesicles. Research indicates that grafting and symbiotic relationships in plants can facilitate interspecific transfer at the proteome, RNome, and DNA levels [24, 154]. By investigating DNA transfer pathways, researchers discovered that distinct filamentous structures form between cells of different plant species during callus tissue formation. After labeling chloroplasts from two plant species, researchers observed that heterologous chloroplasts are transferred to neighboring cells via plasmodesmata, a mode of transport facilitated by cell wall pores.

Table 2 Published reports of intercellular organelle transfer[a]

Classification of organelles	Organelle cargo	From (donor cell type)	To (recipient cell type)	Biological mechanisms	Ref.
Energy-supplying organelles	Chloroplasts	Halimeda borneensis	Plakobranchus ocellatus	Chloroplast acquisition without the gene transfer in kleptoplastic sea slugs, Plakobranchus ocellatus	[31]
		Food algae	Sacoglossan sea slugs	Sacoglossan sea slugs puncture the cell wall of food algae to suck out the protoplasm. The chloroplasts in the protoplasm are transported to the sea slug's intestinal tract, and the sequestered chloroplasts (kleptoplasts) maintain the photosynthetic activity in the cell for days to months.	[30]
		dsRed-Sterile tobacco	YFP-Sterile tobacco	Chloroplasts achieve intercellular transfer of entire organelles and genomic-level transfer through intercellular connections between plant cells.	[115]
	Mitochondria	MSCs	ECs	During cell transplantation, perivascular MSCs transiently transferred mitochondria to neighbouring ECs through TNTs, enhancing their bioenergetics and overall fitness, and particularly their engraftment ability.	[29]
		MC-38/B16F10/MCF7/MDA-MB-231/Jurkat	Tumor-infiltrating lymphocytes (TIL)	Mitochondria with mitochondrial DNA mutations transferred from cancer cells to T cells in the tumor microenvironment (TME) cause T cell dysfunction.	[28]
		Neural stem cells (NSC)	Mouse mammary carcinoma cells (4T1)	Cancer-associated neurons enhance cancer metabolic plasticity by transferring mitochondria to cancer cells.	[27]
		Rat/mouse astrocytes	Rat/Mouse primary neurons	Astrocytes in mice can also release functional mitochondria into neurons, contributing to endogenous neuroprotection and neuroregeneration mechanisms after stroke.	[27]
		Adipocytes	Macrophages	Adipocytes transfer mitochondria to macrophages in white and brown adipose tissue to maintain metabolic homeostasis.	[177]
		Adipocytes	Macrophages	Intercellular mitochondrial transfer to macrophages regulates white adipose tissue homeostasis and is impaired in obesity.	[138]
		Astrocytes	Glioblastoma cells	GAP43-mediated transfer of functional mitochondria from astrocytes to glioblastoma cells induces tumor-growth-promoting metabolic, signaling, and epigenetic reprogramming.	[178]
		Bone marrow stromal cells	Leukemia blast cells	Autotrophy recovery decreased extracellular lactate production, increased ATP, mitochondrial membrane potential, and O_2 consumption.	[232]
		In vivo TME	Melanoma and mammary carcinoma cells	Autotrophic recovery	[97]
		BM or LT or BAU-MSCs	Bronchial epithelial cells	Restoration of respiratory capacity and tumorigenic potential	[233]
		Osteoblast dendritic networks	Primary mouse bone cells	N.D.	[133]
		MSCs	Mitochondrial DNA mutation GM10742 cells	ER-mediated intercellular mitochondrial transfer within osteoblast dendritic networks influences the balance between bone resorption and formation through communication with osteoblasts and osteoclasts.	[234]
		Stromal lineage cells (SLCs)	Macrophages	EV-Mito released by mesenchymal stem cells (MSCs) creates super-donors by enhancing mitochondrial transfer. Super-EV-Mito rescues mitochondrial DNA defects in LHON male mice and alleviates LHON-related symptoms. SLC rapidly senses injury signals and establishes connections with resident macrophages via nanotubes, transferring mitochondria from SLC to neighboring activated macrophages through nanotubes.	[230]

(Continued)

Classification of organelles	Organelle cargo	From (donor cell type)	To (recipient cell type)	Biological mechanisms	Ref.
Endomembrane organelles	Endosomes	Rat pheochromocytoma cell	Rat pheochromocytoma cell	The concept of tunnel nanotubes is proposed for the first time, and it is discovered that tunnel nanotubes facilitate the transfer of membrane vesicles and organelles.	[15]
		Rat kidney cell	Rat kidney cell	It was discovered that intercellular endocytic organelles exchange frequently and continuously through tunneling nanotubes via a myosin-dependent mechanism.	[103]
		Human macrophage	Human macrophage	HIV-1 hijacks macrophage endocytosis and cytoskeletal mechanisms to achieve high-speed intercellular endosomal transport.	[134]
	Golgi/ER	Rat hippocampal astrocyte	Rat hippocampal astrocyte	It can mediate diverse organelle transfers in rat hippocampal astrocytes and neurons.	[37]
		Human macrophage	Human macrophage	Viruses hijack the endoplasmic reticulum and Golgi apparatus within cells to accomplish intercellular delivery.	[38]
		Rat hippocampal astrocyte	Rat hippocampal astrocyte	Multiple organelle transfers mediated in rat hippocampal astrocytes and neurons.	[37]
		Rat pheochromocytoma cell	Rat pheochromocytoma cell	Transfer of lysosomes as cargo through intercellular nanotubes	[15]
		Mouse neuronal CAD cell	Mouse neuronal CAD cell	Prion hijacking and TNT-mediated intercellular transfer enables retrograde transport of prions into the central nervous system.	[36]
Degradation-associated organelles	Lysosomes	Rat ventricular cardiomyocyte	Rat fibroblast	Long-distance intercellular connections between cardiomyocytes and cardiac fibroblasts mediated by membrane nanotubes	[35]
		Rat ventricular cardiomyocyte	Rat ventricular cardiomyocyte		
		Rat fibroblast	Rat ventricular cardiomyocyte		
		Rat fibroblast	Rat fibroblast		
	Melanosome	Chicken embryo skin melanocyte	Keratinocytes	GFP-melanocytes release membrane vesicles, each containing a single (not multiple) melanosome, which are ultimately incorporated into keratinocytes.	[34]
		Human melanocyte	Human keratinocyte	Melanocyte-specific, lysosome-associated organelles (melanosomes) transfer from melanocytes to keratinocytes to protect skin from harmful ultraviolet radiation (UVR).	[33]
		Human keratinocyte	Human keratinocyte		
		Mouse melanocyte	Mouse keratinocyte	Mammalian pigmentation is driven by the intercellular transfer of pigment-containing melanosomes from the apical dendrites of melanocytes to surrounding keratinocytes.	[211]
Other types of organelles	Lipid droplets	AML12 cells	AML12 cells	Cd promotes lipid droplet transfer between hepatocytes. TNTs and molecular motors cooperate to achieve the intercellular transfer of lipid droplets.	[40]
		Human microvascular endothelial cells (HMEC-1)	Human microvascular endothelial cells (HMEC-1)	For the first time, it has been demonstrated that tunnel nanotubes in endothelial cells contain not only lysosomes and mitochondria, but also lipid droplets.	[39]

[a]YFP: yellow fluorescent protein; GAP43: growth-associated protein 43; N.D.: not detected; ER: endoplasmic reticulum; LHON: Leber hereditary optic neuropathy; HIV-1: human immunodeficiency virus type 1; CAD cell: cis-acting anti-repression sequence deficient cell; GFP: green fluorescent protein.

This interplant organelle transfer ensures not only the resistance developed within the callus population, but also plant hormone synthesis within the callus region, ultimately enabling wound healing.

In summary, the section presents research findings demonstrating that the unidirectional or bidirectional transfer of energy-supplying organelles between animals and plants has become a crucial link in intercellular signaling and material exchange (Fig. 6) [21, 24, 127]. This transfer process bridges donor and recipient cells, ultimately enabling energy mutualism, gene-level transfer, and even self-regulation of the life cycle. This process may serve as the primary mechanism for interspecies transmission of non-nuclear DNA in these two multicellular organisms. Analyzing the intercellular transfer of energy-related organelles can provide potential targets and regulatory strategies for studying the control of intercellular energy transfer, including energy complementation and enhanced energy predation.

2.3.2 *Endomembrane organelles*

Endosomes are the primary group of single-membrane organelles within cells. They play crucial roles in protein synthesis, processing, material transport, and spatial localization [155–157]. To secrete or transfer proteins from the cell interior to the plasma membrane, endosomal organelles generate a series of membrane-bound organelles with dynamic membranes. These membrane vesicles, the endoplasmic reticulum, and the Golgi apparatus consistently function as core components that regulate intracellular protein

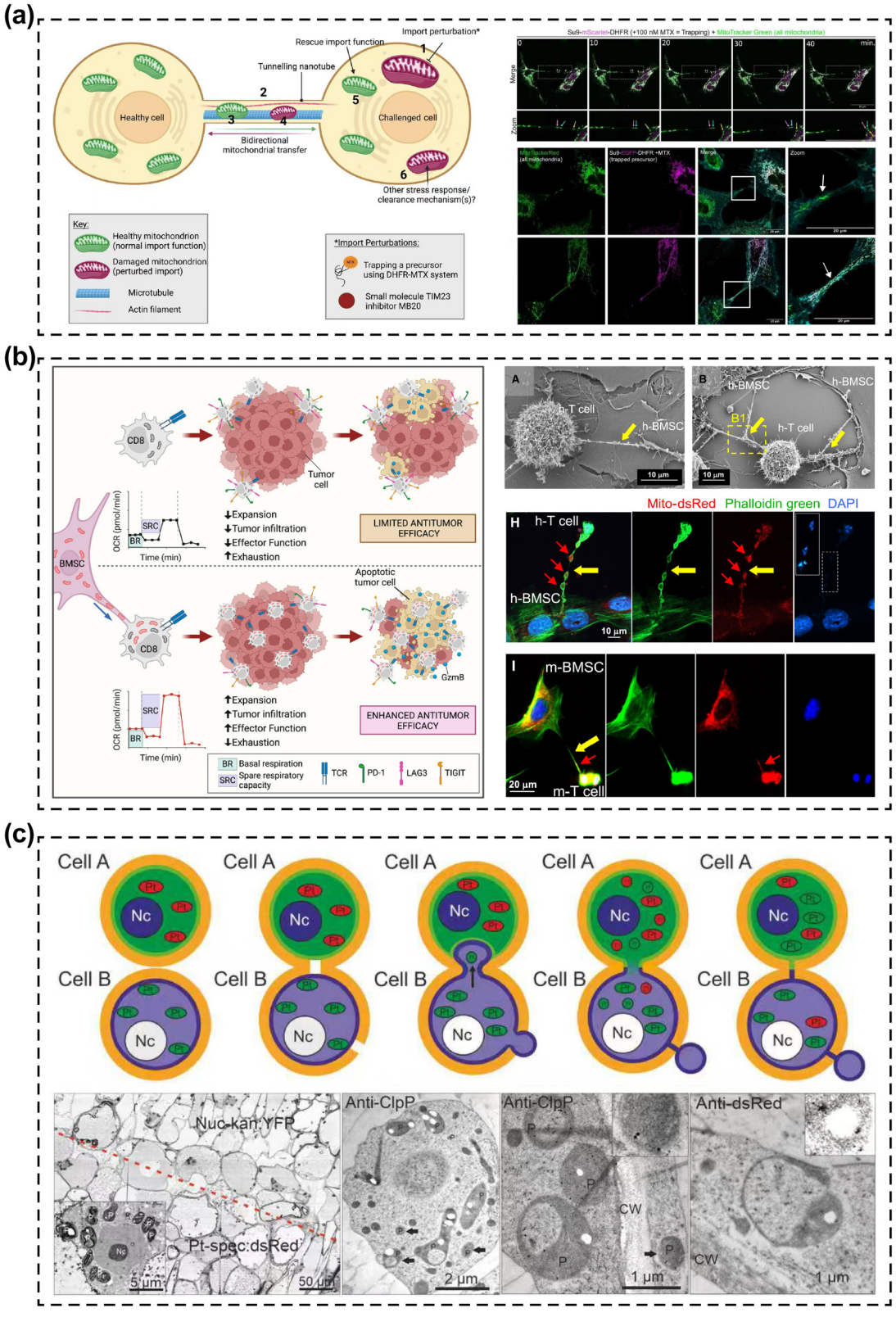


Figure 6 Energy-supplying organelles serve as a vital component in intercellular transfer. (a) As a hot topic in intercellular organelle transfer, researchers have discovered through fluorescence co-localization techniques that cells transport mitochondria through tunneling nanotubes to import healthy mitochondria while discarding those blocked at import sites [21]. Reproduced with permission from Ref. [21], © Needs, H. I. et al. 2024. (b) SEM and fluorescence visualization revealed that intercellular mitochondrial transfer mediated by nanotubes enhances T-cell metabolic adaptability and antitumor efficacy [127]. Reproduced with permission from Ref. [127], © Baldwin, J. G. et al. Published by Elsevier Inc 2024. (c) By TEM visualization, plant cells can form new intercellular connections—pores—through localized breakdown of cell walls, enabling chloroplast transfer and gene-level transfers [24]. Reproduced with permission from Ref. [24], © Hertle, A. P. et al. some rights reserved; exclusive licensee American Association for the Advancement of Science 2021.

pathways [158]. Recent research on viral transmission and disease progression has revealed that certain viruses can hijack host cell organelles, such as the endoplasmic reticulum and the Golgi apparatus, to execute infection strategies via intercellular nanotubes [37, 38]. Furthermore, endosomal vesicles contain various active compounds, including proteins and enzymes. Intercellular organelle transfer delivers these vesicles through TNT conduits to adjacent cells, inducing or activating signaling responses in neighboring cells and achieving paracrine regulation. Studies have demonstrated that labeling target fluorescent proteins in astrocytes allows one to quantify the transfer rates of the endoplasmic reticulum, the Golgi apparatus, and endosomes within TNT tubes between glial cells [15, 37, 103, 134]. In glial cells and neurons, for example, cytotoxic particles such as Aβ can hijack lipid membrane vesicles or organelles through TNT and transfer them to another cell. This occurs particularly in astrocytes or rat neurons, where these particles accumulate excessively [37]. Overall, cells can activate, interpret, and enhance their resistance to signals from neighboring cells by transferring membrane-bound organelles, such as the Golgi apparatus or the endoplasmic reticulum (Fig. 7) [37, 72]. Following viral infection, these organelles can also serve as camouflage to facilitate cross-cell infection. Therefore, elucidating such organelle transfer mechanisms aids in the study of co-infection drugs and the mechanisms underlying intercellular protein transfer.

2.3.3 *Degradation-associated organelles*

Within cells, organelles such as lysosomes and their derivative units use pathways like ubiquitination and phosphatase hydrolysis to break down proteins inside the cell, which regulates the rate of enzymatic reactions [15, 35, 36]. Lysosomes are highly dynamic organelles that primarily rely on diffusion for their intracellular movement. However, cell-to-cell interactions can facilitate lysosomal transport along microfilaments and microtubules via adenosine triphosphate (ATP) and motor proteins such as dynein. Research has revealed that, within TNT networks formed between endothelial progenitor cells, lysosomes can be found transferring to stressed human umbilical vein endothelial cells (HUVECs) [159]. This process relocates activated lysosomes to stressed cells, rebuilding the lysosomal pool within them and enhancing endothelial cell viability [160]. Concurrently, the transfer process enables the recipient cells to rapidly clear damaged organelles by leveraging the lysosomal contents, kinases, and proteases involved in the transport. Similar organelle transfer mechanisms are also observed in oligodendrocyte precursor cells (OPCs) in Alzheimer's disease models [161]. In these models, OPCs interact directly with neuronal systems to regulate lysosomal exocytosis in neurons. This process enhances the potential for neuronal repair and contributes to the prevention of neural damage and pathological progression.

On the other hand, nanotubes facilitate the transfer of melanosomes when cells process excess intracellular materials. Research indicates that, within the adhesion space between melanocyte dendrites and keratinocytes, the latter phagocytose extracellular vesicles formed at the tips of the former's dendrites, ultimately completing melanosome transfer [33]. Additionally, synaptosomal protein aggregates associated with lysosomes undergo unidirectional transfer from neurons to microglia, contributing to disease onset. External stimuli can also induce lysosomal translocation within cells. Studies show that H9c2 myoblasts can internalize quantum dot-labeled exogenous markers into lysosomes and secrete them extracellularly and simultaneously [162].

Overall, lysosomes—as the primary intracellular organelles for hydrolysis and metabolism—facilitate enhanced resistance to injury and extended lifespan in recipient cells through intercellular transfer (Fig. 8) [32, 36, 160]. They perform crucial repair and protective functions in hematopoietic stem cells, neural cells, and epithelial cells. Research on intercellular degradation-associated organelles directly impacts cellular protein homeostasis and functional expression, providing regulatory targets for intercellular protein differential analysis, drug resistance in diseases, and signaling factor transmission.

2.3.4 *Other types of organelles*

Another type of organelle associated with intracellular material storage is the lipid storage compartment, or lipid droplet. These droplets serve as cellular lipid reservoirs and centers for lipid synthesis and protein storage. The number and persistence of lipid droplets are closely linked to pathological conditions such as inflammation and hypoxia. In endothelial cells, the number of lipid droplets increases during hypoxia, ultimately triggering angiogenesis [163, 164]. Consequently, researchers aim to investigate lipid droplets as reservoirs for signaling lipids and their transport functions. Recent studies reveal that lipid droplets can undergo rapid transfer via cell-to-cell TNT (Fig. 9) [39, 40]. These studies show that lipid droplets act as an emerging cargo within endothelial cells, mediating diverse forms of endothelial cell adhesion and angiogenesis. Researchers characterized the transfer of lipid droplets as bidirectional movement along TNT, a mechanism that facilitates intercellular cytoplasmic streaming. Understanding this intercellular transport of lipid droplets provides new targets for studying lipid signaling and angiogenesis. The transfer of more types of organelles continues to be explored, and as functional factories within cells, organelle transfer still holds immense research potential and value.

3 Organelle transfer influences the "socialization" networks of organisms

Intercellular organelle transfer affects donor cells, recipient cells, and the multicellular microenvironment simultaneously. Therefore, it is helpful to distinguish and classify the effects of organelle transfer based on the affected entities [25]. Since existing research on organelle transfer primarily focuses on mitochondria, this section will categorize recent studies in this field separately (Fig. 10).

3.1 Effects on donor cells

Research on organelle transfer depends on donor cells, from which the organelles originate. In co-culture environments, these cells can donate internal organelles, such as mitochondria. For example, when mesenchymal stem cells (MSCs) are co-cultured with A549 cells and one cell type develops mitochondrial dysfunction, the co-cultured MSCs or fibroblasts can donate their internal mitochondria to restore aerobic respiration [165, 166]. This significantly increases ATP levels and other indicators in the A549 cells. Meanwhile, the donor cells, whether MSCs or fibroblasts, can maintain their own viability while supplying organelles [27, 28]. Most reports indicate that mitochondrial transfer via TNT does not significantly impair the intracellular environment of the donor cells [37, 124, 167, 168]. However, donor cells still exhibit varying degrees of suppression in respiratory and metabolic capacity as exporters [124, 169, 170]. In disease models, such as tumor models,

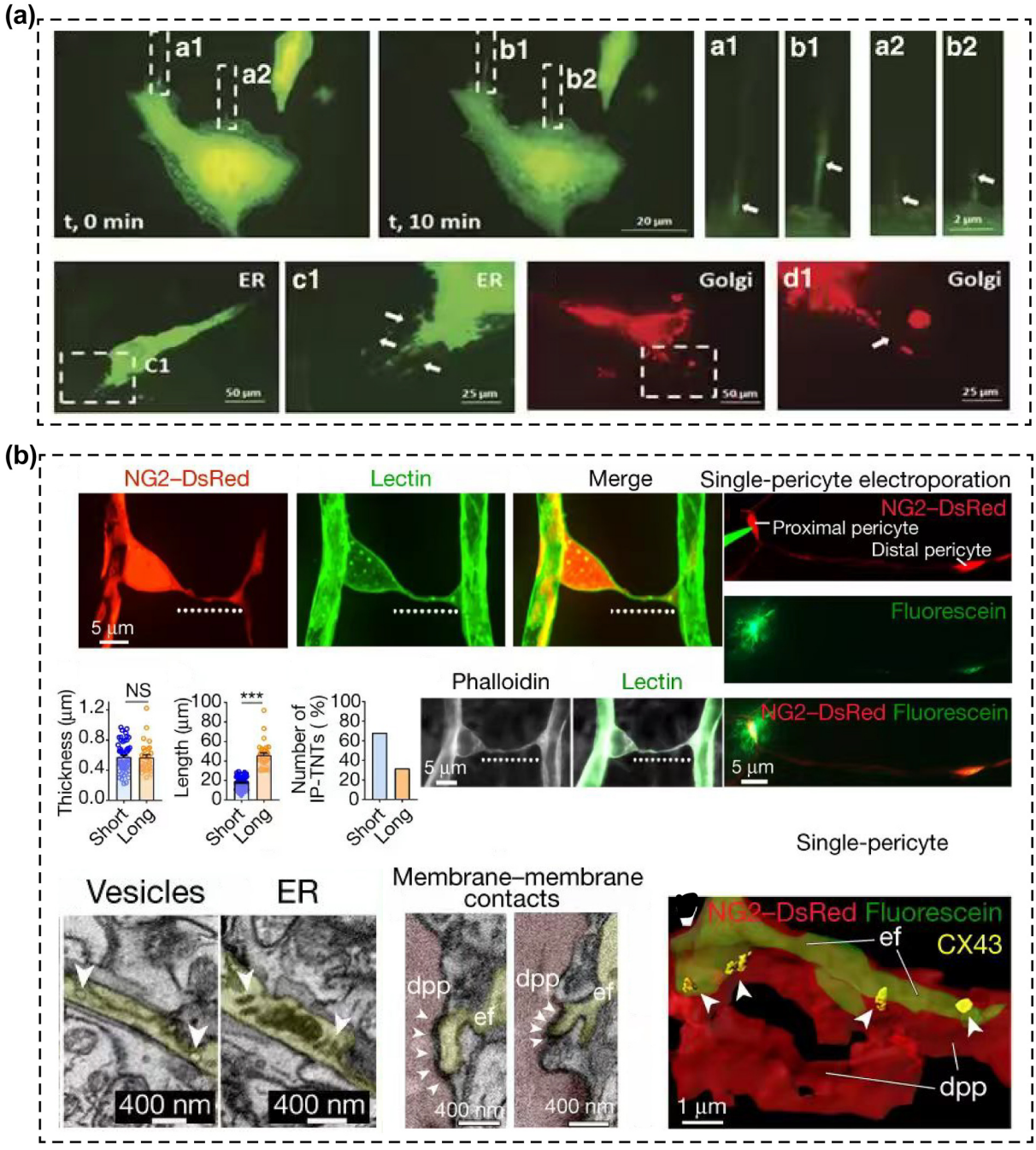


Figure 7 Endomembrane organelles serve as a component of intercellular transport. (a) Researchers discovered through fluorescent labeling that between hippocampal astrocytes and neurons containing H_2O_2, TNTs transfer endoplasmic reticulum, mitochondria, golgi apparatus, and endosomes. This intercellular communication serves as a mechanism for cells to respond to harmful signals and transfer cellular material or energy to another cell [37]. Reproduced with permission from Ref. [37], © Macmillan Publishers Limited 2010. (b) Researchers have utilized fluorescent labeling of the cytoskeleton and various organelles, supplemented by focused ion beam-scanning electron microscope (FIB-SEM)-SEM and higher magnification 3D visualization, to discover interplasmic tunnel nanotubes (IP-TNTs) for the first time, and demonstrated that cytoplasmic components such as vesicles, endoplasmic reticulum, and mitochondria are transportable components via IP-TNTs [72]. Reproduced with permission from Ref. [72], © Alarcon-Martinez, L. et al. under exclusive licence to Springer Nature Limited 2020.

tumor cells hijack mitochondria from nearby immune cells. This renders the donor immune cells [167, 171], such as effector T cells [172, 173], immunologically inactive [60, 113]. This process transforms the T cells into immunodeficient cells without killing them immediately [174]. Similarly, in infection models such as rhabdovirus-infected cells, the virus hijacks the host cell and begins transferring organelles that carry viral genes and proteins. However, this process avoids rapidly killing the donor cell [38]. Instead, it maintains the cell at a low metabolic state, turning it into a persistent transmission node.

Generally, donor cells that donate organelles do not experience short-term impacts on their physiological activities [37, 124, 167–170]. However, in the long term, transferring their organelles places donor cells in a state of energy deficiency or hijacking [124, 175, 176]. According to existing research, the effects of organelle donation and unidirectional organelle transfer originating

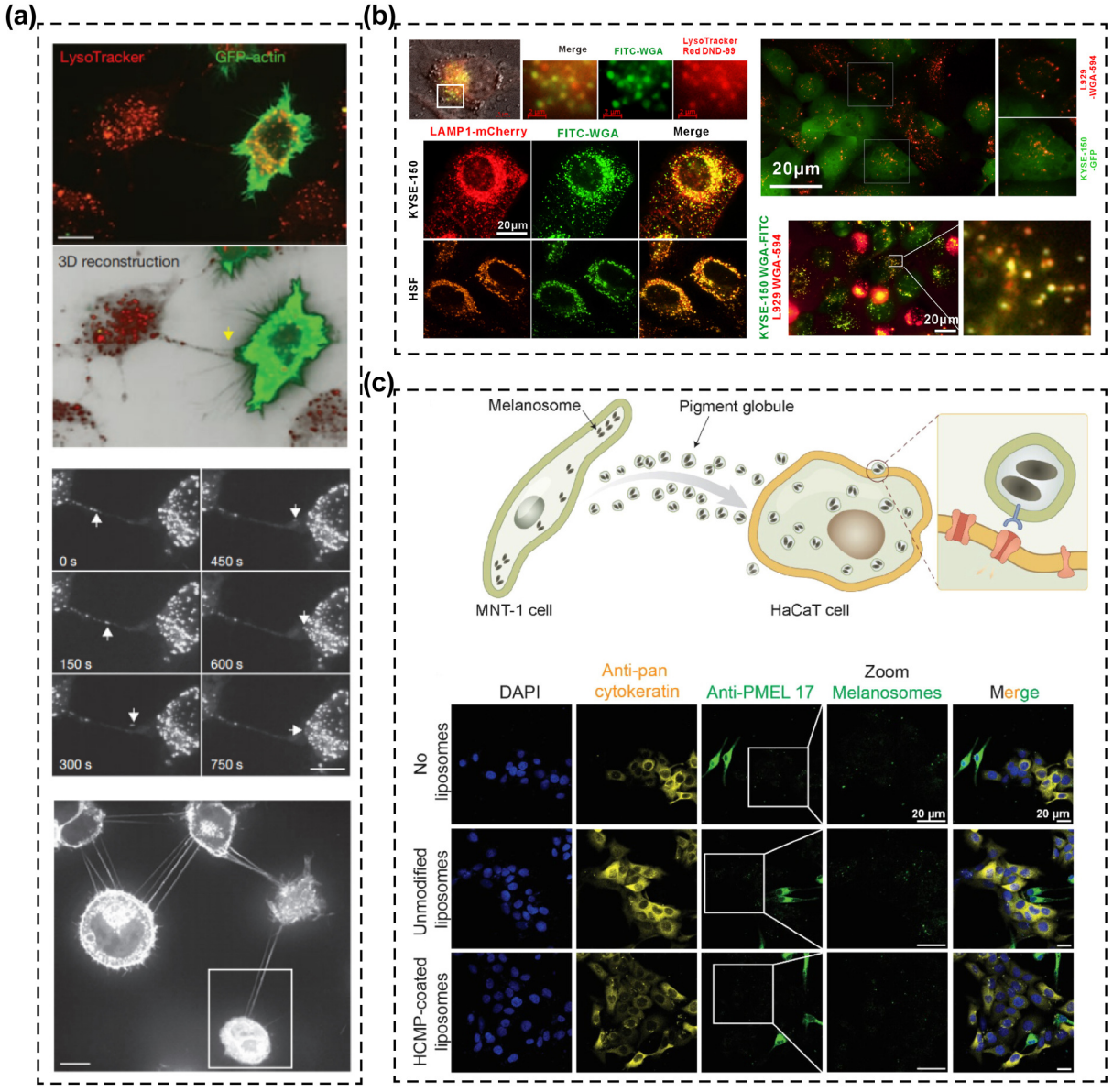


Figure 8 Degradation-associated organelles regulate cellular activities through intercellular crosstalk that demonstrated by fluorescence co-localization. (a) TNTs, the most prevalent intercellular transfer pathway, are membrane-bound tubular tunnels extending from the plasma membrane [36]. Reproduced with permission from Ref. [36], © Springer Nature Limited 2009. (b) EVs formed from the cell membrane represent another pathway for organelle transfer [160]. Reproduced with permission from Ref. [160], © Asian Surgical Association and Taiwan Society of Coloproctology. Publishing services by Elsevier B.Vé 2025. (c) Certain organelles, such as mitochondria, can be secreted into the extracellular environment and internalized by neighboring cells [32]. Reproduced with permission from Ref. [32], © American Chemical Society 2025.

from the donor cell itself exert profound impacts on cellular redox and metabolism [27, 28, 177, 178].

3.2 Effects on receptor cells

Beneficiary cells typically assume the role of being assisted or rescued. Researchers have discovered that organelle transfer not only triggers reprogramming of the recipient cells [26, 79, 80, 83, 97, 177, 179–182]. This is because the recipient cells clear these externally sourced organelles after they fulfill their functional roles. Upon receiving organelles, recipient cells enhance ATP production, reduce lactate output, and improve adaptability to the external environment [183]. This alleviates cellular sensitivity. The impact on the intracellular environment extends beyond organelle function post-transfer and triggers programs that clear and repair damaged units within the recipient cells [175, 184]. Research indicates that, in bone tissue, osteocytes perforate their internal mitochondria into doughnut-shaped structures and transport them as cargo to adjacent damaged areas [184]. Upon receiving these dysfunctional mitochondrial bodies or fragments, the recipient osteocytes activate mitochondrial autophagy. On the one hand, it eliminates damaged mitochondria within the cell [185–188]. On the other hand, it generates new, fully functional endogenous mitochondria, ultimately restoring vital cellular activities [184]. However, transferring organelles is not entirely non-cytotoxic to recipient cells. Due to clearance mechanisms within recipient cells, excessive concentrations of transferred organelles can directly and significantly damage them [186, 189, 190]. Thus, mitochondrial transfer — and indeed, the transfer of various organelles — has a

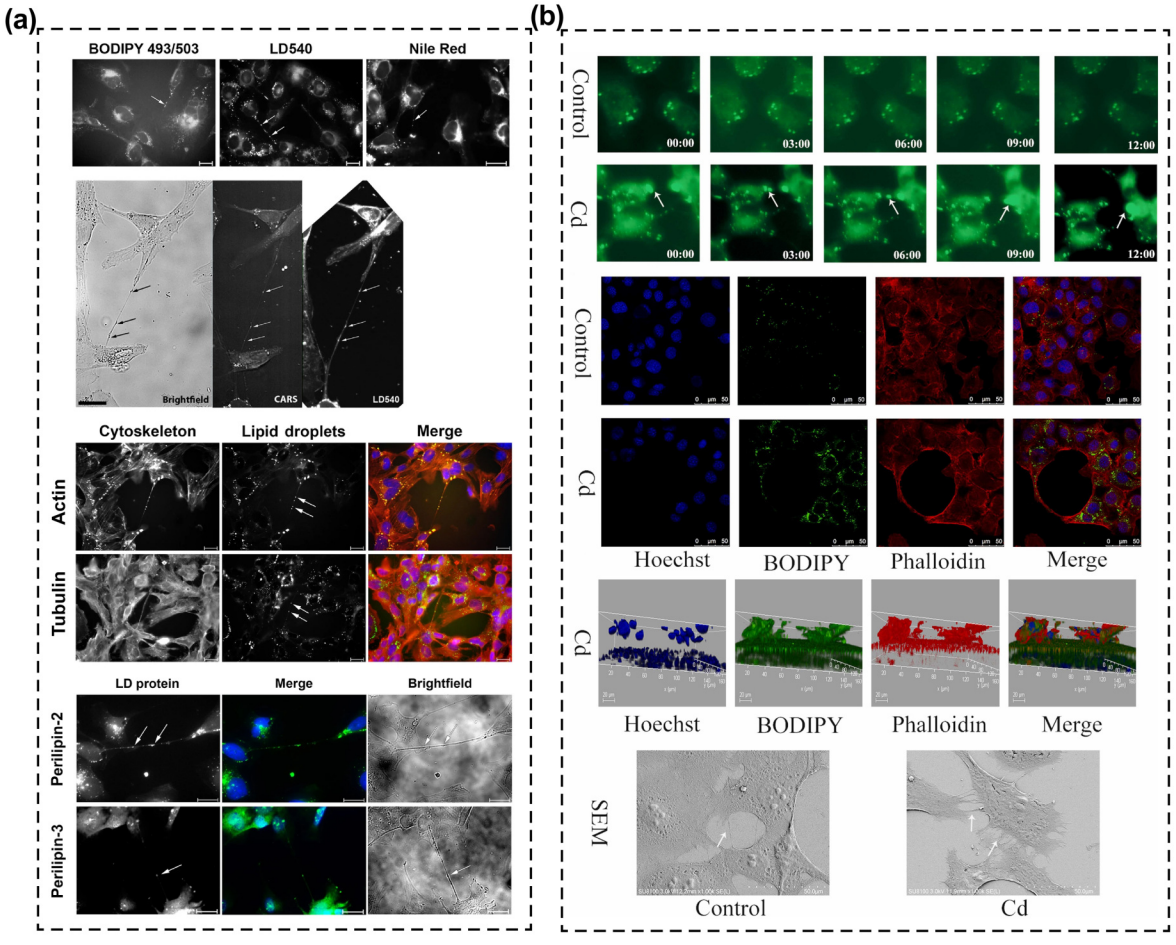


Figure 9 Lipid droplets as novel mediators of organelle transfer between cells. (a) Researchers have demonstrated for the first time that lipid droplets serve as cargo for TNT, thereby revealing a novel mechanism for intercellular communication [39]. Reproduced with permission from Ref. [39], © Astanina, K. et al. 2015. (b) Researchers have demonstrated for the first time that migrating lipid droplets can act as signaling molecules to trigger an inflammatory storm effect, promoting lipid accumulation in surrounding cells [40]. Reproduced with permission from Ref. [40], © Elsevier B.V. All rights reserved 2023. The experiments described in the above article were conducted using fluorescence-labeled organelles and the cytoskeleton.

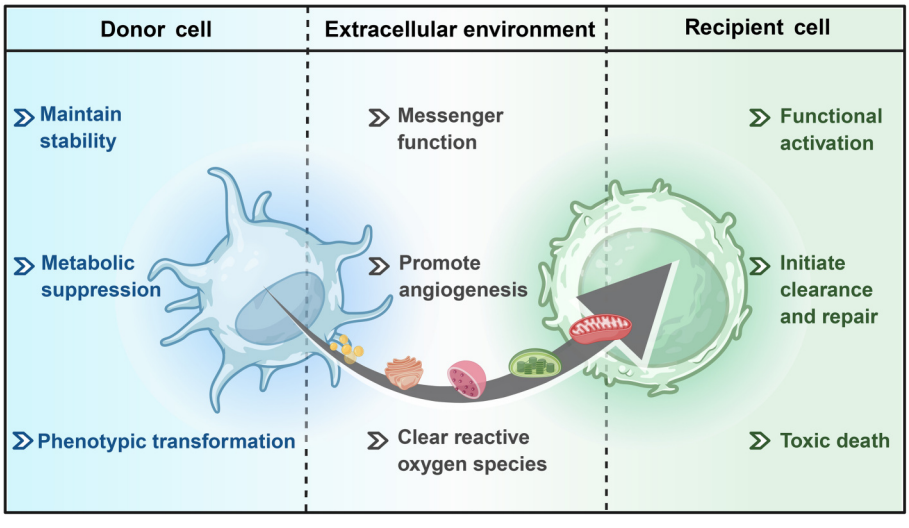


Figure 10 Multilevel profound effects induced by organelle transfer. During transfer, organelles act as signals that influence the homeostasis of donor cells, recipient cells, and the cellular microenvironment. When cells donate or supply organelles, donor cells maintain homeostasis or monitor organelle quality through short-term, spontaneous organelle transfer. However, prolonged organelle supply ultimately leads to phenotypic changes or even cell death. Once released into the extracellular environment, these free or vesicle-borne organelles function as signaling molecules for long-distance transmission. They assist cell colonization, enhance angiogenesis, and even protect cells by metabolizing reactive oxygen species (ROS) via residual enzymes within the microenvironment. Receptor cells, typically beneficiaries of organelle transfer, rapidly activate functions upon organelle acquisition to perform cleanup and repair tasks. Simultaneously, the infusion of heterologous organelles may disrupt cellular homeostasis and inhibit normal physiological functions.

dual effect on the recipient cell environment. For example, during lysosomal transfer, recipient cells that receive excessive lysosomes may develop cystinosis due to high concentrations of cystine crystals within the lysosomes, which can ultimately lead to cell death.

In summary, these observations suggest that organelle transfer between cells influences the internal environment of recipient cells. Unless the transfer involves toxic particles or disguised organelles hijacked by viral infections, recipient cells activate their self-protective mechanisms in response. This ultimately facilitates recovery and enables cells to withstand external stressors and stimuli.

3.3 Effects on the extracellular environment of multicellular groups

Unlike *in vitro*, cells within living organisms do not exist in a 2D culture space. Rather, they survive and function within the microspaces formed by cell-to-cell connections [76]. Furthermore, due to the non-totipotent nature of differentiated cells, cellular life activities are contingent on interactions among multiple cells. It can be posited that all the tissues in a multicellular animal body exist in a "socialization" form, utilizing biomolecules such as cytokines and signaling molecules to communicate with each other. This signaling exchange is contingent upon the cell's active uptake capacity for substances in the extracellular space and its ability to process extracellular materials. Upon acquiring information, the cell further processes it and transmits it to neighboring cells, ultimately achieving localized responses. In multicellular organisms, a variety of processes, including cell-to-cell communication, migration, and long-distance signaling, are contingent upon the liquid space surrounding cells [177]. At the microscopic level, this space is filled with mucoproteins or extracellular vesicles. Research indicates that these vesicles may contain organelles released via exocytosis that can be taken up by distant or freely moving cells within the space [191–193]. Studies suggest that free mitochondria or mitochondria-derived vesicles frequently exist in the extracellular space, which may be linked to mitochondrial quality control, cellular self-protection, and immune signaling [194]. Researchers discovered that migration bodies, which contain numerous mitochondria, are abundant in the trails left by highly migratory cells [114, 117]. This process of clearing and renewing active intracellular organelles ensures that highly invasive cells maintain high-intensity mitochondrial metabolism throughout their movement. Conversely, under conditions of ischemia-reperfusion or severe hypoxia, mesenchymal stem cells expel active mitochondria into the extracellular matrix via exocytosis [195]. These free-floating mitochondria promote angiogenesis, restore redox balance in oxygenated environments, and scavenge reactive oxygen species and other oxidative components [194]. Thus, organelle transfer often uses the extracellular matrix as a transport pathway or delivery space. Organelle transfer also modifies the extracellular environment within multicellular clusters, thereby providing protection to the organism [114, 117].

On the whole, organelle transfer significantly alters the extracellular environment, affecting it in ways that differ from its impact on the intracellular environments of donor and recipient cells. Once in the extracellular space, these free-floating organelles function as messengers, triggering distant cells to perform specific physiological functions. This process ultimately facilitates recovery and provides supportive effects for the donor cells and microenvironment.

4 Inspiration and application prospects of organelle transfer

During the evolutionary process of living organisms, eukaryotic cells initiated a type of appropriation-based symbiotic relationship, such as "endosymbiosis" [11, 12]. Through this "asset-light transfer", including intracellular synthesis or ability workshop appropriation, more complex and powerful abilities are combined differently among individuals, enabling cells to better adapt to their living environment. The result is that cells and multicellular organisms were able to borrow, exploit, or absorb other organisms at various levels, and species can become more diverse than when they exist independently. Examples in animals include fly venom in golden poison frogs [196], chloroplasts of green algae in sea slugs [30, 31], and the carbon-nitrogen symbiosis between shallow-sea corals and zooxanthellae [197]. These endosymbiotic conditions transcend contractual boundaries, fusing into a unified whole and ultimately initiating the process of organelle transfer between existing cells. Just as cells utilize "integrated modules" instead of "autonomous production", research on intercellular organelles has targeted manipulable and applicable biomedical value and the potential to study organismal evolution.

4.1 Exploring more diverse mechanisms of organelle transfer

The inter-organelle transport processes currently being analyzed in depth are confined to mitochondria. This is due to the unique structure of mitochondria and their DNA, which makes them easier to track among various organelles [198]. At the same time, mitochondria serve as central nodes that regulate numerous biological processes in cells. Consequently, mitochondrial transport plays a crucial role in cellular metabolism, redox reactions, signal transduction, and the clearance and renewal of intracellular substances [199–205]. However, functional hubs within cells extend beyond mitochondria. Examples include lysosomes, which are centers for degradation and enzyme regulation [206]; the endoplasmic reticulum and the golgi apparatus, which are centers for protein synthesis and ion storage [207, 208]; and lipid droplets, which are centers for lipid metabolism and storage [209, 210]. These organelles and subcellular structures are significant in terms of their size, function, and practical value. In recent years, research on organelle transfer between cells has expanded to include a broader range of organelles and transport mechanisms. Scientists have identified the endoplasmic reticulum and the golgi apparatus as targets for viral hijacking, while lysosomes and their subcellular derivatives serve as vehicles for transporting pigments and enzymes between cells [33, 34, 37, 38, 134, 211]. These studies open new avenues for investigating diverse organelle transfer pathways and provide valuable research frameworks. The future promises the revelation of more intricate organelle transfer mechanisms, the deconstruction of fundamental organelle transfer structures, and the discovery of additional intracellular signaling pathways mediated by post-transfer organelles. Multifaceted analyses of organelles during intercellular transport will significantly advance fields such as cell biology and basic medical research.

4.2 Blocking or transplanting organelles with practical value

Based on the previous in-depth study of the effects of organelle transfer on donor and recipient cells and the extracellular

environment, we examined the biological mechanisms at playing in various physiological and biochemical settings and disease models. Here, we explore and categorize the implications of this double-edged sword in practical applications (Fig. 11). Researchers have discovered that damaged cells in tumors and neurological diseases steal organelles from normal cells, even immune cells, to restore their function [27, 212, 213]. This undermines the organism's ability to combat disease. Thus, externally regulating and blocking organelle transfer could enable clinical applications in diseases characterized by high metabolic activity, intense intercellular signaling, and substantial material transfer. Studies indicate that reducing fibroblast growth factor 13 (FGF13) protein expression in neurons improves mitochondrial release from dopaminergic neurons and modulates mitochondrial-induced glial inflammation [214]. Conversely, cancer cells rely extensively on mitochondrial transfer. Research demonstrates that significantly suppressing mitochondrial transfer by reducing mitochondrial Rho GTPase 2 (MIRO2) protein expression ultimately mitigates the migratory and invasive properties of tumor margin cells, such as those in squamous cell carcinoma of the skin [109]. Researchers can also use cell membrane protein-engineered liposomes to block the intercellular transfer of melanosomes [32]. This approach improves pigmentary disorder occurrence and offers a non-pharmaceutical therapeutic strategy for melanoma. In summary, blocking intercellular organelle transfer can mitigate diseases caused by abnormalities in recipient cells by improving the impact of the transfer process on the recipient cell's internal environment.

When it comes to transplanting immune cells, stem cells, and organs/tissues, the intercellular transfer of organelles significantly supports the recipient cell's internal environment. Another research direction involves actively promoting or artificially transplanting organelles to enhance recipient cells' metabolic activity and achieve artificial regulation of cellular function [215–221]. Research has shown that delivering mitochondria to immune cells via TNT significantly enhances and restores mitochondrial immune activity in tumor killing. Transferring healthy, intact mitochondria into cells promotes the infiltration of $CD8^+$ T cells and chimeric antigen receptor T-cells (CAR T) into lymphoid tissues, thereby boosting their killing capacity across multiple cancer models [127]. In addition to these methods of organelle delivery aided by stem cells, researchers have explored targeted transplantation of organelles to specific cells by encapsulating them in extracellular vesicles or loading them onto polymers and capsules [222]. Studies indicate that transplanting mitochondria into atherosclerotic regions enhances reparative macrophages' role in vascular regeneration and increases endothelial and smooth muscle cell proliferation [215, 223]. Furthermore, transplanting non-functional mitochondria into target cells can increase mitochondrial autophagy in stromal cells and enhance the renewal of endogenous mitochondria in endothelial cells, ultimately aiding in the repair of endothelial tissue [29, 224]. These transplantation strategies demonstrate significant application value in fields such as cardiomyopathy, vascular disease, and immunology [222, 225–228]. By leveraging nanodelivery systems, mitochondrial transplantation can be extended to oral administration via capsules or nanomotors [219]. Dual protection from polymer membranes and capsules

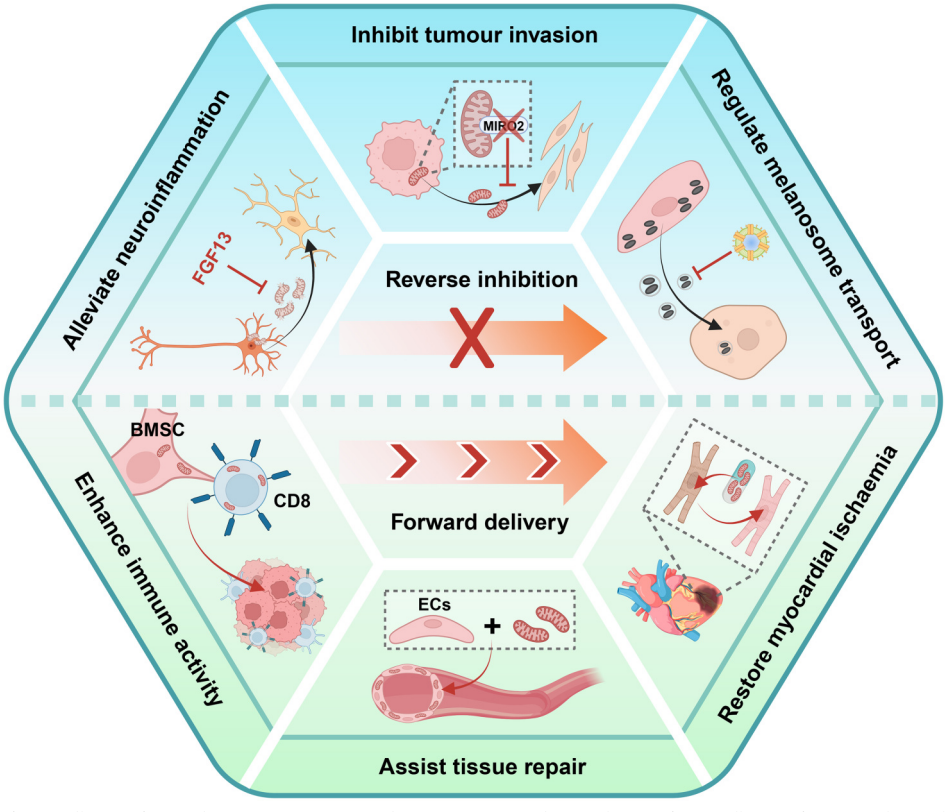


Figure 11 Application of organelle transfer regulation as an emerging therapeutic approach. Regulation of organelle transfer primarily involves blocking the transfer process and employing exogenous transplantation strategies. As a key hallmark of malignant diseases, organelle transfer is accompanied by organelle plundering and exacerbated inflammation. Existing research addresses neurological disorder alleviation, tumor transplantation, and pigment deposition mitigation. Concurrently, organelle transplantation enhances existing therapeutic approaches—such as boosting immune cell capabilities to improve immune infiltration, facilitating tissue repair through mitochondrial transplantation, and slowing disease progression in myocardial dysfunction disorders via exogenous supplementation.

safeguards the mitochondria during delivery to the gut. This enables their subsequent targeted release into the bloodstream, where they can restore ischemic heart disease (IHD) by targeting cardiomyocytes. In summary, organelle transplantation and transfer in biological applications can facilitate engineered interventions for various diseases via artificial forward blocking, reverse inhibition, and deliberate input (Fig. 12) [32, 215, 219, 229].

Beyond the two aforementioned therapeutic applications leveraging organelle transfer, additional approaches await discovery and exploration by researchers. The transfer of organelles, predominantly involving the endoplasmic reticulum, has been observed to frequently accompany the propagation of viral infections. In this process, viruses employ a strategy of camouflage within the organelles, thereby evading and escaping the immune cells tasked with their clearance [37, 38, 70]. Building on this, future research may involve a comparison of organelles in virus-infected cells with those in healthy cells, with a view to identifying characteristic sites that emerge post-infection, potentially aiding in their clearance. Conversely, this organelle-based camouflage strategy has the potential to inform the development of preventative measures and vaccines for viral infections. The incorporation of inactive viruses within modified organelles has the potential to elicit immune responses in animal models without triggering severe immune reactions. In summary, organelle transfer can be regarded as an emerging biological mechanism with considerable application potential. These approaches hold considerable promise as novel pathways for developing detection, prevention, and therapeutic strategies.

4.3 The long-term need for developing and researching organelle transfer

Current research approaches for detecting organelle transfer rely heavily on imaging equipment and fluorescent labelling dyes. Advances in imaging technology, particularly the advent of high-resolution microscopy, have enabled researchers to visualize organelle transfer with greater precision. This enables live visualization without staining, which significantly accelerates studies on organelle transfer mediated by TNTs. Current research primarily relies on real-time monitoring via high-resolution microscopy and visualization of fluorescently labelled target organelles using laser confocal microscopy. Another major advancement in organelle transfer studies is advances in fluorescent labelling dyes, with organelle dyes and fluorescent protein labelling techniques providing high-resolution, cost-effective solutions for studying organelle movement. Researchers can use flow cytometry to analyze organelle-specific proteins labelled with fluorescent or isotopic markers to confirm the transfer process.

However, these methods have limitations. In experiments, our research team discovered that labeling dyes may undergo cross-cell dye transfer. When labeling organelles, dye molecules can become free within donor cells. These substances can ultimately transfer to recipient cells via intercellular channels or other transport mechanisms. This leads to the labeling of recipient organelles by these free organelle probes. In such cases, mislabeling and dye cross-staining can lead to false positives during visualization and misinterpretation. Similarly, labeling intracellular proteins can cause internal protein transfer to be mistaken for organelle transfer. Previous literature has emphasized the urgent need for technological advancements in visualizing organelle transfer processes.

Here, we advocate for the development of more precise organelle labeling and visualization techniques. In order to facilitate the visualization of organelle transfer processes, it is proposed that existing fluorescence labelling approaches be integrated with reporter protein/gene technologies, thus enabling the visualization of intercellular organelle transfer. Alternatively, the utilization of divergent expression levels of protein molecules — or even nucleic acid sequences—that vary significantly between cell types has the potential to facilitate differential classification through omics strategies. For instance, mitochondria exhibit marked mtDNA differences between cell types and possess distinct internal RNA compositions. This differentiation enables researchers to employ more precise methods to obtain evidence of organelle transfer. In order to investigate the fate changes of organelles after cellular entry and the impact of intercellular organelle transfer on cellular life activities, analysis of purified organelles and the performance of single-cell transplantation can more accurately reconstruct the effects of single organelle transfer on cells. This approach has the dual benefits of eliminating interference from other intercellular molecules and enabling the development of standardized detection protocols for quantifying organelle transfer effects through the determinism of single-cell transplantation. Recently, the organelle transfer visualization tool FluidFM has emerged, utilizing hollow nanoscale probes to inject and transplant organelles into living cells. This approach facilitates improved research into the physiological and biochemical functions of transplanted organelles in living cells. Another novel research strategy involves the isotope labeling of mitochondrial substances, followed by purification and reinjection to track the fate, functional expression, and spatial localization of transferred organelles.

As a whole, the limited availability of organelle transfer tracing methods hinders research into organelle transfer mechanisms within cells and the identification of new transfer pathways. As future research delves deeper into organelles and explores meaningful organelle transfer as a clinical tool, novel technologies that are highly precise and sensitive will be required to capture imaging, recordings, and visualization of pathways of organelles between cells. Furthermore, it is difficult to achieve universal and frequently occurring organelle transfer processes at scale in 2D or *in vitro* 3D cultures. Therefore, drugs that can broadly induce or initiate organelle transfer may be key to rapid growth in this field of research.

5 Conclusions

The field of organelle transport within cells and multicellular organisms is growing annually. This growth is revealing an emerging landscape of studies centered on mitochondrial transfer and the movement of various metabolic and storage-related organelles. Advancements in cell biology, molecular biology, and high-precision instrumentation have driven this progress. Using these tools, researchers have uncovered the structural basis of organelle transfer and transport. These structures are similar to those involved in intercellular signaling and secretion, such as vesicles, tunnels, and membrane perforations. They enable the transfer of intact organelles and their subcellular structures between cells, thereby altering neighboring cells' biological functions. Additionally, a growing number of organelles have been observed to undergo spontaneous or forced transfer under normal physiological conditions and abnormal stress states. This intercellular organelle transfer, driven by vital functions or self-

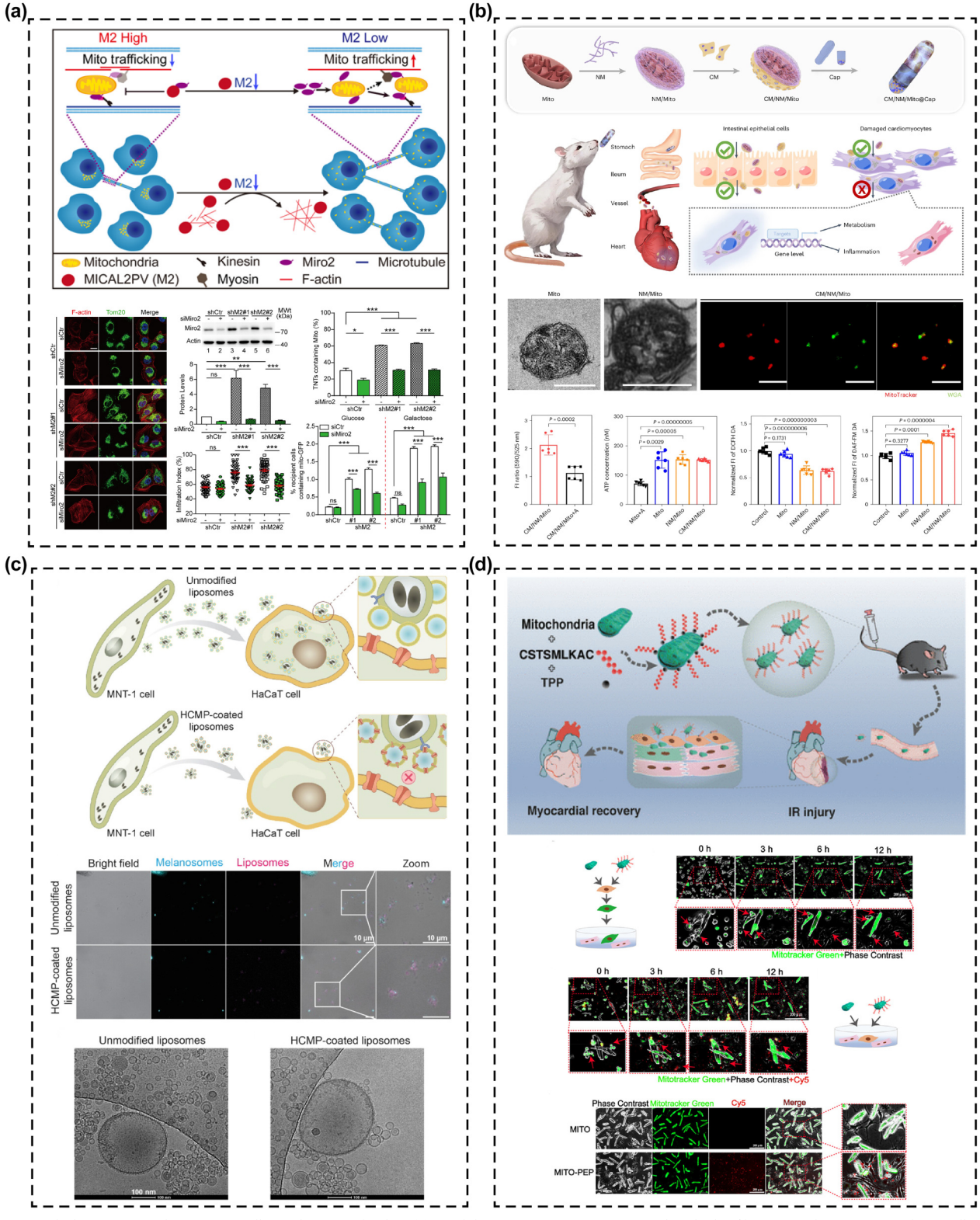


Figure 12 Blocking or transplanting organelles with practical value. (a) Modulating Miro2 suppresses mitochondrial infiltration and transport in shM2 cells [229]. Reproduced with permission from Ref. [229], © Wang, F. et al. 2021. (b) By releasing nitric oxide, nanomotor-based systems construct nanomotor-driven mitochondrial chemotaxis toward damaged cardiac tissue. These systems are absorbed and retained by damaged cardiomyocytes, thereby promoting transplanted mitochondria to fully restore energy metabolism functions [215]. Reproduced with permission from Ref. [215], © Wu, Z. et al. under exclusive licence to Springer Nature Limited 2024. (c) The construction of hydrogel-based culture microfluidic platform (HCMP)-coated liposomes can interfere with melanin granule transfer and regulate vital functions [32]. Reproduced with permission from Ref. [32], © American Chemical Society 2025. (d) Researchers formed the PEP–TPP–mitochondria complex by conjugating the peptide (PEP). This enabled efficient endocytosis of transplanted mitochondria by cardiomyocytes or their transfer to cardiomyocytes via endothelial cells, thereby alleviating myocardial ischemia-reperfusion injury [219]. Reproduced with permission from Ref. [219], © Wang, F. et al. 2021.

protection, provides a theoretical foundation for signaling pathways, drug targets, and cellular structural deconstruction. As our understanding of the transfer process deepens, we increasingly recognize the pivotal role of environmental changes before and after transfer in altering cellular fate. This review categorizes environmental changes based on their effects on the intracellular environments of donor and recipient cells, the extracellular spaces between multicellular organisms, and the distant extracellular environment. Based on tangible outcomes and potential disease implications arising from these environmental impacts, the paper explores the double-edged sword effect of organelle transfer and its potential applications in medicine and other fields. By integrating existing research on blocking and facilitating organelle transfer, the paper proposes application scenarios for the next phase of organelle research, including exploring the use of diverse migratory organelles in transplantation and developing targeted drugs based on current findings. Considering the current limitations and bottlenecks in organelle transfer research, we propose that future studies in this field rely heavily on higher-precision, more sensitive visualization tools and drugs capable of inducing widespread organelle transfer under controlled conditions. As discussed in this review, organelle transfer between cells is a universal biological phenomenon that has evolved throughout the history of life and occurs under various stress conditions as well as spontaneously. This paper delves into the structural basis of organelle transfer, the types of transferable organelles, the effects of transfer on the cellular environment, and potential applications. While significant obstacles remain in organelle transfer research, we contend that a deeper understanding of organelle delivery pathways, optimal transfer conditions, and the biological significance of post-transfer events is fundamental to achieving breakthroughs in clinical organelle transfer and transplantation.

Data availability

Not applicable.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (Nos. 92569103, and 32271400), the Key Project of Tianjin Natural Science Foundation (No. 25JCJQJC00210), and the State Key Laboratory of Synthetic Biology (Open Fund Project No. HSK202504). We thank the Core Facility of Research Center of Basic Medical Sciences at Tianjin Medical University for technical support.

Declaration of competing interest

The authors declare no conflict of interest. They have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

Author contribution statement

K. X. Y.: Conceptualisation, research and manuscript drafting. Z. X. Z.: Conceptualisation, research and manuscript drafting. F. Y. Z.: Funding acquisition, comprehensive evaluation. N. S. Q.: Funding acquisition, comprehensive evaluation. H. N. H.: Funding acquisition, comprehensive evaluation. B. Z.: Funding acquisition, comprehensive evaluation.

Informed consent

Not applicable.

Ethics statement

Not applicable.

Use of AI statement

None.

References

[1] Vosseberg, J.; Van Hooff, J. J. E.; Köstlbacher, S.; Panagiotou, K.; Tamarit, D.; Ettema, T. J. G. The emerging view on the origin and early evolution of eukaryotic cells. *Nature* **2024**, *633*, 295–305.

[2] De Duve, C. The origin of eukaryotes: A reappraisal. *Nat. Rev. Genet.* **2007**, *8*, 395–403.

[3] López-García, P.; Moreira, D. The syntrophy hypothesis for the origin of eukaryotes revisited. *Nat. Microbiol.* **2020**, *5*, 655–667.

[4] Gray, M. W. The evolutionary origins of organelles. *Trends Genet.* **1989**, *5*, 294–299.

[5] Weiss, M. C.; Sousa, F. L.; Mrnjavac, N.; Neukirchen, S.; Roettger, M.; Nelson-Sathi, S.; Martin, W. F. The physiology and habitat of the last universal common ancestor. *Nat. Microbiol.* **2016**, *1*, 16116.

[6] Krupovic, M.; Dolja, V. V.; Koonin, E. V. The LUCA and its complex virome. *Nat. Rev. Microbiol.* **2020**, *18*, 661–670.

[7] Moreira, D.; Le Guyader, H.; Philippe, H. The origin of red algae and the evolution of chloroplasts. *Nature* **2000**, *405*, 69–72.

[8] Rumpho, M. E.; Summer, E. J.; Manhart, J. R. Solar-powered sea slugs. *Mollusc/algal chloroplast symbiosis. Plant Physiol.* **2000**, *123*, 29–38.

[9] Bhattacharya, D.; Pelletreau, K. N.; Price, D. C.; Sarver, K. E.; Rumpho, M. E. Genome analysis of *Elysia chlorotica* egg DNA provides No evidence for horizontal gene transfer into the germ line of this kleptoplastic mollusc. *Mol. Biol. Evol.* **2013**, *30*, 1843–1852.

[10] Pierce, S. K.; Fang, X. D.; Schwartz, J. A.; Jiang, X. T.; Zhao, W.; Curtis, N. E.; Kocot, K. M.; Yang, B. C.; Wang, J. Transcriptomic evidence for the expression of horizontally transferred algal nuclear genes in the photosynthetic sea slug, *Elysia chlorotica*. *Mol. Biol. Evol.* **2012**, *29*, 1545–1556.

[11] Cornejo-Castillo, F. M.; Inomura, K.; Zehr, J. P.; Follows, M. J. Metabolic trade-offs constrain the cell size ratio in a nitrogen-fixing symbiosis. *Cell* **2024**, *187*, 1762–1768.e9.

[12] Coale, T. H.; Loconte, V.; Turk-Kubo, K. A.; Vanslembrouck, B.; Mak, W. K. E.; Cheung, S.; Ekman, A.; Chen, J. H.; Hagino, K.; Takano, Y. et al. Nitrogen-fixing organelle in a marine alga. *Science* **2024**, *384*, 217–222.

[13] Jiang, D.; He, J. Z.; Yu, L. The migrasome, an organelle for cell-cell communication. *Trends Cell Biol.* **2025**, *35*, 205–216.

[14] Gong, Z. Y.; Wu, T. L.; Zhao, Y. N.; Guo, J. H.; Zhang, Y.; Li, B. J.; Li, Y. C. Intercellular tunneling nanotubes as natural biophotonic conveyors. *ACS Nano* **2025**, *19*, 1036–1043.

[15] Rustom, A.; Saffrich, R.; Markovic, I.; Walther, P.; Gerdes, H. H. Nanotubular highways for intercellular organelle transport. *Science* **2004**, *303*, 1007–1010.

[16] Wang, M. J.; Wang, W. D.; Chopp, M.; Zhang, Z. G.; Zhang, Y. Therapeutic and diagnostic potential of extracellular vesicle (EV)-mediated intercellular transfer of mitochondria and mitochondrial components. *J. Cereb. Blood Flow Metab.*, in press, DOI: 10.1177/0271678X251338971.

[17] Wang, B.; Li, D. D.; Pan, C. L.; Wang, Y. M.; Tan, Y. D.; Yang, Y. J.; Liu, H. F.; Yao, Z. R.; Zhang, H.; Wang, Z. C. Platelet-derived

extracellular vesicles alleviate psoriatic inflammation via mitochondrial transfer to macrophages. *Exp. Dermatol.* **2025**, *34*, e70152.
[18] Heatlie, J. K.; Lazniewska, J.; Moore, C. R.; Johnson, I. R. D.; Nturubika, B. D.; Williams, R.; Ward, M. P.; O'leary, J. J.; Butler, L. M.; Brooks, D. A. Extracellular vesicles and tunnelling nanotubes as mediators of prostate cancer intercellular communication. *Biomolecules* **2024**, *15*, 23.
[19] Jeppesen, D. K.; Sanchez, Z. C.; Kelley, N. M.; Hayes, J. B.; Ambroise, J.; Koory, E. N.; Krystofiak, E.; Taneja, N.; Zhang, Q.; Dungan, M. M. et al. Blebbisomes are large, organelle-rich extracellular vesicles with cell-like properties. *Nat. Cell Biol.* **2025**, *27*, 438–448.
[20] Suh, J.; Lee, Y. S. Mitochondria as secretory organelles and therapeutic cargos. *Exp. Mol. Med.* **2024**, *56*, 66–85.
[21] Needs, H. I.; Glover, E.; Pereira, G. C.; Witt, A.; Hübner, W.; Dodding, M. P.; Henley, J. M.; Collinson, I. Rescue of mitochondrial import failure by intercellular organellar transfer. *Nat. Commun.* **2024**, *15*, 988.
[22] Griessinger, E.; Moschoi, R.; Biondani, G.; Peyron, J. F. Mitochondrial transfer in the leukemia microenvironment. *Trends Cancer* **2017**, *3*, 828–839.
[23] Norris, R. P. Transfer of mitochondria and endosomes between cells by gap junction internalization. *Traffic* **2021**, *22*, 174–179.
[24] Hertle, A. P.; Haberl, B.; Bock, R. Horizontal genome transfer by cell-to-cell travel of whole organelles. *Sci. Adv.* **2021**, *7*, eabd8215.
[25] Rogers, R. S.; Bhattacharya, J. When cells become organelle donors. *Physiology* **2013**, *28*, 414–422.
[26] Hayakawa, K.; Esposito, E.; Wang, X. H.; Terasaki, Y.; Liu, Y.; Xing, C. H.; Ji, X. M.; Lo, E. H. Transfer of mitochondria from astrocytes to neurons after stroke. *Nature* **2016**, *535*, 551–555.
[27] Hoover, G.; Gilbert, S.; Curley, O.; Obellianne, C.; Lin, M. T.; Hixson, W.; Pierce, T. W.; Andrews, J. F.; Alexeyev, M. F.; Ding, Y. et al. Nerve-to-cancer transfer of mitochondria during cancer metastasis. *Nature* **2025**, *644*, 252–262.
[28] Ikeda, H.; Kawase, K.; Nishi, T.; Watanabe, T.; Takenaga, K.; Inozume, T.; Ishino, T.; Aki, S.; Lin, J.; Kawashima, S. et al. Immune evasion through mitochondrial transfer in the tumour microenvironment. *Nature* **2025**, *638*, 225–236.
[29] Lin, R. Z.; Im, G. B.; Luo, A. C.; Zhu, Y. L.; Hong, X. C.; Neumeyer, J.; Tang, H. W.; Perrimon, N.; Melero-Martin, J. M. Mitochondrial transfer mediates endothelial cell engraftment through mitophagy. *Nature* **2024**, *629*, 660–668.
[30] Pierce, S. K.; Curtis, N. E. Cell biology of the chloroplast symbiosis in sacoglossan sea slugs. *Int. Rev. Cell Mol. Biol.* **2012**, *293*, 123–148.
[31] Maeda, T.; Takahashi, S.; Yoshida, T.; et al. Chloroplast acquisition without the gene transfer in kleptoplastic sea slugs, *Plakobranchus ocellatus*. *eLife* **2021**, *10*, e60176.
[32] Liu, C. H.; Liu, Y. C.; Xue, C. H.; Yang, C.; Weitz, D. A.; Jahnke, K. Engineering liposomes with cell membrane proteins to disrupt melanosome transfer between cells. *ACS Nano* **2025**, *19*, 22988–23000.
[33] Singh, S. K.; Kurfurst, R.; Nizard, C.; Schnebert, S.; Perrier, E.; Tobin, D. J. Melanin transfer in human skin cells is mediated by filopodia-a model for homotypic and heterotypic lysosome‐related organelle transfer. *FASEB J.* **2010**, *24*, 3756–3769.
[34] Tadokoro, R.; Murai, H.; Sakai, K. I.; Okui, T.; Yokota, Y.; Takahashi, Y. Melanosome transfer to keratinocyte in the chicken embryonic skin is mediated by vesicle release associated with rho-regulated membrane blebbing. *Sci. Rep.* **2016**, *6*, 38277.
[35] He, K. M.; Shi, X. L.; Zhang, X. J.; Dang, S.; Ma, X. W.; Liu, F.; Xu, M.; Lv, Z. Z.; Han, D.; Fang, X. H. et al. Long-distance intercellular connectivity between cardiomyocytes and cardiofibroblasts mediated by membrane nanotubes. *Cardiovasc. Res.* **2011**, *92*, 39–47.
[36] Gousset, K.; Schiff, E.; Langevin, C.; Marijanovic, Z.; Caputo, A.; Browman, D. T.; Chenouard, N.; de Chaumont, F.; Martino, A.; Enninga, J. et al. Prions hijack tunnelling nanotubes for intercellular spread. *Nat. Cell Biol.* **2009**, *11*, 328–336.
[37] Wang, Y.; Cui, J.; Sun, X.; Zhang, Y. Tunneling-nanotube development in astrocytes depends on p53 activation. *Cell Death Differ.* **2011**, *18*, 732–742.
[38] Kadiu, I.; Gendelman, H. E. Macrophage bridging conduit trafficking of HIV-1 through the endoplasmic reticulum and Golgi network. *J. Proteome Res.* **2011**, *10*, 3225–3238.
[39] Astanina, K.; Koch, M.; Jüngst, C.; Zumbusch, A.; Kiemer, A. K. Lipid droplets as a novel cargo of tunnelling nanotubes in endothelial cells. *Sci. Rep.* **2015**, *5*, 11453.
[40] Sun, J.; Yan, L. Q.; Chen, Y.; Wang, T.; Ali, W.; Ma, Y. G.; Yuan, Y.; Gu, J. H.; Bian, J. C.; Liu, Z. P. et al. TFAM-mediated intercellular lipid droplet transfer promotes cadmium-induced mice nonalcoholic fatty liver disease. *J. Hazard. Mater.* **2024**, *465*, 133151.
[41] Shekhar, S.; Guo, H. L.; Colin, S. P.; Marshall, W.; Kanso, E.; Costello, J. H. Cooperative hydrodynamics accompany multicellular-like colonial organization in the unicellular ciliate *stentor*. *Nat. Phys.* **2025**, *21*, 624–631.
[42] Sogabe, S.; Hatleberg, W. L.; Kocot, K. M.; Say, T. E.; Stoupin, D.; Roper, K. E.; Fernandez-Valverde, S. L.; Degnan, S. M.; Degnan, B. M. Pluripotency and the origin of animal multicellularity. *Nature* **2019**, *570*, 519–522.
[43] Allen, J. F. Why chloroplasts and mitochondria retain their own genomes and genetic systems: Colocation for redox regulation of gene expression. *Proc. Natl. Acad. Sci. USA* **2015**, *112*, 10231–10238.
[44] Chen, S. S.; Liao, Z. Y.; Xu, P. L. Mitochondrial control of innate immune responses. *Front. Immunol.* **2023**, *14*, 1166214.
[45] Henne, W. M. Organelle homeostasis principles: How organelle quality control and inter-organelle crosstalk promote cell survival. *Dev. Cell* **2021**, *56*, 878–880.
[46] Zhu, J. J.; Thompson, C. B. Metabolic regulation of cell growth and proliferation. *Nat. Rev. Mol. Cell Biol.* **2019**, *20*, 436–450.
[47] Fang, J. D.; Zhang, H.; Pan, Y.; Smith, Z. J.; Chu, K. Label-free analysis of organelle interactions using organelle-specific phase contrast microscopy (OS-PCM). *ACS Photonics* **2023**, *10*, 1093–1103.
[48] Tamura, T.; Fujisawa, A.; Tsuchiya, M.; Shen, Y. Y.; Nagao, K.; Kawano, S.; Tamura, Y.; Endo, T.; Umeda, M.; Hamachi, I. Organelle membrane-specific chemical labeling and dynamic imaging in living cells. *Nat. Chem. Biol.* **2020**, *16*, 1361–1367.
[49] Schessner, J. P.; Albrecht, V.; Davies, A. K.; Sinitcyn, P.; Borner, G. H. H. Deep and fast label-free Dynamic Organellar Mapping. *Nat. Commun.* **2023**, *14*, 5252.
[50] Xu, H. J.; Gao, J.; Cai, M. J.; Chen, J. L.; Zhang, Q. R.; Li, H. R.; Wang, H. D. Structural mechanism analysis of orderly and efficient vesicle transport by high-resolution imaging and fluorescence tracking. *Anal. Chem.* **2020**, *92*, 6555–6563.
[51] Rosado, A.; Bayer, E. M. Geometry and cellular function of organelle membrane interfaces. *Plant Physiol.* **2021**, *185*, 650–662.
[52] Wu, S. Q.; Tian, L. F. Multiphase model membraneless organelles. *Nat. Chem.* **2022**, *14*, 1095–1097.
[53] Otsuka, S.; Ellenberg, J. Mechanisms of nuclear pore complex assembly-two different ways of building one molecular machine. *FEBS Lett.* **2018**, *592*, 475–488.
[54] Archibald, J. M. Endosymbiosis and eukaryotic cell evolution. *Curr. Biol.* **2015**, *25*, R911–R921.
[55] Zahn, L. M.; Vinson, V.; Riddihough, G.; Wigginton, N. S.; Gough, N. R.; Hines, P. J.; Lavine, M. S.; Yeston, J.; Fahrenkamp-Uppenbrink, J.; Mueller, K. L. et al. This week in science. *Science* **2016**, *351*, 676–678.
[56] Guindani, C.; Da Silva, L. C.; Cao, S. P.; Ivanov, T.; Landfester, K.

Synthetic cells: From simple bio‐inspired modules to sophisticated integrated systems. *Angew. Chem., Int. Ed.* **2022**, *61*, e202110855.
[57] Nemani, N.; Carvalho, E.; Tomar, D.; Dong, Z. W.; Ketschek, A.; Breves, S. L.; Jaña, F.; Worth, A. M.; Heffler, J.; Palaniappan, P. et al. MIRO-1 determines mitochondrial shape transition upon GPCR activation and Ca^{2+} stress. *Cell Rep.* **2018**, *23*, 1005–1019.
[58] López‐Doménech, G.; Covill‐Cooke, C.; Ivankovic, D.; Halff, E. F.; Sheehan, D. F.; Norkett, R.; Birsa, N.; Kittler, J. Miro proteins coordinate microtubule‐ and actin‐dependent mitochondrial transport and distribution. *EMBO J.* **2018**, *37*, 321–336.
[59] Zhang, N.; Bing, T.; Shen, L. Y.; Song, R. S.; Wang, L. L.; Liu, X. J.; Liu, M. R.; Li, J.; Tan, W. H.; Shangguan, D. H. Intercellular connections related to cell-cell crosstalk specifically recognized by an aptamer. *Angew. Chem., Int. Ed.* **2016**, *55*, 3914–3918.
[60] Melwani, P. K.; Pandey, B. N. Tunneling nanotubes: The intercellular conduits contributing to cancer pathogenesis and its therapy. *Biochim. Biophys. Acta Rev. Cancer* **2023**, *1878*, 189028.
[61] Heinke, L. Connecting cells through TNT. *Nat. Rev. Mol. Cell Biol.* **2025**, *26*, 6.
[62] Raposo, G.; Stoorvogel, W. Extracellular vesicles: Exosomes, microvesicles, and friends. *J. Cell Biol.* **2013**, *200*, 373–383.
[63] Xu, M. X.; Ji, J.; Jin, D. D.; Wu, Y.; Wu, T.; Lin, R. J.; Zhu, S. Z.; Jiang, F.; Ji, Y. F.; Bao, B. J. et al. The biogenesis and secretion of exosomes and multivesicular bodies (MVBs): Intercellular shuttles and implications in human diseases. *Genes Dis.* **2023**, *10*, 1894–1907.
[64] Martens, S.; McMahon, H. T. Mechanisms of membrane fusion: Disparate players and common principles. *Nat. Rev. Mol. Cell Biol.* **2008**, *9*, 543–556.
[65] Hurtley, S. M. Tunneling nanotubes under the microscope. *Science* **2019**, *363*, 704.
[66] Sartori-Rupp, A.; Cordero Cervantes, D.; Pepe, A.; Gousset, K.; Delage, E.; Corroyer-Dulmont, S.; Schmitt, C.; Krijnse-Locker, J.; Zurzolo, C. Correlative cryo-electron microscopy reveals the structure of TNTs in neuronal cells. *Nat. Commun.* **2019**, *10*, 342.
[67] Korenkova, O.; Liu, S. Y.; Prlesi, I.; Pepe, A.; Albadri, S.; Del Bene, F.; Zurzolo, C. Tunneling nanotubes enable intercellular transfer in zebrafish embryos. *Dev. Cell* **2025**, *60*, 524–534.e3.
[68] Brewer, G. Nanotubes power up T cells. *Nat. Rev. Cancer* **2025**, *25*, 5.
[69] Wang, X.; Gerdes, H. H. Transfer of mitochondria via tunneling nanotubes rescues apoptotic PC12 cells. *Cell Death Differ.* **2015**, *22*, 1181–1191.
[70] Michita, R. T.; Tran, L. B.; Bark, S. J.; Kumar, D.; Toner, S. A.; Jose, J.; Mysorekar, I. U.; Narayanan, A. Zika virus NS1 drives tunneling nanotube formation for mitochondrial transfer and stealth transmission in trophoblasts. *Nat. Commun.* **2025**, *16*, 1803.
[71] Chakraborty, R.; Nonaka, T.; Hasegawa, M.; Zurzolo, C. Tunnelling nanotubes between neuronal and microglial cells allow bi-directional transfer of α-synuclein and mitochondria. *Cell Death Dis.* **2023**, *14*, 329.
[72] Alarcon-Martinez, L.; Villafranca-Baughman, D.; Quintero, H.; Kacerovsky, J. B.; Dotigny, F.; Murai, K. K.; Prat, A.; Drapeau, P.; Di Polo, A. Interpericyte tunnelling nanotubes regulate neurovascular coupling. *Nature* **2020**, *585*, 91–95.
[73] Guan, B. J.; Liu, Y. D.; Xie, B. W.; Zhao, S. L.; Yalikun, A.; Chen, W. W.; Zhou, M. H.; Gu, Q.; Yan, D. W. Mitochondrial genome transfer drives metabolic reprogramming in adjacent colonic epithelial cells promoting TGFβ1-mediated tumor progression. *Nat. Commun.* **2024**, *15*, 3653.
[74] Armingol, E.; Baghdassarian, H. M.; Lewis, N. E. The diversification of methods for studying cell-cell interactions and communication. *Nat. Rev. Genet.* **2024**, *25*, 381–400.
[75] Maeda, A.; Fadeel, B. Mitochondria released by cells undergoing TNF-α-induced necroptosis act as danger signals. *Cell Death Dis.* **2014**, *5*, e1312.
[76] Boudreau, L. H.; Duchez, A. C.; Cloutier, N.; Soulet, D.; Martin, N.; Bollinger, J.; Paré, A.; Rousseau, M.; Naika, G. S.; Lévesque, T. et al. Platelets release mitochondria serving as substrate for bactericidal group IIA-secreted phospholipase A_2 to promote inflammation. *Blood* **2014**, *124*, 2173–2183.
[77] Lyamzaev, K. G.; Nepryakhina, O. K.; Saprunova, V. B.; Bakeeva, L. E.; Pletjushkina, O. Y.; Chernyak, B. V.; Skulachev, V. P. Novel mechanism of elimination of malfunctioning mitochondria (mitoptosis): Formation of mitoptotic bodies and extrusion of mitochondrial material from the cell. *Biochim. Biophys. Acta* **2008**, *1777*, 817–825.
[78] Clark, M. A.; Shay, J. W. Mitochondrial transformation of mammalian cells. *Nature* **1982**, *295*, 605–607.
[79] Caicedo, A.; Fritz, V.; Brondello, J. M.; Ayala, M.; Dennemont, I.; Abdellaoui, N.; de Fraipont, F.; Moisan, A.; Prouteau, C. A.; Boukhaddaoui, H. et al. MitoCeption as a new tool to assess the effects of mesenchymal stem/stromal cell mitochondria on cancer cell metabolism and function. *Sci. Rep.* **2015**, *5*, 9073.
[80] Masuzawa, A.; Black, K. M.; Pacak, C. A.; Ericsson, M.; Barnett, R. J.; Drumm, C.; Seth, P.; Bloch, D. B.; Levitsky, S.; Cowan, D. B. et al. Transplantation of autologously derived mitochondria protects the heart from ischemia-reperfusion injury. *Am. J. Physiol. Heart Circ. Physiol.* **2013**, *304*, H966–H982.
[81] Gollihue, J. L.; Patel, S. P.; Eldahan, K. C.; Cox, D. H.; Donahue, R. R.; Taylor, B. K.; Sullivan, P. G.; Rabchevsky, A. G. Effects of mitochondrial transplantation on bioenergetics, cellular incorporation, and functional recovery after spinal cord injury. *J. Neurotrauma* **2018**, *35*, 1800–1818.
[82] Emani, S. M.; Piekarski, B. L.; Harrild, D.; Del Nido, P. J.; McCully, J. D. Autologous mitochondrial transplantation for dysfunction after ischemia-reperfusion injury. *J. Thorac. Cardiovasc. Surg.* **2017**, *154*, 286–289.
[83] McCully, J. D.; Cowan, D. B.; Pacak, C. A.; Toumpoulis, I. K.; Dayalan, H.; Levitsky, S. Injection of isolated mitochondria during early reperfusion for cardioprotection. *Am. J. Physiol. Heart Circ. Physiol.* **2009**, *296*, H94–H105.
[84] Kesner, E. E.; Saada-Reich, A.; Lorberboum-Galski, H. Characteristics of mitochondrial transformation into human cells. *Sci. Rep.* **2016**, *6*, 26057.
[85] Kitani, T.; Kami, D.; Matoba, S.; Gojo, S. Internalization of isolated functional mitochondria: Involvement of macropinocytosis. *J. Cell. Mol. Med.* **2014**, *18*, 1694–1703.
[86] Liu, D. L.; Gao, Y. S.; Liu, J.; Huang, Y. G.; Yin, J. H.; Feng, Y. Y.; Shi, L. J.; Meloni, B. P.; Zhang, C. Q.; Zheng, M. H. et al. Intercellular mitochondrial transfer as a means of tissue revitalization. *Signal Transduct. Target. Ther.* **2021**, *6*, 65.
[87] Fu, Y.; Zhang, S. S.; Xiao, S. H.; Basheer, W. A.; Baum, R.; Epifantseva, I.; Hong, T. T.; Shaw, R. M. Cx43 isoform GJA1-20k promotes microtubule dependent mitochondrial transport. *Front. Physiol.* **2017**, *8*, 905.
[88] Bell, C. L.; Shakespeare, T. I.; Smith, A. R.; Murray, S. A. Visualization of annular gap junction vesicle processing: The interplay between annular gap junctions and mitochondria. *Int. J. Mol. Sci.* **2019**, *20*, 44.
[89] Qin, Y. M.; Jiang, X.; Yang, Q.; Zhao, J. Q.; Zhou, Q.; Zhou, Y. H. The functions, methods, and mobility of mitochondrial transfer between cells. *Front. Oncol.* **2021**, *11*, 672781.
[90] Dhein, S.; Salameh, A. Remodeling of cardiac gap junctional cell-cell coupling. *Cells* **2021**, *10*, 2422.
[91] Cetin-Ferra, S.; Francis, S. C.; Cooper, A. T.; Neikirk, K.; Marshall, A. G.; Hinton, A. Jr; Murray, S. A. Mitochondrial connexins and mitochondrial contact sites with gap junction structure. *Int. J. Mol. Sci.* **2023**, *24*, 9036.
[92] Li, H. Y. Z.; Wang, C.; He, T.; Zhao, T. F.; Chen, Y. Y.; Shen, Y. L.;

Zhang, X. M.; Wang, L. L. Mitochondrial transfer from bone marrow mesenchymal stem cells to motor neurons in spinal cord injury rats via gap junction. *Theranostics* **2019**, *9*, 2017–2035.

[93] Luo, X. L.; Zeng, W. Q.; Xiong, E. F.; Wang, Z. M.; Huang, J. S.; Luo, M. Q.; He, Z. X.; Liu, J. Y.; Yuan, D. D. Hypoxia-preconditioning human bone marrow-derived mesenchymal stem cells induce high-quality mitochondrial transfer through gap junctions to alleviate ischemia-reperfusion injury in liver graft. *Cell Commun. Signal.* **2025**, *23*, 495.

[94] Yang, J. H.; Liu, L.; Oda, Y.; Wada, K.; Ago, M.; Matsuda, S.; Hattori, M.; Goto, T.; Ishibashi, S.; Kawashima-Sonoyama, Y. et al. Extracellular vesicles and Cx43-gap junction channels are the main routes for mitochondrial transfer from ultra-purified mesenchymal stem cells, RECs. *Int. J. Mol. Sci.* **2023**, *24*, 10294.

[95] Önfelt, B.; Nedvetzki, S.; Yanagi, K.; Davis, D. M. Cutting edge: Membrane nanotubes connect immune cells. *J. Immunol.* **2004**, *173*, 1511–1513.

[96] Austefjord, M. W.; Gerdes, H. H.; Wang, X. Tunneling nanotubes: Diversity in morphology and structure. *Commun. Integr. Biol.* **2014**, *7*, e27934.

[97] Spees, J. L.; Olson, S. D.; Whitney, M. J.; Prockop, D. J. Mitochondrial transfer between cells can rescue aerobic respiration. *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 1283–1288.

[98] Jayaprakash, A. D.; Benson, E. K.; Gone, S.; Liang, R.; Shim, J.; Lambertini, L.; Toloue, M. M.; Wigler, M.; Aaronson, S. A.; Sachidanandam, R. Stable heteroplasmy at the single-cell level is facilitated by intercellular exchange of mtDNA. *Nucleic Acids Res.* **2015**, *43*, 2177–2187.

[99] Phinney, D. G.; Di Giuseppe, M.; Njah, J.; Sala, E.; Shiva, S.; St Croix, C. M.; Stolz, D. B.; Watkins, S. C.; Di, Y. P.; Leikauf, G. D. et al. Mesenchymal stem cells use extracellular vesicles to outsource mitophagy and shuttle microRNAs. *Nat. Commun.* **2015**, *6*, 8472.

[100] Morrison, T. J.; Jackson, M. V.; Cunningham, E. K.; Kissenpfennig, A.; Mcauley, D. F.; O'Kane, C. M.; Krasnodembskaya, A. D. Mesenchymal stromal cells modulate macrophages in clinically relevant lung injury models by extracellular vesicle mitochondrial transfer. *Am. J. Respir. Crit. Care Med.* **2017**, *196*, 1275–1286.

[101] Islam, M. N.; Das, S. R.; Emin, M. T.; Wei, M.; Sun, L.; Westphalen, K.; Rowlands, D. J.; Quadri, S. K.; Bhattacharya, S.; Bhattacharya, J. Mitochondrial transfer from bone-marrow-derived stromal cells to pulmonary alveoli protects against acute lung injury. *Nat. Med.* **2012**, *18*, 759–765.

[102] Arkwright, P. D.; Luchetti, F.; Tour, J.; Roberts, C.; Ayub, R.; Morales, A. P.; Rodríguez, J. J.; Gilmore, A.; Canonico, B.; Papa, S. et al. Fas stimulation of T lymphocytes promotes rapid intercellular exchange of death signals via membrane nanotubes. *Cell Res.* **2010**, *20*, 72–88.

[103] Gurke, S.; Barroso, J. F. V.; Hodneland, E.; Bukoreshtliev, N. V.; Schlicker, O.; Gerdes, H. H. Tunneling nanotube (TNT)-like structures facilitate a constitutive, actomyosin-dependent exchange of endocytic organelles between normal rat kidney cells. *Exp. Cell Res.* **2008**, *314*, 3669–3683.

[104] Plotnikov, E. Y.; Khryapenkova, T. G.; Galkina, S. I.; Sukhikh, G. T.; Zorov, D. B. Cytoplasm and organelle transfer between mesenchymal multipotent stromal cells and renal tubular cells in co-culture. *Exp. Cell Res.* **2010**, *316*, 2447–2455.

[105] Otsu, K.; Das, S.; Houser, S. D.; Quadri, S. K.; Bhattacharya, S.; Bhattacharya, J. Concentration-dependent inhibition of angiogenesis by mesenchymal stem cells. *Blood* **2009**, *113*, 4197–4205.

[106] Diokmetzidou, A.; Maracani, A.; Pellattiero, A.; Cardenas-Rodriguez, M.; Rivière, E. A.; Scorrano, L. Metastatic breast cancer cells are selectively dependent on the mitochondrial cristae-shaping protein OPA1. *Cell Death Dis.* **2025**, *16*, 539.

[107] Watson, D. C.; Bayik, D.; Storevik, S.; Moreino, S. S.; Sprowls, S. A.; Han, J. H.; Augustsson, M. T.; Lauko, A.; Sravya, P.; Røsland, G. V. et al. GAP43-dependent mitochondria transfer from astrocytes enhances glioblastoma tumorigenicity. *Nat. Cancer* **2023**, *4*, 648–664

[108] Sun, C.; Liu, X. X.; Wang, B.; Wang, Z. H.; Liu, Y.; Di, C. X.; Si, J.; Li, H. Y.; Wu, Q. F.; Xu, D. et al. Endocytosis-mediated mitochondrial transplantation: Transferring normal human astrocytic mitochondria into glioma cells rescues aerobic respiration and enhances radiosensitivity. *Theranostics* **2019**, *9*, 3595–3607.

[109] Cangkrama, M.; Liu, H.; Wu, X. Y.; Yates, J.; Whipman, J.; Gäbelein, C. G.; Matsushita, M.; Ferrarese, L.; Sander, S.; Castro-Giner, F. et al. miRO2-mediated mitochondrial transfer from cancer cells induces cancer-associated fibroblast differentiation. *Nat. Cancer* **2025**, *6*, 1714–1733.

[110] Zhang, H. Y.; Yu, X. X.; Ye, J. F.; Li, H. Y.; Hu, J.; Tan, Y. H.; Fang, Y.; Akbay, E.; Yu, F. L.; Weng, C. et al. Systematic investigation of mitochondrial transfer between cancer cells and T cells at single-cell resolution. *Cancer Cell* **2023**, *41*, 1788–1802.e10.

[111] Bjerring, J. S.; Khodour, Y.; Peterson, E. A.; Sachs, P. C.; Bruno, R. D. Intercellular mitochondrial transfer contributes to microenvironmental redirection of cancer cell fate. *FEBS J.* **2025**, *292*, 2306–2322.

[112] Cañadas, I.; Murayama, T.; Galluzzi, L. mtDNA transfer from senescent cancer cells to MDSCs promotes immunosuppression. *Trends Cancer* **2025**, *11*, 716–718

[113] Del Vecchio, V.; Rehman, A.; Panda, S. K.; Torsiello, M.; Marigliano, M.; Nicoletti, M. M.; Ferraro, G. A.; De Falco, V.; Lappano, R.; Lieto, E. et al. Mitochondrial transfer from adipose stem cells to breast cancer cells drives multi-drug resistance. *J. Exp. Clin. Cancer Res.* **2024**, *43*, 166.

[114] Jiao, H. F.; Jiang, D.; Hu, X. Y.; Du, W. Q.; Ji, L. L.; Yang, Y. Z.; Li, X. P.; Sho, T.; Wang, X.; Li, Y. et al. Mitocytosis, a migrasome-mediated mitochondrial quality-control process. *Cell* **2021**, *184*, 2896–2910.e13.

[115] Liu, Y.; Fu, T. L.; Li, G. R.; Li, B. Y.; Luo, G. Q.; Li, N.; Geng, Q. Mitochondrial transfer between cell crosstalk-an emerging role in mitochondrial quality control. *Ageing Res. Rev.* **2023**, *91*, 102038.

[116] Duan, X.; Li, Y. Z.; Yi, K. X.; Guo, F. L.; Wang, H. Y.; Wu, P. H.; Yang, J.; Mair, D. B.; Morales, E. A.; Kalab, P. et al. Dynamic organelle distribution initiates actin-based spindle migration in mouse oocytes. *Nat. Commun.* **2020**, *11*, 277.

[117] Ma, L.; Li, Y.; Peng, J. Y.; Wu, D. N.; Zhao, X. X.; Cui, Y. T.; Chen, L. L.; Yan, X. J.; Du, Y. N.; Yu, L. Discovery of the migrasome, an organelle mediating release of cytoplasmic contents during cell migration. *Cell Res.* **2015**, *25*, 24–38.

[118] Malekpour, K.; Hazrati, A.; Soudi, S.; Hashemi, S. M. Mechanisms behind therapeutic potentials of mesenchymal stem cell mitochondria transfer/delivery. *J. Control. Release* **2023**, *354*, 755–769.

[119] Zhang, L.; Liu, Q.; Hu, H. R.; Zhao, L.; Zhu, K. Y. Progress in mesenchymal stem cell mitochondria transfer for the repair of tissue injury and treatment of disease. *Biomed. Pharmacother.* **2022**, *153*, 113482.

[120] Jin, S.; Cordes, N. ATM controls DNA repair and mitochondria transfer between neighboring cells. *Cell Commun. Signal.* **2019**, *17*, 144.

[121] Cheng, S.; Zhou, L.; Wang, W. Y.; Zhang, M. J.; Yang, Q. C.; Da Wang, W.; Wang, K. H.; Sun, Z. J.; Zhang, L. Mitochondria-loading erythrocytes transfer mitochondria to ameliorate inflammatory bone loss. *Acta Biomater.* **2025**, *195*, 225–239.

[122] Wang, K. H.; Zhou, L.; Mao, H. Q.; Liu, J. Y.; Chen, Z.; Zhang, L. Intercellular mitochondrial transfer alleviates pyroptosis in dental pulp damage. *Cell Prolif.* **2023**, *56*, e13442.

[123] Im, G. B.; Melero-Martin, J. M. Mitochondrial transfer in endothelial cells and vascular health. *Trends Cell Biol.*, in press, DOI: 10.1016/j.tcb.2025.04.004.

[124] Jiang, D.; Gao, F.; Zhang, Y. L.; Wong, D. S. H.; Li, Q.; Tse, H. F.; Xu, G. F.; Yu, Z. D.; Lian, Q. Z. Mitochondrial transfer of

mesenchymal stem cells effectively protects corneal epithelial cells from mitochondrial damage. *Cell Death Dis.* **2016**, *7*, e2467.

[125] Headley, C. A.; Gautam, S.; Olmo-Fontanez, A.; Garcia-Vilanova, A.; Dwivedi, V.; Schami, A.; Weintraub, S.; Tsao, P. S.; Torrelles, J. B.; Turner, J. Mitochondrial transplantation promotes protective effector and memory $CD4^+$ T cell response during *Mycobacterium tuberculosis* infection and diminishes exhaustion and senescence in elderly $CD4^+$ T cells. *Adv. Sci.* **2024**, *11*, 2401077.

[126] Tiku, V.; Tan, M. W.; Dikic, I. Mitochondrial functions in infection and immunity. *Trends Cell Biol.* **2020**, *30*, 263–275.

[127] Baldwin, J. G.; Heuser-Loy, C.; Saha, T.; Schelker, R. C.; Slavkovic-Lukic, D.; Strieder, N.; Hernandez-Lopez, I.; Rana, N.; Barden, M.; Mastrogiovanni, F. et al. Intercellular nanotube-mediated mitochondrial transfer enhances T cell metabolic fitness and antitumor efficacy. *Cell* **2024**, *187*, 6614–6630.e21.

[128] Wang, Z. L.; Wang, Q.; Cao, H. M.; Wang, Z. Y.; Wang, D. Y.; Liu, J. J.; Gao, T. X.; Ren, C. H.; Liu, J. F. Mitochondrial localized *in situ* self‐assembly reprogramming tumor immune and metabolic microenvironment for enhanced cancer therapy. *Adv. Mater.* **2024**, *36*, 2311043.

[129] Cai, W. J.; Mao, S. H.; Wang, Y.; Gao, B. C.; Zhao, J. Y.; Li, Y. Z.; Chen, Y. N.; Zhang, D.; Yang, J. T.; Yang, G. L. An engineered hierarchical hydrogel with immune responsiveness and targeted mitochondrial transfer to augmented bone regeneration. *Adv. Sci.* **2024**, *11*, 2406287.

[130] Changaei, M.; Azimzadeh Tabrizi, Z.; Karimi, M.; Kashfi, S. A.; Koochaki Chahardeh, T.; Hashemi, S. M.; Soudi, S. From powerhouse to modulator: Regulating immune system responses through intracellular mitochondrial transfer. *Cell Commun. Signal.* **2025**, *23*, 232.

[131] Guan, F.; Wu, X. M.; Zhou, J. T.; Lin, Y. Z.; He, Y. Q.; Fan, C. M.; Zeng, Z. Y.; Xiong, W. Mitochondrial transfer in tunneling nanotubes-a new target for cancer therapy. *J. Exp. Clin. Cancer Res.* **2024**, *43*, 147.

[132] Chang, X. Y.; Wang, W. X. Passing the parcels: Intercellular nanoplastics transfer in mussels *perna viridis* with activated immunomodulation. *Environ. Sci. Technol.* **2025**, *59*, 8177–8188.

[133] Gao, J. J.; Qin, A.; Liu, D. L.; Ruan, R.; Wang, Q. Y.; Yuan, J.; Cheng, T. S.; Filipovska, A.; Papadimitriou, J. M.; Dai, K. R. et al. Endoplasmic reticulum mediates mitochondrial transfer within the osteocyte dendritic network. *Sci. Adv.* **2019**, *5*, eaaw7215.

[134] Kadiu, I.; Gendelman, H. E. Human immunodeficiency virus type 1 endocytic trafficking through macrophage bridging conduits facilitates spread of infection. *J. Neuroimmune Pharmacol.* **2011**, *6*, 658–675.

[135] Soukar, J.; Singh, K. A.; Aviles, A.; Hargett, S.; Kaur, H.; Foster, S.; Roy, S.; Zhao, F.; Gohil, V. M.; Singh, I. et al. Nanomaterial-induced mitochondrial biogenesis enhances intercellular mitochondrial transfer efficiency. *Proc. Natl. Acad. Sci. USA* **2025**, *122*, e2505237122.

[136] Zhang, C.; Hao, H.; Wang, Y. S.; Mu, N.; Jiang, W. H.; Zhang, Z. H.; Yin, Y.; Yu, L.; Chang, A. C. Y.; Ma, H. Intercellular mitochondrial component transfer triggers ischemic cardiac fibrosis. *Sci. Bull.* **2023**, *68*, 1784–1799.

[137] He, H.; Huang, W. W.; Pan, Z. G.; Wang, L. J.; Yang, Z. Q.; Chen, Z. X. Intercellular mitochondrial transfer: Therapeutic implications for energy metabolism in heart failure. *Pharmacol. Res.* **2025**, *211*, 107555.

[138] Brestoff, J. R.; Wilen, C. B.; Moley, J. R.; Li, Y. J.; Zou, W.; Malvin, N. P.; Rowen, M. N.; Saunders, B. T.; Ma, H. M.; Mack, M. R. et al. Intercellular mitochondria transfer to macrophages regulates white adipose tissue homeostasis and is impaired in obesity. *Cell Metab.* **2021**, *33*, 270–282.e8.

[139] Yan, W. H.; Diao, S.; Fan, Z. P. The role and mechanism of mitochondrial functions and energy metabolism in the function regulation of the mesenchymal stem cells. *Stem Cell Res. Ther.* **2021**, *12*, 140.

[140] Liu, Q.; Zhang, X. X.; Zhu, T. X.; Xu, Z. H.; Dong, Y. C.; Chen, B. Mitochondrial transfer from mesenchymal stem cells: Mechanisms and functions. *Mitochondrion* **2024**, *79*, 101950.

[141] Paliwal, S.; Chaudhuri, R.; Agrawal, A.; Mohanty, S. Regenerative abilities of mesenchymal stem cells through mitochondrial transfer. *J. Biomed. Sci.* **2018**, *25*, 31.

[142] Konari, N.; Nagaishi, K.; Kikuchi, S.; Fujimiya, M. Mitochondria transfer from mesenchymal stem cells structurally and functionally repairs renal proximal tubular epithelial cells in diabetic nephropathy *in vivo*. *Sci. Rep.* **2019**, *9*, 5184.

[143] Gao, Z. M.; Zhang, C. Y.; Peng, F.; Chen, Q. Q.; Zhao, Y. H.; Chen, L. M.; Wang, X.; Chen, X. M. Hypoxic mesenchymal stem cell-derived extracellular vesicles ameliorate renal fibrosis after ischemia-reperfusion injure by restoring CPT1A mediated fatty acid oxidation. *Stem Cell Res. Ther.* **2022**, *13*, 191.

[144] Wei, Y.; Du, X. L.; Guo, H. L.; Han, J. J.; Liu, M. X. Mitochondrial dysfunction and Alzheimer's disease: Pathogenesis of mitochondrial transfer. *Front. Aging Neurosci.* **2024**, *16*, 1517965.

[145] Yang, F. G.; Liang, Y. L.; Wang, X.; Wang, J. T.; Gao, W.; Ye, Q. Y.; Li, X. Y.; Yang, Y.; Li, H. L. The evolution of alzheimer's disease: From mitochondria to microglia. *Ageing Res. Rev.* **2025**, *111*, 102838.

[146] Liang, J. H.; Su, Z. Q.; Su, G. M. Y.; Rasheed, M.; Tang, S. Y.; Sunniya, H.; Maazouzi, M.; Cui, Y. Y.; Wang, J. X.; Wang, X. Z. et al. Strategies to rescue mitochondria in Parkinson's disease: The significance of mitochondrial transfer. *Ageing Res. Rev.* **2025**, *112*, 102856.

[147] Kami, D.; Kitani, T.; Takaoka, Y.; Yoshimoto, Y.; Tabata, Y.; Gojo, S. 340. Cell penetrating peptide can improve the efficacy of mitochondrial transfer. *Mol. Ther.* **2016**, *24*, S136.

[148] Guo, Y. J.; Yu, Y. S.; Hu, S. J.; Chen, Y. Q.; Shen, Z. Y. The therapeutic potential of mesenchymal stem cells for cardiovascular diseases. *Cell Death Dis.* **2020**, *11*, 349.

[149] Chen, J.; Fu, C. Y.; Shen, G. R.; Wang, J. Y.; Xu, L. T.; Li, H. Y. Z.; Cao, X.; Zheng, M. Z.; Shen, Y. L.; Zhong, J. J. et al. Macrophages induce cardiomyocyte ferroptosis via mitochondrial transfer. *Free Radic. Biol. Med.* **2022**, *190*, 1–14.

[150] Mori, D.; Miyagawa, S.; Kawamura, T.; Hata, H.; Ueno, T.; Toda, K.; Kuratani, T.; Kurata, H.; Nishida, H.; Sawa, Y. P315 *In-vivo* and vitro mitochondrial transfer from adipose-derived mesenchymal stem cell to ischemic cardiomyocyte. *Eur. Heart J.* **2019**, *40*, ehz747.0150

[151] Xi, W. D.; Chen, W. D.; Sun, W. H.; Li, X. X.; Suo, Z. M.; Jiang, G. H.; Gao, P. J.; Li, Q. Mitochondrial activity regulates the differentiation of skin-derived mesenchymal stem cells into brown adipocytes to contribute to hypertension. *Stem Cell Res. Ther.* **2021**, *12*, 167.

[152] Torralba, D.; Baixauli, F.; Sánchez-Madrid, F. Mitochondria know no boundaries: Mechanisms and functions of intercellular mitochondrial transfer. *Front. Cell Dev. Biol.* **2016**, *4*, 107.

[153] Bennett, M. P.; Vivancos-Koopman, I.; Seewald, L.; Wells, K.; Robinette, T.; Delco, M. L. Intercellular mitochondrial transfer from mesenchymal stem cells to stressed chondrocytes. *Osteoarthritis Cartilage* **2019**, *27*, S51–S52.

[154] Stegemann, S.; Keuthe, M.; Greiner, S.; Bock, R. Horizontal transfer of chloroplast genomes between plant species. *Proc. Natl. Acad. Sci. USA* **2012**, *109*, 2434–2438.

[155] Li, W. J.; Guo, Y. H.; Wang, Q.; Qiu, M. X.; Zhang, Y. D.; Yang, Y. T.; Hu, J. J.; Yang, G. Endoplasmic reticulum junctions serve as a platform for endosome-lysosome interactions through their stop-and-go motion switching. *Sci. Adv.* **2025**, *11*, eadv4437.

[156] Jang, W.; Puchkov, D.; Samsó, P.; Liang, Y. T.; Nadler-Holly, M.; Sigrist, S. J.; Kintscher, U.; Liu, F.; Mamchaoui, K.; Mouly, V. et al. Endosomal lipid signaling reshapes the endoplasmic reticulum to control mitochondrial function. *Science* **2022**, *378*, eabq5209.

[157] Hong, Y. A.; Inagi, R. Endoplasmic reticulum-mediated organelle crosstalk in kidney disease. *Nat. Rev. Nephrol.* **2025**, *21*, 736–755.
[158] Hay, J. C.; Chao, D. S.; Kuo, C. S.; Scheller, R. H. Protein interactions regulating vesicle transport between the endoplasmic reticulum and Golgi apparatus in mammalian cells. *Cell* **1997**, *89*, 149–158.
[159] Petersen, J. D.; Mekhedov, E.; Kaur, S.; Roberts, D. D.; Zimmerberg, J. Endothelial cells release microvesicles that harbour multivesicular bodies and secrete exosomes. *J. Extracell. Biol.* **2023**, *2*, e79.
[160] Li, L.; Chen, J.; Yin, Z. Y.; Wang, W. Lysosome transfer: A novel intercellular communication. *Asian J. Surg.* **2025**, *48*, 5807–5808.
[161] Fang, L. P.; Lin, C. H.; Medlej, Y.; Zhao, R. P.; Chang, H. F.; Guo, Q. L.; Wu, Z. H.; Su, Y. X.; Zhao, N.; Gobbo, D. et al. Oligodendrocyte precursor cells facilitate neuronal lysosome release. *Nat. Commun.* **2025**, *16*, 1175.
[162] Zhang, J. W.; Ma, J. D.; Long, K. R.; Qiu, W. L.; Wang, Y. J.; Hu, Z. H.; Liu, C.; Luo, Y.; Jiang, A. N.; Jin, L. et al. Overexpression of exosomal cardioprotective miRNAs mitigates hypoxia-induced H9c2 cells apoptosis. *Int. J. Mol. Sci.* **2017**, *18*, 711.
[163] Zheng, X. F.; Ho, Q. W. C.; Chua, M. N.; Stelmashenko, O.; Yeo, X. Y.; Muralidharan, S.; Torta, F.; Chew, E. G. Y.; Lian, M. M.; Foo, J. N. et al. Destabilization of β cell FIT2 by saturated fatty acids alter lipid droplet numbers and contribute to ER stress and diabetes. *Proc. Natl. Acad. Sci. USA* **2022**, *119*, e2113074119.
[164] Wan, N.; Hong, Z. P.; Parson, M. A. H.; Korfhage, J. L.; Burke, J. E.; Melia, T. J.; Reinisch, K. M. Spartin-mediated lipid transfer facilitates lipid droplet turnover. *Proc. Natl. Acad. Sci. USA* **2024**, *121*, e2314093121.
[165] Luo, D.; Hu, S. Y.; Tang, C. L.; Liu, G. X. Mesenchymal stem cells promote cell invasion and migration and autophagy‐induced epithelial‐mesenchymal transition in A549 lung adenocarcinoma cells. *Cell Biochem. Funct.* **2018**, *36*, 88–94.
[166] Zhang, Y. M.; Zhang, Z. M.; Guan, Q. L.; Liu, Y. Q.; Wu, Z. W.; Li, J. T.; Su, Y.; Yan, C. L.; Luo, Y. L.; Qin, J. et al. Co-culture with lung cancer A549 cells promotes the proliferation and migration of mesenchymal stem cells derived from bone marrow. *Exp. Ther. Med.* **2017**, *14*, 2983–2991.
[167] Pasquier, J.; Guerrouahen, B. S.; Al Thawadi, H.; Ghiabi, P.; Maleki, M.; Abu-Kaoud, N.; Jacob, A.; Mirshahi, M.; Galas, L.; Rafii, S. et al. Preferential transfer of mitochondria from endothelial to cancer cells through tunneling nanotubes modulates chemoresistance. *J. Transl. Med.* **2013**, *11*, 94.
[168] Sinclair, K. A.; Yerkovich, S. T.; Hopkins, P. M. A.; Chambers, D. C. Characterization of intercellular communication and mitochondrial donation by mesenchymal stromal cells derived from the human lung. *Stem Cell Res. Ther.* **2016**, *7*, 91.
[169] Yao, Y.; Fan, X. L.; Jiang, D.; Zhang, Y. L.; Li, X.; Xu, Z. B.; Fang, S. B.; Chiu, S.; Tse, H. F.; Lian, Q. Z. et al. Connexin 43-mediated mitochondrial transfer of iPSC-MSCs alleviates asthma inflammation. *Stem Cell Rep.* **2018**, *11*, 1120–1135.
[170] Lin, T. K.; Chen, S. D.; Chuang, Y. C.; Lan, M. Y.; Chuang, J. H.; Wang, P. W.; Hsu, T. Y.; Wang, F. S.; Tsai, M. H.; Huang, S. T. et al. Mitochondrial transfer of Wharton's jelly mesenchymal stem cells eliminates mutation burden and rescues mitochondrial bioenergetics in rotenone-stressed MELAS fibroblasts. *Oxid. Med. Cell. Longev.* **2019**, *2019*, 9537504.
[171] Lou, E.; Zhai, E.; Sarkari, A.; Desir, S.; Wong, P.; Iizuka, Y.; Yang, J. B.; Subramanian, S.; Mccarthy, J.; Bazzaro, M. et al. Cellular and molecular networking within the ecosystem of cancer cell communication via tunneling nanotubes. *Front. Cell Dev. Biol.* **2018**, *6*, 95.
[172] Chun, S.; An, J.; Kim, M. S. Mitochondrial transfer between cancer and T cells: Implications for immune evasion. *Antioxidants* **2025**, *14*, 1008.
[173] Goodman, S.; Naphade, S.; Khan, M.; Sharma, J.; Cherqui, S. Macrophage polarization impacts tunneling nanotube formation and intercellular organelle trafficking. *Sci. Rep.* **2019**, *9*, 14529.
[174] Liu, R. Y.; Shan, W. H.; Wang, Z. N.; Wang, H.; Li, C. Y.; Yang, L.; Guo, R. Unveiling mitochondrial transfer in tumor immune evasion: Mechanisms, challenges, and clinical implications. *Front. Immunol.* **2025**, *16*, 1625814.
[175] Burt, R.; Dey, A.; Aref, S.; Aguiar, M.; Akarca, A.; Bailey, K.; Day, W.; Hooper, S.; Kirkwood, A.; Kirschner, K. et al. Activated stromal cells transfer mitochondria to rescue acute lymphoblastic leukemia cells from oxidative stress. *Blood* **2019**, *134*, 1415–1429.
[176] Yip, H. K.; Dubey, N. K.; Lin, K. C.; Sung, P. H.; Chiang, J. Y.; Chu, Y. C.; Huang, C. R.; Chen, Y. L.; Deng, Y. H.; Cheng, H. C. et al. Melatonin rescues cerebral ischemic events through upregulated tunneling nanotube-mediated mitochondrial transfer and downregulated mitochondrial oxidative stress in rat brain. *Biomed. Pharmacother.* **2021**, *139*, 111593.
[177] Borcherding, N.; Jia, W. T.; Giwa, R.; Field, R. L.; Moley, J. R.; Kopecky, B. J.; Chan, M. M.; Yang, B. Q.; Sabio, J. M.; Walker, E. C.et al. Dietary lipids inhibit mitochondria transfer to macrophages to divert adipocyte-derived mitochondria into the blood. *Cell Metab.* **2022**, *34*, 1499–1513.e8.
[178] Semenzato, M.; Scorrano, L. Mind the GAP(43) for mitochondria transfer to glioblastomas. *Nat. Cancer* **2023**, *4*, 588–589.
[179] Cowan, D. B.; Yao, R.; Thedsanamoorthy, J. K.; Zurakowski, D.; Del Nido, P. J.; McCully, J. D. Transit and integration of extracellular mitochondria in human heart cells. *Sci. Rep.* **2017**, *7*, 17450.
[180] Kim, M. J.; Hwang, J. W.; Yun, C. K.; Lee, Y.; Choi, Y. S. Delivery of exogenous mitochondria via centrifugation enhances cellular metabolic function. *Sci. Rep.* **2018**, *8*, 3330.
[181] Chou, S. H. Y.; Lan, J.; Esposito, E.; Ning, M. M.; Balaj, L.; Ji, X. M.; Lo, E. H.; Hayakawa, K. Extracellular mitochondria in cerebrospinal fluid and neurological recovery after subarachnoid hemorrhage. *Stroke* **2017**, *48*, 2231–2237.
[182] Tan, A. S.; Baty, J. W.; Dong, L. F.; Bezawork-Geleta, A.; Endaya, B.; Goodwin, J.; Bajzikova, M.; Kovarova, J.; Peterka, M.; Yan, B. et al. Mitochondrial genome acquisition restores respiratory function and tumorigenic potential of cancer cells without mitochondrial DNA. *Cell Metab.* **2015**, *21*, 81–94.
[183] Qiao, X. H.; Huang, N. W.; Meng, W. R.; Liu, Y. K.; Li, J. J.; Li, C. J.; Wang, W. X.; Lai, Y.; Zhao, Y. J.; Ma, Z. K. et al. Beyond mitochondrial transfer, cell fusion rescues metabolic dysfunction and boosts malignancy in adenoid cystic carcinoma. *Cell Rep.* **2024**, *43*, 114652.
[184] Suh, J.; Kim, N. K.; Shim, W.; Lee, S. H.; Kim, H. J.; Moon, E.; Sesaki, H.; Jang, J. H.; Kim, J. E.; Lee, Y. S. Mitochondrial fragmentation and donut formation enhance mitochondrial secretion to promote osteogenesis. *Cell Metab.* **2023**, *35*, 345–360.e7.
[185] Hutto, R. A.; Rutter, K. M.; Giarmarco, M. M.; Parker, E. D.; Chambers, Z. S.; Brockerhoff, S. E. Cone photoreceptors transfer damaged mitochondria to müller glia. *Cell Rep.* **2023**, *42*, 112115.
[186] Rosina, M.; Ceci, V.; Turchi, R.; Li, C.; Borcherding, N.; Sciarretta, F.; Sánchez-Díaz, M.; Tortolici, F.; Karlinsey, K.; Chiurchiù, V. et al. Ejection of damaged mitochondria and their removal by macrophages ensure efficient thermogenesis in brown adipose tissue. *Cell Metab.* **2022**, *34*, 533–548.e12.
[187] Nicolás-Ávila, J. A.; Lechuga-Vieco, A. V.; Esteban-Martínez, L.; Sánchez-Díaz, M.; Díaz-García, E.; Santiago, D. J.; Rubio-Ponce, A.; Li, J. L.; Balachander, A.; Quintana, J. A. et al. A network of macrophages supports mitochondrial homeostasis in the heart. *Cell* **2020**, *183*, 94–109.e23.
[188] Zhou, X. Y.; Liu, S. Y.; Lu, Y. R.; Wan, M. H.; Cheng, J. Q.; Liu, J. P. MitoEVs: A new player in multiple disease pathology and treatment. *J Extracell. Vesicles* **2023**, *12*, 12320.
[189] Kidwell, C. U.; Casalini, J. R.; Pradeep, S.; Scherer, S. D.; Greiner, D.; Bayik, D.; Watson, D. C.; Olson, G. S.; Lathia, J. D.; Johnson, J.

S. et al. Transferred mitochondria accumulate reactive oxygen species, promoting proliferation. *eLife* **2023**, *12*, e85494.
[190] Zampieri, L. X.; Silva-Almeida, C.; Rondeau, J. D.; Sonveaux, P. Mitochondrial transfer in cancer: A comprehensive review. *Int. J. Mol. Sci.* **2021**, *22*, 3245.
[191] Stephens, O. R.; Grant, D.; Frimel, M.; Wanner, N.; Yin, M.; Willard, B.; Erzurum, S. C.; Asosingh, K. Characterization and origins of cell-free mitochondria in healthy murine and human blood. *Mitochondrion* **2020**, *54*, 102–112.
[192] Stier, A. Human blood contains circulating cell-free mitochondria, but are they really functional. *Am. J. Physiol. Endocrinol. Metab.* **2021**, *320*, E859–E863.
[193] Joshi, A. U.; Minhas, P. S.; Liddelow, S. A.; Haileselassie, B.; Andreasson, K. I.; Dorn II, G. W.; Mochly-Rosen, D. Author correction: Fragmented mitochondria released from microglia trigger A1 astrocytic response and propagate inflammatory neurodegeneration. *Nat. Neurosci.* **2021**, *24*, 289.
[194] Levoux, J.; Prola, A.; Lafuste, P.; Gervais, M.; Chevallier, N.; Koumaiha, Z.; Kefi, K.; Braud, L.; Schmitt, A.; Yacia, A. et al. Platelets facilitate the wound-healing capability of mesenchymal stem cells by mitochondrial transfer and metabolic reprogramming. *Cell Metab.* **2021**, *33*, 688–690.
[195] Andrade-Soares, M.; Alves, M.; Rodrigues-Ferreira, C.; Lopes, J. A.; Crisóstomo, T.; Costa-Sarmento, G.; Takiya, C. M.; Pereira-Acácio, A.; Vieyra, A. Extracellular vesicles from hypoxia-preconditioned mesenchymal stem cells preserve mitochondrial functions and redox homeostasis in ischemia-reperfusion-induced acute kidney injury. *Biochim. Biophys. Acta Gen. Subj.* **2026**, *1870*, 130874.
[196] Coleman, J. L.; Cannatella, D. C. The molecular basis and evolution of toxin resistance in poison frogs. *Evol. Ecol.* **2024**, *38*, 747–780.
[197] Nangammada, S.; Rajan, R. Insights into zooxanthellae densities in corals *Porites lutea* and *Pocillopora meandrina* in lakshadweep atolls. *Reg. Stud. Mar. Sci.* **2024**, *71*, 103417.
[198] Ren, W.; Ge, X. C.; Li, M. Q.; Sun, J.; Li, S. Y.; Gao, S.; Shan, C. Y.; Gao, B. X.; Xi, P. Visualization of cristae and mtDNA interactions via STED nanoscopy using a low saturation power probe. *Light Sci. Appl.* **2024**, *13*, 116.
[199] Ramshesh, V. K.; Lemasters, J. J. Imaging of mitochondrial pH using SNARF-1. In *Mitochondrial Bioenergetics*. Palmeira, C. M.; Moreno, A. J., Eds.; Humana: New York, 2018; pp 243–248.
[200] Teodoro, J. S.; Machado, I. F.; Castela, A. C.; Rolo, A. P.; Palmeira, C. M. The evaluation of mitochondrial membrane potential using fluorescent dyes or a membrane-permeable cation (TPP^+) electrode in isolated mitochondria and intact cells. In *Immunometabolism*. Mishra, S., Ed.; Humana: New York, 2020; pp 197–213.
[201] Birsoy, K.; Wang, T.; Chen, W. W.; Freinkman, E.; Abu-Remaileh, M.; Sabatini, D. M. An essential role of the mitochondrial electron transport chain in cell proliferation is to enable aspartate synthesis. *Cell* **2015**, *162*, 540–551.
[202] Cardaci, S.; Zheng, L.; MacKay, G.; Van Den broek, N. J. F.; Mackenzie, E. D.; Nixon, C.; Stevenson, D.; Tumanov, S.; Bulusu, V.; Kamphorst, J. J. et al. Pyruvate carboxylation enables growth of SDH-deficient cells by supporting aspartate biosynthesis. *Nat. Cell Biol.* **2015**, *17*, 1317–1326.
[203] King, M. P.; Attardi, G. Human cells lacking mtDNA: Repopulation with exogenous mitochondria by complementation. *Science* **1989**, *246*, 500–503.
[204] Sullivan, L. B.; Gui, D. Y.; Hosios, A. M.; Bush, L. N.; Freinkman, E.; Vander Heiden, M. G. Supporting aspartate biosynthesis is an essential function of respiration in proliferating cells. *Cell* **2015**, *162*, 552–563.
[205] May, J. M.; Li, L. Y.; Qu, Z. C.; Cobb, C. E. Mitochondrial recycling of ascorbic acid as a mechanism for regenerating cellular ascorbate. *BioFactors* **2007**, *30*, 35–48.
[206] Ballabio, A.; Bonifacino, J. S. Lysosomes as dynamic regulators of cell and organismal homeostasis. *Nat. Rev. Mol. Cell Biol.* **2020**, *21*, 101–118.
[207] Chen, X. Y.; Shi, C. R.; He, M. H.; Xiong, S. Q.; Xia, X. B. Endoplasmic reticulum stress: Molecular mechanism and therapeutic targets. *Signal Transduct. Target. Ther.* **2023**, *8*, 352.
[208] Nichols, B. J.; Kenworthy, A. K.; Polishchuk, R. S.; Lodge, R.; Roberts, T. H.; Hirschberg, K.; Phair, R. D.; Lippincott-Schwartz, J. Rapid cycling of lipid raft markers between the cell surface and Golgi complex. *J. Cell Biol.* **2001**, *153*, 529–542.
[209] Mathiowetz, A. J.; Olzmann, J. A. Lipid droplets and cellular lipid flux. *Nat. Cell Biol.* **2024**, *26*, 331–345.
[210] Zadoorian, A.; Du, X. M.; Yang, H. Y. Lipid droplet biogenesis and functions in health and disease. *Nat. Rev. Endocrinol.* **2023**, *19*, 443–459.
[211] Wu, X. S.; Masedunskas, A.; Weigert, R.; Copeland, N. G.; Jenkins, N. A.; Hammer, J. A. Melanoregulin regulates a shedding mechanism that drives melanosome transfer from melanocytes to keratinocytes. *Proc. Natl. Acad. Sci. USA* **2012**, *109*, E2101–E2109.
[212] Coarfa, C.; Florentin, D.; Putluri, N.; Ding, Y.; Au, J.; He, D. D.; Ragheb, A.; Frolov, A.; Michailidis, G.; Lee, M. et al. Influence of the neural microenvironment on prostate cancer. *Prostate* **2018**, *78*, 128–139.
[213] Marabitti, V.; Vulpis, E.; Nazio, F.; Campello, S. Mitochondrial transfer as a strategy for enhancing cancer cell fitness: Current insights and future directions. *Pharmacol. Res.* **2024**, *208*, 107382.
[214] Song, N. S.; Wang, X. X.; Ha, L. Q.; Hu, L. M.; Mei, S. Y.; Liang, Y.; Zhao, Y. J.; Yang, X. Y.; Zhang, Q. Y.; Zhou, Y. Z. et al. Neuronal FGF13 inhibits mitochondria‐derived damage signals to prevent neuroinflammation and neurodegeneration in a mouse model of parkinson's disease. *Adv. Sci.* **2025**, *12*, 2503579.
[215] Wu, Z. Y.; Chen, L.; Guo, W. Y.; Wang, J.; Ni, H. Y.; Liu, J. N.; Jiang, W. T.; Shen, J.; Mao, C.; Zhou, M. et al. Oral mitochondrial transplantation using nanomotors to treat ischaemic heart disease. *Nat. Nanotechnol.* **2024**, *19*, 1375–1385.
[216] Chang, J. C.; Wu, S. L.; Liu, K. H.; Chen, Y. H.; Chuang, C. S.; Cheng, F. C.; Su, H. L.; Wei, Y. H.; Kuo, S. J.; Liu, C. S. Allogeneic/xenogeneic transplantation of peptide-labeled mitochondria in parkinson's disease: Restoration of mitochondria functions and attenuation of 6-hydroxydopamine-induced neurotoxicity. *Transl. Res.* **2016**, *170*, 40–56.e3.
[217] Maeda, H.; Kami, D.; Maeda, R.; Murata, Y.; Jo, J. I.; Kitani, T.; Tabata, Y.; Matoba, S.; Gojo, S. TAT‐dextran-mediated mitochondrial transfer enhances recovery from models of reperfusion injury in cultured cardiomyocytes. *J. Cell. Mol. Med.* **2020**, *24*, 5007–5020.
[218] Wu, S. H.; Zhang, A. J.; Li, S. M.; Chatterjee, S.; Qi, R. G.; Segura‐ibarra, V.; Ferrari, M.; Gupte, A.; Blanco, E.; Hamilton, D. J. Polymer functionalization of isolated mitochondria for cellular transplantation and metabolic phenotype alteration. *Adv. Sci.* **2018**, *5*, 1700530.
[219] Sun, X. L.; Chen, H.; Gao, R. F.; Qu, Y. N.; Huang, Y.; Zhang, N.; Hu, S. Y.; Fan, F.; Zou, Y. Z.; Hu, K. et al. Intravenous transplantation of an ischemic-specific peptide-TPP-mitochondrial compound alleviates myocardial ischemic reperfusion injury. *ACS Nano* **2023**, *17*, 896–909.
[220] Ikeda, G.; Santoso, M. R.; Tada, Y.; Li, A. M.; Vaskova, E.; Jung, J. H.; O'Brien, C.; Egan, E.; Ye, J. B.; Yang, P. C. Mitochondria-rich extracellular vesicles from autologous stem cell-derived cardiomyocytes restore energetics of ischemic myocardium. *J. Am. Coll. Cardiol.* **2021**, *77*, 1073–1088.
[221] Nakano, T.; Nakamura, Y.; Park, J. H.; Tanaka, M.; Hayakawa, K. Mitochondrial surface coating with artificial lipid membrane improves the transfer efficacy. *Commun. Biol.* **2022**, *5*, 745.

[222] Zhang, T. G.; Miao, C. Y. Mitochondrial transplantation as a promising therapy for mitochondrial diseases. *Acta Pharm. Sin. B* **2023**, *13*, 1028–1035.
[223] Zhang, Y. N.; Sun, X. L.; Jin, Y. W.; Chen, K. H.; Zhang, L.; Gao, X.; Li, M. H.; Yuan, Z.; Jia, J. G.; Sun, A. J. et al. Mitochondrial transplantation augments the reparative capacity of macrophages following myocardial injury. *Adv. Sci.* **2025**, *12*, e06337.
[224] Huynh, K. Artificially transplanted mitochondria in endothelial cells promote mitophagy. *Nat. Rev. Cardiol.* **2024**, *21*, 439.
[225] Lim, G. B. Intracoronary mitochondrial transplantation. *Nat. Rev. Cardiol.* **2020**, *17*, 131.
[226] Lu, X. M. Mitochondrial transplantation: Adaptive bio-enhancement. *Cell Death Dis.* **2025**, *16*, 473.
[227] Saeb-Parsy, K.; Martin, J. L.; Summers, D. M.; Watson, C. J. E.; Krieg, T.; Murphy, M. P. Mitochondria as therapeutic targets in transplantation. *Trends Mol. Med.* **2021**, *27*, 185–198.
[228] Gorick, C.; Debski, A. Mitochondrial transplantation for ischemic heart disease. *Nat. Nanotechnol.* **2024**, *19*, 1247–1248.
[229] Wang, F.; Chen, X. P.; Cheng, H. P.; Song, L.; Liu, J. H.; Caplan, S.; Zhu, L.; Wu, J. Y. MICAL2PV suppresses the formation of tunneling nanotubes and modulates mitochondrial trafficking. *EMBO Rep.* **2021**, *22*, e52006
[230] Chi, A. N.; Yang, B. C.; Dai, H.; Li, X. Y.; Mo, J. H.; Gao, Y.; Chen, Z. H.; Feng, X.; Ma, M. H.; Li, Y. Q. et al. Stem leydig cells support macrophage immunological homeostasis through mitochondrial transfer in mice. *Nat. Commun.* **2024**, *15*, 2120.
[231] Cai, W. J.; Zhang, J. L.; Yu, Y. Q.; Ni, Y. Q.; Wei, Y.; Cheng, Y. H.; Han, L. T.; Xiao, L. Y.; Ma, X. X.; Wei, H. J. et al. Mitochondrial transfer regulates cell fate through metabolic remodeling in osteoporosis. *Adv. Sci.* **2023**, *10*, 2204871.
[232] Marlein, C. R.; Zaitseva, L.; Piddock, R. E.; Robinson, S. D.; Edwards, D. R.; Shafat, M. S.; Zhou, Z. G.; Lawes, M.; Bowles, K. M.; Rushworth, S. A. NADPH oxidase-2 derived superoxide drives mitochondrial transfer from bone marrow stromal cells to leukemic blasts. *Blood* **2017**, *130*, 1649–1660.
[233] Kumar, B.; Garcia, M.; Weng, L.; Jung, X.; Murakami, J. L.; Hu, X.; McDonald, T.; Lin, A.; Kumar, A. R.; DiGiusto, D. L. et al. Acute myeloid leukemia transforms the bone marrow niche into a leukemia-permissive microenvironment through exosome secretion. *Leukemia* **2018**, *32*, 575–587.
[234] Wang, Y.; Yu, H. Y.; Yi, Z. J.; Qi, L. Y.; Yang, J. S.; Xie, H. X.; Zhao, M.; Liu, N. H.; Chen, J. Q.; Zhou, T. J. et al. Super mitochondria-enriched extracellular vesicles enable enhanced mitochondria transfer. *Nat. Commun.* **2025**, *16*, 9448.