Pharmacological Research 208 (2024) 107382

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Mitochondrial Transfer as a Strategy for Enhancing Cancer Cell Fitness: Current Insights and Future Directions

Veronica Marabitti [1], Elisabetta Vulpis [1], Francesca Nazio [2], Silvia Campello [*,2]

Department of Biology, University of Rome Tor Vergata, Rome 00133, Italy

ARTICLE INFO

Keywords:
Mitochondria transfer
tumor microenvironment
metabolic alterations
cancer therapy

ABSTRACT

It is now recognized that tumors are not merely masses of transformed cells but are intricately interconnected with healthy cells in the tumor microenvironment (TME), forming complex and heterogeneous structures. Recent studies discovered that cancer cells can steal mitochondria from healthy cells to empower themselves, while reducing the functions of their target organ. Mitochondrial transfer, i.e. the intercellular movement of mitochondria, is recently emerging as a novel process in cancer biology, contributing to tumor growth, metastasis, and resistance to therapy by shaping the metabolic landscape of the tumor microenvironment. This review highlights the influence of transferred mitochondria on cancer bioenergetics, redox balance and apoptotic resistance, which collectively foster aggressive cancer phenotype. Furthermore, the therapeutic implications of mitochondrial transfer are discussed, emphasizing the potential of targeting these pathways to overcome drug resistance and improve treatment efficacy.

1. Introduction

Mitochondria, often referred to as the powerhouse of the cell, play a pivotal role in cellular metabolism, energy production, and apoptosis. In cancer, mitochondria exhibit remarkable plasticity, undergoing dynamic changes that support tumor initiation, progression, dissemination and therapeutic resistance. Dysfunctional mitochondria are frequently observed in cancer cells, characterized by alterations in mitochondrial morphology, metabolism, and bioenergetics. These alterations enable cancer cells to adapt to the demanding metabolic requirements of uncontrolled proliferation, often shifting towards glycolytic metabolism even in the presence of oxygen, a phenomenon known as the Warburg effect [1]. Furthermore, by modulating mitochondrial function, cancer cells can rewire their metabolic pathways to use alternative fuels and survive under hostile conditions, such as nutrient deprivation and hypoxia [2]. This intrinsic adaptive plasticity of mitochondria confers a survival advantage to cancer cells, allowing them to maintain energy homeostasis, resist apoptosis, and thrive in the tumor microenvironment (TME) [3]. In cancer, mitochondria plasticity is influenced by various intracellular processes, including alterations in mitochondrial dynamics [4]. Moreover, the interaction between mitochondria and other cellular organelles, such as the endoplasmic reticulum and lysosomes, contributes to mitochondrial plasticity by regulating calcium homeostasis, lipid metabolism, and autophagy. Increasing evidence shows that mitochondrial homeostasis can also be regulated by intercellular communications [5].

Abbreviations: **ABL,**, c-Abelson; **ALL**, acute myeloid leukemia; **AML,**, Acute myeloid leukemia; **BCR,**, breakpoint cluster region; **BM,**, Bone marrow; **BMSCs,**, Bone marrow stem cells; **CAF,**, cancer-associated fiboblast; **CAR,**, chimeric antigen receptor; **cGAS,**, cyclic GMP-AMP synthase; **CIC,**, cell-in-cell; **CML,**, chronic myeloid leukemia; **DAMPs,**, damage-associated molecular patterns; **Drp1,**, dynamin-related protein 1; **EMT,**, epithelial-mesenchimal transition; **EV,**, extracellular vesicle; **GBM,**, glioblastoma; **GBMSCs,**, glioblastoma stem cells; **GJ,**, gap junction; **HMGB1,**, high mobility group box 1; **LSCC,**, Laryngeal squamous cell carcinoma; **Miro,**, Mitochondrial Rho MIRO GTPase; **mitoEV,**, mitochondria-containing extracellular vesicle; **MM,**, multiple myeloma; **MSCs,**, mesenchimal stem cells; **mTOR,**, mammalian target of rapamycin; **NOX2,**, NADPH oxidase 2; **PARKIN,**, Parkin RBR E3 ubiquitin-protein ligase; **PCs,**, plasma cells; **PD-L1,**, programmed death-ligand 1; **PI3K,**, phosphoinositide-3-kinase; **PINK1,**, PTEN-induced kinase 1; **RHOT1,**, Ras homolog family member T1; **ROS,**, reactive oxygen species; **SMT,**, somatic mutation theory; **STING,**, stimulator of interferon genes; **TASCs,**, tumor-activated stromal cells; **TMs,**, tumor microtubes; **TMZ,**, temozolomide; **TNT,**, tunelling nanotube.

* Corresponding author.
E-mail address: silvia.campello@uniroma2.it (S. Campello).
[1] These authors equally contributed to this work
[2] These authors equally last-authored this work

https://doi.org/10.1016/j.phrs.2024.107382
Received 8 June 2024; Received in revised form 8 August 2024; Accepted 26 August 2024
Available online 30 August 2024

Mitochondria typically distribute themselves during cell division and differentiation, passing directly from parent to daughter cells along with their mitochondrial DNA through a process called vertical inheritance [6]. Interestingly, over the past twenty years, recent research unveiled the capability of cells to export mitochondria and to transfer them to different and unrelated cell types. This mechanism is known as horizontal mitochondrial transfer (HMT), a process that holds significant implications for health and disease [7,8]. In recent years, it was proven that cancer cells are able to deliver mitochondria to other malignant cells (homotypic transfer), as well as to acquire mitochondria from healthy cell populations present in the TME (heterotypic transfer), through multiple mechanisms following intrinsic (e.g. reduced mitochondrial function) and extrinsic (e.g. hypoxic extracellular milieu) stimuli [7–9].

This review provides a detailed overview of the roles of HMT in different cancer types. The mechanisms of cell-cell interactions and global or context-specific consequences of HMT in the regulation of TME will be described, with a particular focus on the potential of targeting HMT as a strategy to improve anti-cancer therapy.

2. Mechanisms of horizontal mitochondrial transfer

Multiple cell-type-specific mechanisms of mitochondrial transfer have been linked to various physiological and pathological processes in different tissues. Cancer cells have shown to be capable of releasing mitochondria by establishing direct or indirect cell-cell interactions that will be described below (Fig. 1).

2.1. Tunneling nanotubes (TNTs)

Amongst the cellular structures highly contributing to cell-to-cell communication are tunneling nanotubes: long, membranous protrusions connecting distant cells that were discovered in 2004 by Rustom and colleagues [10]. These cellular extensions are unique as they allow the transfer of various-sized cargoes, from small molecules (e.g. calcium ions) and macromolecules (nucleic acids, proteins, etc.) to entire organelles, including mitochondria. These long tubular structures, with 50–1500 nm diameters, can span several tens to hundreds of microns, connecting two distant cells together, thus forming extensive intercellular networks. Formation of TNTs has been observed in a number of cancer cell types, [11], either connecting cancer cells together or cancer cells to healthy stromal cells, notably mesenchymal stem cells (MSCs). Examples of the latter include bidirectional TNTs connections from nonmalignant IOSE human ovarian epithelial cells to SKOV3 ovarian cancer cells, stromal MC3T3 murine osteoblast cells to K7M2 osteosarcoma cells, or HeLa cells to fibroblasts [12,13]. Mitochondria, as well as endosomes, lysosomes, ribosomes, are well-known TNT cargoes [14], and molecular motors such as Myosin Va, Myosin X [15], dynein and kinesin have been shown to be essential for trafficking through TNTs along actin fibers and microtubules [16–20]. Amongst the

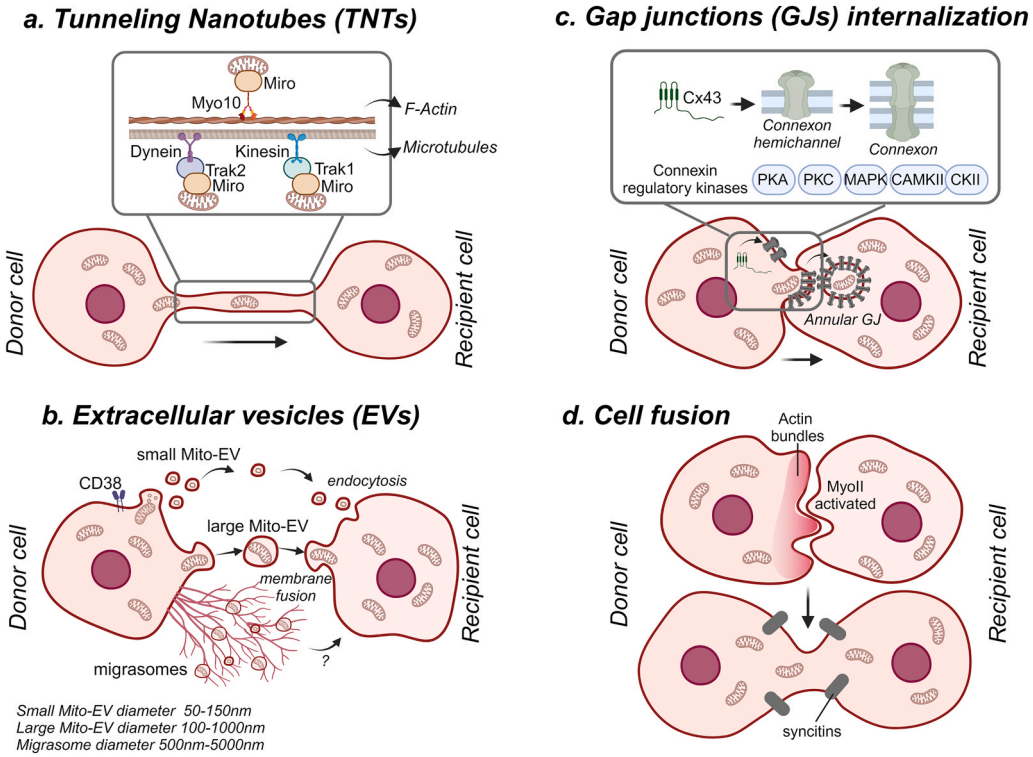

Fig. 1. Routes of mitochondrial transfer from donor to recipient cells. a) Trafficking of mitochondria through tunneling nanotubes (TNTs) occurs via actin filaments and microtubules connecting donor-to-recipient cytoplasms. This process involves molecular motors such as myosins, kinesin and dynein as well as adaptors such as Miro proteins, Trak1 and Trak2. b) Extracellular vesicles (EVs) can mediate mitochondrial transfer between two distant cells. Their size varies from 50 nm to 5000 nm and they can shuttle either intact or fragmented mitochondria. Mitochondria-containing EVs bud off or are secreted/released from donor cells, and then are taken up by recipient cells by fusing with their plasma membrane. c) Cx43-mediated gap junctions (GJs) facilitate mitochondrial transfer at cell-cell junctions. Trafficking of mitochondria through GJs can occur when recipient cells' plasma membrane invaginates donor cell GJ, forming the so called annular GJ, so leading to the internalization of cytoplasmic content, including donor mitochondria. The figure depicts the formation of connexon channels from a single transmembrane connexin that is regulated by phosphorylation of Cx43, performed by the indicated protein kinases. d) Cell fusion facilitates the sharing of mitochondria during either transient or permanent fusion of the plasma membrane of two cells. This process is preceded by the remodeling of actin filaments in the donor cell to form bundles, and by the activation of Myosin II in the recipient cell. Expression of syncitins in the cell surface of two fusing cells is required for a complete fusion. Created with BioRender.com. Miro: Mitochondrial Rho (MIRO) GTPases; Trak1: Trafficking Kinesin Protein 1; Trak2: Trafficking Kinesin Protein 2; Myo10: Myosin 10; Cx43: Connexin 43; MyoII: Myosin II; PKA: Protein kinase A; PKC: Protein kinase C; MAPK1: Mitogen-Activated Protein Kinase 1; CAMKII: Calcium/Calmodulin Dependent Protein Kinase II; CKII: Casein Kinase II.

key regulators of the directionality of TNT-mediated mitochondrial trafficking is the small GTPase Miro1, which was found to be upregulated in the mitochondrial membrane of donor cells [21]. The most important role of Miro1 is the regulation of mitochondrial movement and distribution within (and among) cells, acting as an adaptor linking organelles to cytoskeleton-associated motor proteins. In line with this function, deletion of Miro1 in mouse embryonic fibroblast (MEFs) results in the perinuclear clustering of mitochondria, altering intracellular ATP:ADP gradients, and impairs energy-expensive cell migratory processes [22]. Although the majority of studies focused on the multiple functions of Miro1 in pathophysiological contexts [23–27], its implication in several cancer settings is newly emerging [28]. In particular, Miro1-dependent mitochondrial control is crucial to face oxidative stress [27]. In cancer cells with aberrant oxidative phosphorylation, mitochondrial transfer is necessary to initiate tumor progression and intracellular positioning of mitochondria is crucial for further invasion and metastasis.

Both intrinsic and extrinsic cancer features can influence mitochondrial transfer by means of TNTs formation. It was reported that, under oxidative stress conditions, upregulation of p53 and activation of the AKT-PI3K-mTOR signaling pathway triggers the formation of TNTs from stressed cells to non-stressed cells, and induces the transcellular transport of four organelles including mitochondria [11]. P53, indeed, as an oncosuppressor, could control cellular homeostasis through the induction of intracellular material transfer to prevent intracellular toxicity. Given these functions, targeting TNTs formation could be of great therapeutic interest to curtail vital cancer processes and improve treatment efficacy.

2.2. Extracellular vesicles (EVs)

Extracellular vesicles are a heterogeneous group of biological nanoparticles that can be classified according to the cellular compartment they originate from and their morphology and size. In details, EVs comprise exosomes (~30–150 nm in diameter) [29], microvesicles (~200–1000 nm), large oncosomes (>1000 nm) [30], apoptotic vesicles (~50–2000 nm), and the newly described exomeres (<50 nm) [31] and migrasomes [32].

In the last decades, EVs raised a great interest because of their ability to carry and "protect" biologically active molecules in the extracellular environment and through the body fluids; for this reason, they are considered an important means of intercellular communication. These vesicles are structurally composed by a lipidic bilayer enclosing their heterogeneous molecular cargo composed of lipids [33], proteins [34], nucleic acids (DNA, RNA, microRNA) [35] and organelles such as mitochondria [36]. Stress or injury induce cells to encapsulate mitochondria or mitochondrial fragments into EVs, defined as mitoEVs, in a regulated way [37]. Different studies describe the presence of multiple types of mitochondrial components in mitoEVs, such as mitochondrial DNA (mtDNA) fragments, full-length mtDNA, mitochondrial proteins and even intact mitochondria [38–41], depending on the EVs size [42,43]. For instance, Johnson and colleagues described the presence of intact mitochondria in CD19+ large extracellular vesicles, identified in diagnostic samples of acute lymphoblastic leukemia patients [44]. In migrating cells, the damaged mitochondria are uploaded in migrasomes to maintain the homeostasis of the mitochondrial pool and their quality, with a process called '*mitocytosis*' [45]. Mechanistically, mitocytosis is regulated by the coordinated action of KIF5B, a protein that control the outward movement of mitochondria [46], the pro-fission factor dynamin-related protein 1 (Drp1) [47] and Myosin19, a myosin isoform that binds both mitochondria and actin [48–50].

Mitochondria-containing EVs, once released into the extracellular environment, enter into bodily fluids, such as blood or interstitial fluid, and are internalized by recipient cells through mechanisms like endocytosis, phagocytosis, or direct membrane fusion [51,52]. Nowadays, the mechanisms governing mitochondrial encapsulation, release and uptake by EVs need to be fully elucidated. Indeed, tumor cells can exploit mitochondrial transfer to enhance their survival and metastatic potential (see below).

2.3. Gap Junctions (GJs)

Gap junctions are clusters of intercellular channels (assembled connexins, Cx) facilitating the exchange of small molecules, such as nutrients (with molecular mass <1000 Da) among neighboring cells [53] to protect cells from injury, or participating on clathrin-dependent EV endocytosis [54]. Over 20 known Cx isoforms, Cx43 is the most expressed and studied. Cx43 is involved in a series of physiological functions, such as vesicle transport and mitochondrial respiration. While the canonical role of GJ limits the possibility to transfer organelles, it has been observed an alternative structure, called connexosome or annular gap junction, formed when one of the two connected cells engulf the gap junction, together with part of the plasma membrane and cytosol of its neighboring cell, to form a double membrane vesicle. Several works suggest that this structure may facilitate the transfer of mitochondria as well other cytoplasmic components among cells [55–59]. Horizontal mitochondrial transfer associated with gap junctions was reported to occur through Cx43 gap junctions within ovarian follicles [58] or from donor hematopoietic progenitors to stromal cells [60]. This evidence supports the idea that exchange of these organelles could shape cell fate even in the TME. Interestingly, Cx43 is documented to be involved also in TNT formation in various other scenarios of mitochondrial transfer, including asthmatic inflammation, viral infections, and leukemia [61–63], proposing a broader role for the connexin system in mediating mitochondrial transfer beyond gap junctions.

2.4. Cell fusion

Cell fusion is a process by which two individual cells fuse their plasma membranes to form a multinucleate cell [64]. When two cells are juxtaposed, cytosolic constituents and organelles are hence evenly or, in some cases, partially shared [65], resulting in the delivery of mitochondria [66]. Cell-cell fusion can happen by homotypic (hybrids of two identical cell types) or heterotypic (hybrids of different cell types) mechanisms. Homotypic cell fusion predominantly occurs in physiologic processes, e.g. placentation and myogenesis, while both homo- and hetero-typic fusion events occur in cancer cells and in the TME between cancer cells and MSCs [67–69], macrophages [70,71], fibroblasts [72–74] or endothelial cells [75] respectively. In addition, cumulative reports have demonstrated that cancer cells can obtain new cellular features from cell fusions within the microenvironment [76,77]. In line with this, primary glioblastoma cells were found to take up mitochondria by engulfing tumor-activated stromal cells (TASCs), thereby sequestering TASCs' cellular components for themselves [78]. The principal molecular determinants of cell fusion are syncytins, the only fusogens expressed in humans, which were found to be upregulated in tumors such as neuroblastoma and endometrial cancer [79]. The expression of these proteins is fundamental to acquire pro-fusogenic properties and is propaedeutic to cell fusion initiation, thus its expression could become a biomarker to detect and study cell hybrids within tumors. Moreover, changes in intracellular contractile elements of cytoskeletal proteins have a profound influence on cell fusion events. These changes are mainly orchestrated by GTPases Rac1 and Cdc42, and the Arp2/3-WASP complex which reorganize the actinic cytoskeleton and promote an actin-mediated cell motility. Several tumors display overexpression of Arp2/3 that was found to be strictly associated with disease progression and metastases of several tumor types, including breast, lung, colorectal, prostate, and pancreas [80].

Recently, there has been growing skepticism about the somatic mutation theory (SMT) as a comprehensive explanation for all aspects of tumorigenesis. New theories suggest that abnormal mitochondria might play a critical role in the development of tumors. According to Seyfried

and Shelton's work, when the nuclei of normal cells are transplanted into the enucleated cytoplasm of tumor cells, the resulting cells can exhibit malignant behavior [81]. This opens the hypothesis that cytoplasmic abnormalities, e.g. those caused by dysfunctional mitochondria, may drive tumorigenesis rather than changes in nuclear genes. However, it is important to note that the malignant transformation of normal cells *via* cell fusion has been observed *in vivo* in a limited subset of solid tumors, such as breast, ovarian, colon, lung, renal cancers [82,83]. This indicates that the process may not be universal across all types of cancer. This could be explained by the fact that this process is known to be dependent on genetic instability levels, as well as on stemness features, which can be highly variable in different cancer types [82–84].

3. Biological functions of mitochondrial transfer in tumors

Both homotypic and heterotypic mitochondrial exchanges have been reported to play a role in tumor biology shaping cancer evolution at multiple levels, including regulation of the intratumoral metabolic state, the TME, the recognition by immune cells and ultimately metastases formation. Here, we review the main known functions of HMT in cancer biology (Fig. 2).

3.1. Cancer metabolism

A number of studies demonstrate that several cell types in the tumor-surrounding tissue can donate functional mitochondria to tumor cells. As a first result, cancer cells, that usually display high mtDNA damage and mitochondrial dysfunction, will benefit from mitochondrial supply. Cancer cells, after receiving mitochondria, restore mitochondrial respiration, which is reduced in several tumor types with respect to glycolysis, due to the Warburg effect. This metabolic boost potentiates cancer cell proliferation and malignant features, while reducing donor cell metabolic capacity. The first observations of this phenomenon was made using mitochondrial DNA-depleted cancer cells (ρ° cancer cells) in models of both breast cancer and melanoma both *in vitro* and *in vivo* [85]. The investigators demonstrated that the absence of mitochondrial respiratory functions impacts both tumor growth and the metastatic capability of ρ° cancer cells, while the acquisition of mtDNA from the TME of the host mouse re-established oxidative phosphorylation (OXPHOS) and tumor growth [85]. Interestingly, Bajzikova and co-workers elucidate that, after mtDNA uptake, the rescue of cancer cell proliferation depends on OXPHOS-induced reactivation of dihydroorotate dehydrogenase (DHODH)-driven pyrimidine synthesis, rather than on ATP production [86]. Another work highlighted that the direct transfer of intact mitochondria from MSCs was responsible for the mtDNA gain described above [87]. A prominent role in this context is

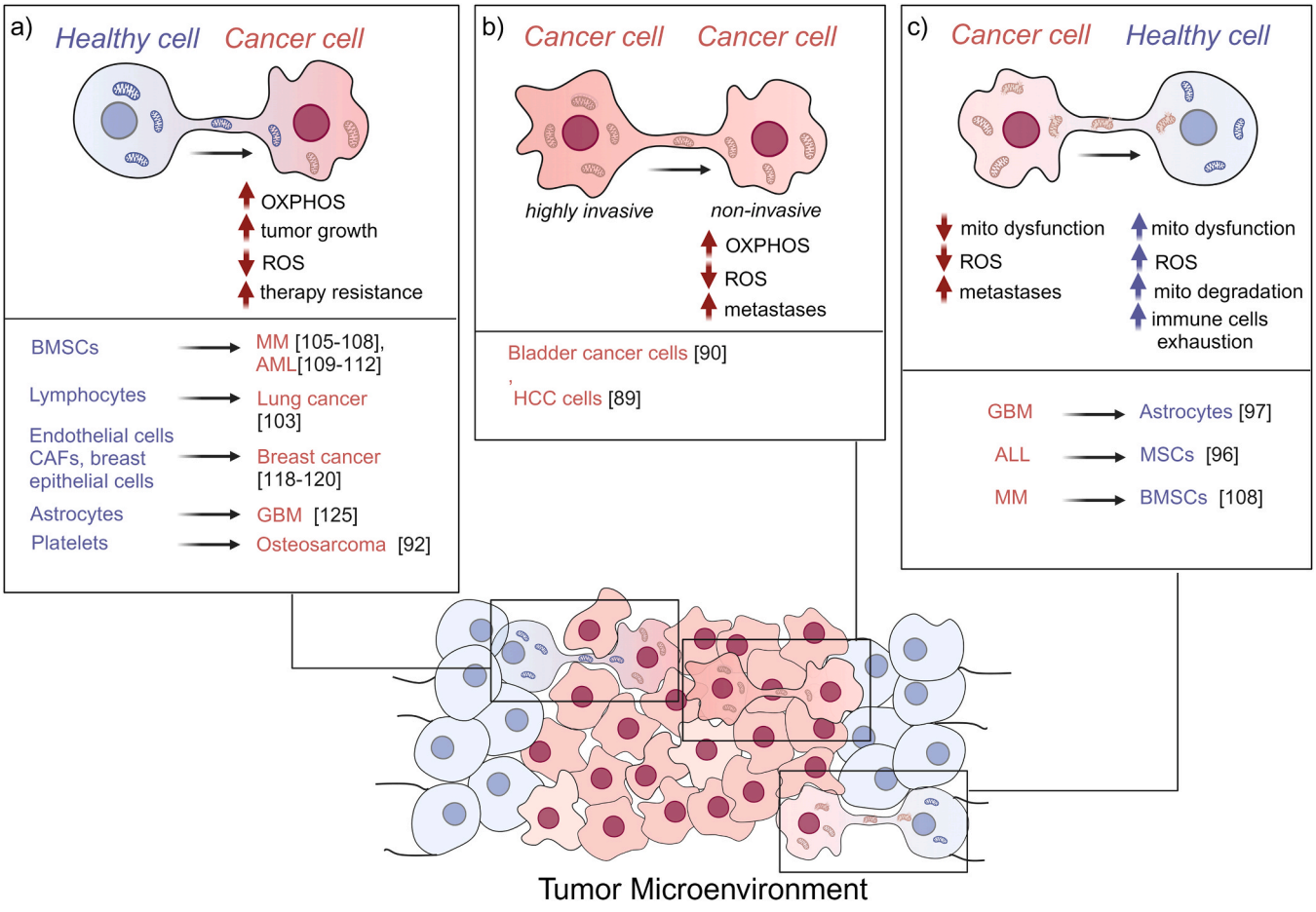

Fig. 2. Horizontal mitochondrial transfer (HMT) in the TME and its biological effects. Transfer of mitochondria in the TME can occur via multiple intercellular connections. a) Cancer cells can steal mitochondria from healthy cells (e.g. CAF, astrocytes, MSCs) as a mechanism to potentiate OXPHOS, to reduce ROS levels and to enhance cancer growth or therapy resistance. b) Mitochondria can be transferred among different cancer cells shaping malignant properties in recipient cells. Mitochondria derived from high invasive cells can trigger new invasion capabilities in non-invasive recipient cancer cells. c) Cancer cells can deliver their damaged mitochondria to surrounding healthy cells in the TME, keeping their own mitochondrial quality control and outsourcing mitochondrial degradation to recipient cells. This event can favor tumor growth and relieve mitochondrial dysfunction in the donor cells, while inducing oxidative stress, metabolic impairment and immune escape in healthy recipient cells. Types of both donor cells and recipient tumors are indicated. Created with BioRender.com.

also exerted by cancer-associated fibroblasts (CAFs) which are involved in the metabolic reprogramming in solid tumors. Indeed, highly glycolytic CAFs, that do not exploit mitochondria as energy source, were reported to donate their mitochondria to adjacent prostate cancer cells boosting their OXPHOS capacity [88]. Thus, intercellular mitochondrial transfer mediated by CAFs could be considered as an additional way to support high energy in the TME; the enhancement of consuming malignant cells metabolism contributes to their enhanced malignancy. These series of studies put in light the relevance of mitochondrial respiration in tumor formation and point to mitochondrial acquisition from healthy cells as a founding event during tumorigenesis. Nevertheless, it may be important to determine which tumor-derived molecules may signal the need for mitochondrial supply to other cells in the microenvironment. Identification of those signals, that could result from mitochondrial dysfunction or from tumor-specific metabolic programs, could be critical to deepen our knowledge as well as to develop a targeted therapeutic intervention.

3.2. Cancer metastasis

A number of studies indicated that the acquisition of mitochondria could not only satisfy the metabolic requirements of cancer cells, but could also enable them with new malignant properties, ultimately leading to metastases. It is widely recognized that mitochondria are core regulators of metabolic reprogramming required for cancer cells to metastasize, and glycolysis, together with the associated lactate metabolism, promotes cancer cell invasion and epithelial-mesenchymal transition (EMT) programs. Numerous studies reported a key role for homotypic HMT in the promotion of invasion and metastases. In particular, the direct transfer of mitochondria from highly invasive cells led to an increase in cell migration and metastatic potential to low invasive cells [89,90]. This effect was found to be driven by F-actin redistribution, regulating cell-cell communications between bladder cancer cells [90]. Accordingly, the exchange of mitochondria through TNTs between HCC cells was found to trigger new invasion abilities in non-invasive recipient cells through the HMGB1-RHOT1 molecular axis [89]. Particularly interesting is RHOT1, a protein involved in mitochondrial transport that can regulate the spatial localization of mitochondria within and between cells [91]. Currently, the role of RHOT1 in mitochondrial positioning is mostly studied in neurons [23–25], and its involvement in cancer is still underappreciated. Several studies report an upregulation of RHOT1 in pancreatic cancer patients consistent with its genetic down regulation, resulting in reduced migration and invasion of SW1990 pancreatic cancer cells [28]. Deepening our knowledge about specific regulators of mitochondrial positioning within cancer cells and among them would be significant to understand mitochondrial dependent control of cancer metastases. A different function for mitochondrial transfer in cancer metastases was recently reported in a work by Zhang and colleagues. They discovered that osteosarcoma cells can acquire mitochondria from platelets: in contrast to other studies revealing the rescue of aerobic respiration after mitochondrial transfer in cancer cells, they found that platelets-derived mitochondria induced a metabolic shift, increasing anaerobic glycolysis while reducing ROS levels both *in vitro* and *in vivo* [92]. In line with these findings, the induction of mitochondrial dysfunction in platelets led to the transfer of damaged mitochondria to cancer cells, activating PINK1-Parkin dependent mitophagy and ultimately reducing the incidence of metastases *in vivo* [92]. The authors suggest targeting platelet-derived mitochondria as a strategy to counteract lung metastases, through the impairment of metabolic shift in primary osteosarcoma cells [92]. These studies underscore the key role of mitochondrial transfer in modulating multiple stages of cancer, through their direct effect both on cancer cell metabolism and on regulation of signal transduction pathways during cancer progression.

3.3. Mitochondria clearance

While most studies have clarified the role of cancer cells as recipients of healthy mitochondria from various cell populations within the TME, cancer cells can also act as donors of damaged mitochondria. The intercellular exchange of unhealthy mitochondria is a phenomenon that has been highlighted in different physiopathological conditions involving damaged tissue repair, inflammation, thermogenesis, neurodegenerative diseases, myocardial fibrosis and also in cancer (reviewed by Li et al., 2024) [93]. Damaged or depolarized mitochondria are mainly degraded by intracellular pathways including the fine-tuned regulation between fusion and fission processes and mitophagy, a selective form of mitochondrial autophagy enabling entire organelle degradation. Transcellular degradation of mitochondria was first revealed between retinal ganglion axons and astrocytes [94]. The authors observed EV-engulfed mitochondria being extruded by axonal protrusions and being internalized and degraded via mitophagy by astrocytes. This phenomenon, termed '*transmitophagy*', is gaining increasing attention and has been proposed as a mechanism to protect neurons and prevent neuroinflammation in both Alzheimer and Parkinson's diseases [95]. Cancer cells can also deliver their damaged mitochondria to normal cells within their microenvironment to adapt to various conditions and avoid the overload of intracellular quality control machinery, thus favoring tumor progression [96]. Moreover, it was demonstrated that *in vitro* induction of hypoxia resulted in transferring mitochondria via TNTs from glioblastoma (GBM) cells to human primary astrocytes after co-culture [97]. Tumor-derived mitochondria were enlarged or fused and harbored mtDNA mutations. As a result, recipient astrocytes changed their metabolism becoming more reliant on glucose and glutamine [97]. In addition, mitochondrial exchange between GBM cancer cells and astrocytes confers protection to non-tumor astrocytes from hypoxic conditions, suggesting a pivotal role in GBM response to therapy. These studies underlie the relevance of HMT as a means to mitigate the effects of mitochondrial dysfunction. Given that cancer cells can be both recipients and donors of mitochondria, it will be highly relevant to study the context-dependent regulation of this phenomenon. Differential metabolic states may dictate the directionality of mitochondrial transfer. OXPHOS-dependent cancers would preferentially import functional mitochondria to increase respiration, while glycolytic cancers would prefer to reduce intracellular ROS by outsourcing mitochondrial degradation. Furthermore, intratumor heterogeneity could influence metabolic-dependent regulation of mitochondrial transfer within the same tumor mass.

3.4. Anti-cancer immunity

Mitochondrial transfer can impact immune regulation and this phenomenon elicits great interest in oncology because of its potential role in modulating the TME and, thus, influencing immune responses against tumor cells. The regulation of anticancer immune activity by mitochondrial exchange represents a complex interplay among cancer cells, immune cells, and the TME. The HMT between immune cells and cancer cells has been reported to have both anti-tumor and pro-tumor effects through different mechanisms [11,98,99]. For instance, the release of mtDNA into the cytoplasm can trigger innate immune signaling pathways, such as the pathway of cyclic GMP-AMP synthase (cGAS) and stimulator of interferon genes (STING), acting as damage-associated molecular patterns (DAMPs) and leading to the production of proinflammatory cytokines and the activation of anti-tumor immune responses [100,101]. Conversely, the mitochondrial transfer from lymphocyte to cancer cells modulates the immunosuppressive characteristics of the TME both through TNTs and EVs [102], by the up-regulation of Programmed Death-Ligand 1 (PD-L1) and thus the inhibition of lymphocyte cytotoxic activity, together with the induction of tumor cell proliferation [11,103]. In addition, cancer cells are described to be able to hijack mitochondria using TNTs, depriving

immune cells of these powerhouse organelles crucial for their activation and at the same time empowering their own metabolism. This unidirectional transfer of mitochondria (from immune cells to cancer cells) is associated with poor clinical outcomes and can be considered as a mechanism of immune evasion [98,104]. Further effort is needed to elucidate the precise mechanisms underlying this mitochondrial exchange with the aim of developing innovative therapeutic strategies targeting mitochondrial transfer for cancer immunotherapy.

4. Mitochondrial transfer in different cancer types

4.1. Mitochondrial transfer in hematological cancers

The transfer of mitochondria between hematological cancer cells and surrounding non-cancerous cells, such as stromal and/or blood vessels in bone marrow (BM) TME, influences disease progression, metastasis formation, drug resistance, immune escape, immune surveillance and the TME.

4.1.1. Multiple myeloma (MM)

MM, a widespread hematological cancer characterized by an abnormal clonal proliferation of malignant plasma cells (PCs) in BM. Malignant clones interaction with bone marrow stromal cells (BMSCs) was found to be critical for MM cells survival [105]. Interestingly, mitochondrial transfer from BMSCs to MM cells has been shown to support the metabolic demands of the tumor cells, supporting their survival and proliferation. Marlein and coworkers, indeed, showed that MM cells acquired mitochondria from BMSCs through CD38-dependent tumor-derived TNT. After mitochondrial transfer, MM relies on both oxidative phosphorylation and glycolysis with a consequent increase in cellular respiration and proliferation [105]. Other factors involved in the mitochondrial transfer process are CXCL12 and its receptor CXCR4 [106]. In fact, it was demonstrated that the Plerixafor-mediated inhibition of CXCR4 results in a decreased transmission of mitochondria between MSCs and MM cells [107]. Interestingly, a recent research described that the mitochondrial transfer between BMSCs and MM cells could be bidirectional and could be mainly mediated by TNTs, and in part by cell fusion. This process is enhanced by chemotherapeutic treatment in a dose-dependent manner; this results, on one hand, in increasing high ATP-MM cell survival and reducing mitochondrial superoxide levels, on the other hand enhancing superoxide levels in BMSCs. The supporting effect of mitochondrial transfer between MM cells and BMSCs could be prevented with the administration of an inhibitor of oxidative phosphorylation that influences MM cell metabolism [108].

4.1.2. Acute myeloid leukemia (AML)

The role of BMSCs in the interaction with transformed cells has been studied also in AML, a very aggressive hematological cancer that arises in the BM by an abnormal proliferation of transformed myeloid cells. In AML, NADPH oxidase-2 (NOX-2) drives the transfer of mitochondria by producing superoxide that stimulates BMSCs with a consequent increase of cancer cell survival [109]. Besides the supporting role of BMSCs through the mitochondrial transmission, this process can affect AML chemoresistance. In fact, some evidence demonstrated that stromal cells are able to transfer intact mitochondria to AML cells *via* endocytic pathways, resulting in a promotion of OXPHOS-dependent ATP production and influencing AML susceptibility to cytarabine (or Ara-C) [110,111]. Under these conditions, it was described that metformin, a widely used pharmaceutical for type II diabetes treatment, inhibits the transport of healthy mitochondria in AML cells, thus reducing the resistance to Ara-C acquired after mitochondria transferring [112]. Furthermore, the transfer of mitochondria in this malignancy occurs by both TNTs or endocytic pathways and it could represent a promising therapeutic target because of its role in influencing the chemotherapeutic susceptibility of cancer cells [113]. The mentioned studies strengthen the importance of stromal cells in supporting cancer cells through the mitochondrial transfer in BM TME in the context of AML.

4.1.3. Chronic myeloid leukemia (CML)

CML is a myeloproliferative disease of BM often caused by a reciprocal translocation of a part of chromosomes 9 and 22 leading to the formation of BCR-ABL fusion gene. Similarly to the other mentioned hematological tumors, the surrounding cells in TME plays an important role in favoring drug resistance and inhibiting CML cell apoptosis thanks to the intercellular interaction including the exchange of mitochondria through TNTs [114].

4.1.4. Acute lymphoblastic leukemia (ALL)

Finally, HMT has been demonstrated in ALL, a tumor that emerges following malignant transformation of lymphoblast, a precursor of the lymphoid line of blood cells, and is characterized by the development of large numbers of immature lymphocytes. In this pathological context, the mitochondrial transfer can occur through CD19 expressing EVs that can be considered as biomarkers for this type of cancer [44]. ALL includes T cell acute lymphoblastic leukemia (T-ALL) and B cell acute lymphoblastic leukemia (B-ALL), depending on the type of progenitor that underwent the transformation. In these malignancies, the mitochondrial transfer promotes cancer development and cell survival. Differently from AML that imports mitochondria from stromal cells to meet its energy requirements, T-ALL is characterized by a glycolytic metabolism and needs to secrete mitochondria in order to decrease ROS levels. A work by Wang and colleagues revealed a bidirectional transfer of mitochondria between MSCs and T-ALL cells via TNTs [96]. Following chemotherapy, indeed, T-ALL cells transferred a significantly higher number of mitochondria to adherent MSCs compared to the mitochondria received from MSCs. This resulted in decreased mitochondrial ROS production and enhanced resistance to chemotherapy [96]. In a recent study, the authors demonstrated that B-ALL-derived MSCs acquire a CAF phenotype, following the administration of chemotherapeutic drugs as Ara-C or erythromycin. These MSCs transfer their mitochondria to B-ALL cells by TNTs, thereby protecting cancer cells from ROS-induced cell death and reducing their susceptibility to drug treatment [115].

4.2. Mitochondrial transfer in solid tumors

Up to date, HMT in solid tumors seems to rely on TNTs as the main delivery route [116]. Cells of mesenchymal origin and CAFs are the most common mitochondrial donor cells. However, TME is composed of many different cell types, and competition among cells could have a significant influence on mitochondrial transfer. Furthermore, the structural organization of tumor masses can result in distinct metabolic features within cancer cells, influencing the specific pattern of mitochondrial spread. Both the donation and acceptance of mitochondria by cancer cells have been observed in solid tumors, with most evidence highlighting cancer cells as recipients of mitochondria from populations in the TME to enhance their malignant properties.

4.2.1. Lung cancer

A pioneering study from Spees et al. (2006), by means of in vitro co-culture experiments, first observed active mitochondria transferring from MSCs tomtDNA-depleted A549 lung cancer cells, leading to the restoration of aerobic respiration [117]. More recently, lung cancer cells were found to partially fuse with infiltrated lymphocytes to share mitochondria. This relevant work revealed the occurrence of heterotypic cell-in-cell structures (CICs) by histochemistry, indicating the entry of one type of living cells into another type of cell in a wide spectrum of clinical lung cancer tissue specimens [103]. Intriguingly, they found that CIC positively correlates with lung cancer malignancy *in vivo*. Through specific labeling of lymphocyte mitochondria with MitoTracker Red CMXRos, the authors observed that CIC-dependent pro-tumorigenesis

essentially relies on the donation of mitochondria from infiltrating lymphocytes to cancer cells [103]. Indeed, mice xenografting with LLC cells previously incubated with lymphocyte-derived mitochondria resulted in enhanced tumor progression *in vivo* that was associated with increased PD-L1 expression, activation of ROS-dependent MAPK pathway activation and enhanced glucose metabolism, supporting tumor proliferation and immune evasion. These studies present a novel perspective on the role of mitochondria in immune-tumor cell interactions in the TME in the setting of lung cancer. In this view, mitochondrial-related CICs of immune cells and tumor cells may be a novel indicator of lung cancer prognosis, providing a novel target for the treatment of chemotherapy-resistant lung cancer.

4.2.2. Breast cancer

Heterotypic mitochondrial transfer was reported to have a significant role in breast cancer even if the evidence collected *in vivo* is still limited and partially controversial. Breast cancer cells have been found to form TNTs with several surrounding cell populations, through *in vitro* experiments, and to receive mitochondria from endothelial cells [118], CAFs [119], MSCs [118], and immune cells respectively [98]. All this evidence strengthens the hypothesis that breast cancer malignancy could be potentiated by the acquisition of mitochondria from cells in the microenvironment [119].

Strikingly, a very recent paper reported breast cancer cells hijacking mitochondria from immune cells via physical nanotubes, thereby metabolically empowering tumor cells while depleting immune populations in the microenvironment. Indeed, pharmacologic combination of L-778123, an inhibitor of farnesyltransferase and geranylgeranyltransferase 1, which partially inhibited nanotube formation and mitochondrial transfer, with PD-L1 inhibitor improved the antitumor outcomes *in vivo,* in a xenograft immunocompetent breast cancer model [98]. Considering these findings, the acquisition of mitochondria through nanotubes could emerge as a novel target for the development of next-generation immunotherapy agents against cancer.

In contrast with this evidence, and in line with a theory of cancer being driven from mitochondrial dysfunction, two independent papers documented an anti-tumor effect of cancer mitochondria restoration when healthy mitochondria were artificially transplanted *in vitro,* into breast cancer cells in culture [99,120]. Accordingly, Elliot and colleagues documented that the transfer of isolated mitochondria from normal breast epithelial cells MCF-12A to both MCF-7 and MDA-MB-231 breast cancer cells and adriamycin-resistant NCI/ADR-Res ovarian cancer cells reduced cancer cell growth and increased cell sensitivity to chemotherapeutic drugs such as doxorubicin, paclitaxel and carboplatin [120]. Furthermore, mitochondrial transfer from healthy cells via a Pep-1-mediated mechanism further supported impaired viability of MCF-7 breast cancer cells [99], and suppression of tumorigenicity *in vivo* in orthotopic mouse models, by using MDA-MB-231 human breast cancer cells [121]. Intriguingly, this opposite result underlies the tricky regulatory role of mitochondria in cancer cells, especially in occurrence of cellular mitochondrial transfer initiated by the synergistic or paracrine regulation from the peripheral environments.

4.2.3. Brain tumors

Brain tumors are complex diseases that are able to hijack cellular processes normally present in healthy tissues of the central nervous system. A number of studies point to a prominent role for both homotypic and heterotypic tumor cell connectivity in the malignancy and in the response to therapy.

Indeed, a pioneer work by Osswald *et al.*, first discovered the existence of ultra-long tubular protrusions in both astrocytomas and glioblastoma, whose number and length increases with tumor progression and correlates with dismal prognosis in patients [122]. This observation led to the discovery of the so-called tumor microtubes (TMs), filopodia-like structures, that can reach a length of 500 micrometers, resembling neuronal protrusions and that possess a potential prognostic value. The existence of TMs has been exclusively demonstrated in brain tumors and not in other cancers, to date. Respect to TNTs, TMs are remarkably thicker (average 1.7 μm vs. less than 1.0 μm), longer (several hundred μm, up to 500 μm vs. 30 μm on average), and have a significantly longer lifespan (over 200 days vs. a few hours) [123].

Since their initial discovery, numerous papers have demonstrated that the establishment of these kinds of synapses among brain cancer cells renders them more aggressive and refractory to radiotherapy-induced cell death [122,124].

Growth-associated protein 43 (GAP43), a neuronal protein known for its important role in axon guidance, is a major structural protein of TMs. Recently, it has been demonstrated that GBM cells acquire host mitochondria from astrocytes through a contact-dependent mechanism facilitated by GAP43+ structures consistent with TMs, resulting in enhanced metabolic activity and augmented tumorigenicity [125]. TMs structures were also found to mediate the delivery of tumor-derived mitochondria into neighboring astrocytes, resulting in their adaptation to the new tumor-related metabolism and hypoxic conditions. Indeed, under hypoxia, GBM cells establish both TNTs and TMs to deliver their dysfunctional mitochondria to astrocytes, conditions mimicking the TME, suggesting that trafficking of mitochondria may be involved in TM-dependent tumor malignancy [97].

Release of dysfunctional mitochondria to other cells was also proposed to be a mechanism to avoid the overload of mitochondrial quality control mechanisms and delegate the clearance of damaged mitochondria to surrounding cells. Moreover, GBM stem cells (GSCs) were reported to exchange mitochondria with mesenchymal stem cells [126] and tumor-activated stromal cells [78]. This process has been related to the metabolic switch of GSCs, supporting their resistance to standard treatment such as TMZ-based therapy. All this evidence corroborates the importance of studying this vital process in the context of malignant brain tumors to specifically target intercellular bridges to eradicate intrinsically resistant cancer cells.

4.2.4. Other tumors

Interestingly, using syngeneic mouse models, Dong and colleagues have discovered that the formation of melanomas is dependent on the acquisition of host mitochondria [87]. They induced tumorigenesis by inoculating mouse melanoma cells devoid of mtDNA (r0 cells) into syngeneic C57BL/6Nsu9-DsRed2 mice that express red fluorescent protein in mitochondria to trace their movement *in vivo*. Strikingly, they found that horizontal transfer of mitochondria to tumor cells leads to normalization of mitochondrial respiration and this event relies on the activity of key mitochondrial complex I (NDUFV1) and complex II (SDHC) subunits, respectively [87]. In line with this, targeting those complexes result in a significant retardation of melanoma formation pointing to a pivotal function of the electron transport chain in the control of effective mitochondrial transfer in cancer.

Another central player of mitochondrial function found to act as a mediator of mitochondrial exchange is the protein High mobility group protein 1 (HMGB1). HMGB1 is a nucleoprotein involved in maintaining nucleosome integrity and promoting gene transcription in the nucleus. It has been shown to translocate to the cytoplasm to regulate mitochondrial homeostasis and autophagy under hypoxic conditions [127,128] and to control hepatocellular carcinoma (HCC) progression [129]. Mitochondrial transfer has been proven in other cancer settings such as bladder cancer [90], laryngeal carcinoma [55] and pancreatic cancer [130]. These works underlie the concept that cell reprogramming during cancer development fuels mitochondrial exchanges in TME by acting at multiple intracellular levels ranging from nuclear to mitochondrial regulation. Moreover, identification about specific protein players in this process will help us to translate this knowledge to cancer therapy.

5. Targeting HMT in cancer therapy

Understanding mitochondrial-related processes provides new

insights into the metabolic plasticity of cancer cells and highlights potential therapeutic targets for disrupting tumor-supportive mitochondrial exchanges. Indeed, the treatment of several malignant and invasive solid tumors is hindered by insufficient knowledge about the influence of intercellular communication on anti-cancer therapy and vice-versa. Therefore, it is of vital importance to consider cancer as a complex and fully integrated disease in the host tissue.

Mitochondria trafficking represents a communication mechanism that is exploited by cancer cells in their favor. Targeting mitochondrial transfer in cancer therapy holds promising potential to revolutionize current treatment strategies (Fig. 3).

Research has identified several compounds that could disrupt mitochondrial transfer via TNTs, a major route for HMT in cancer. In this view, inhibiting structural determinants of TNTs formation could reduce mitochondrial transfer thereby hindering tumor cell survival and proliferation [131]. Thus, actin polymerization inhibitors, such as cytochalasin B and metformin, have been shown to reduce TNT formation [132]. In addition, Miro1, together with Miro2, could be considered as potential therapeutic targets to specifically block mitochondria delivery from cancer cells through TNTs. Direct inhibition of molecular motors, such as myosins, dynein and kinesins could also represent a strategy to block the bidirectional movement of mitochondria. For instance, it was proposed that pharmacological targeting of Myosin IX-actin interaction, by means of the small-molecule inhibitor J13, is able to reduce cancer cell growth by inducing cytoskeleton-dependent mitochondrial dynamics imbalance [133]. Recent evidence also suggests a strong translational impact for mitochondrial transfer in the context of cancer immunotherapy. Harada and colleagues described for the first time the benefit of artificial transfer of mitochondria into CAR T cells improving their metabolic fitness, leading to enhanced proliferative capacity and cytokine production, and *in vitro* and *in vivo* anti-tumor effects [134]. In this view, transplantation of mitochondria can emerge as a novel target for developing next-generation immunotherapy agents for cancer.

Furthermore, a work from Murphy and colleagues [135] demonstrated that Cx43 is upregulated in GBM. They discovered that both genetic and pharmacological inhibition of Cx43 by using αCT1, a selective inhibitor of Cx43 channel activity, can restore GBM sensitivity to TMZ. However, in this work the authors did not consider the implication of Cx43-dependent intercellular communication through mitochondrial transfer to other cells. TMZ is used also to treat other cancers and ongoing clinical trials are evaluating TMZ as a single agent to treat melanoma [135] and small cell lung cancer [136]. Hence, a combined TMZ and Cx43 inhibitory treatment could provide a new and effective therapy for GBM and other cancers by directly targeting mitochondrial transfer.

Additionally, mitochondrial fission, a process necessary for mitophagy and potentially for HMT, could be a novel therapeutic target. Several reports highlight Drp1, the master regulator of mitochondrial fission, to promote tumorigenic properties in brain tumor-initiating cells, enriched for fragmented mitochondria [137,138]. Indeed, pharmacological Drp1

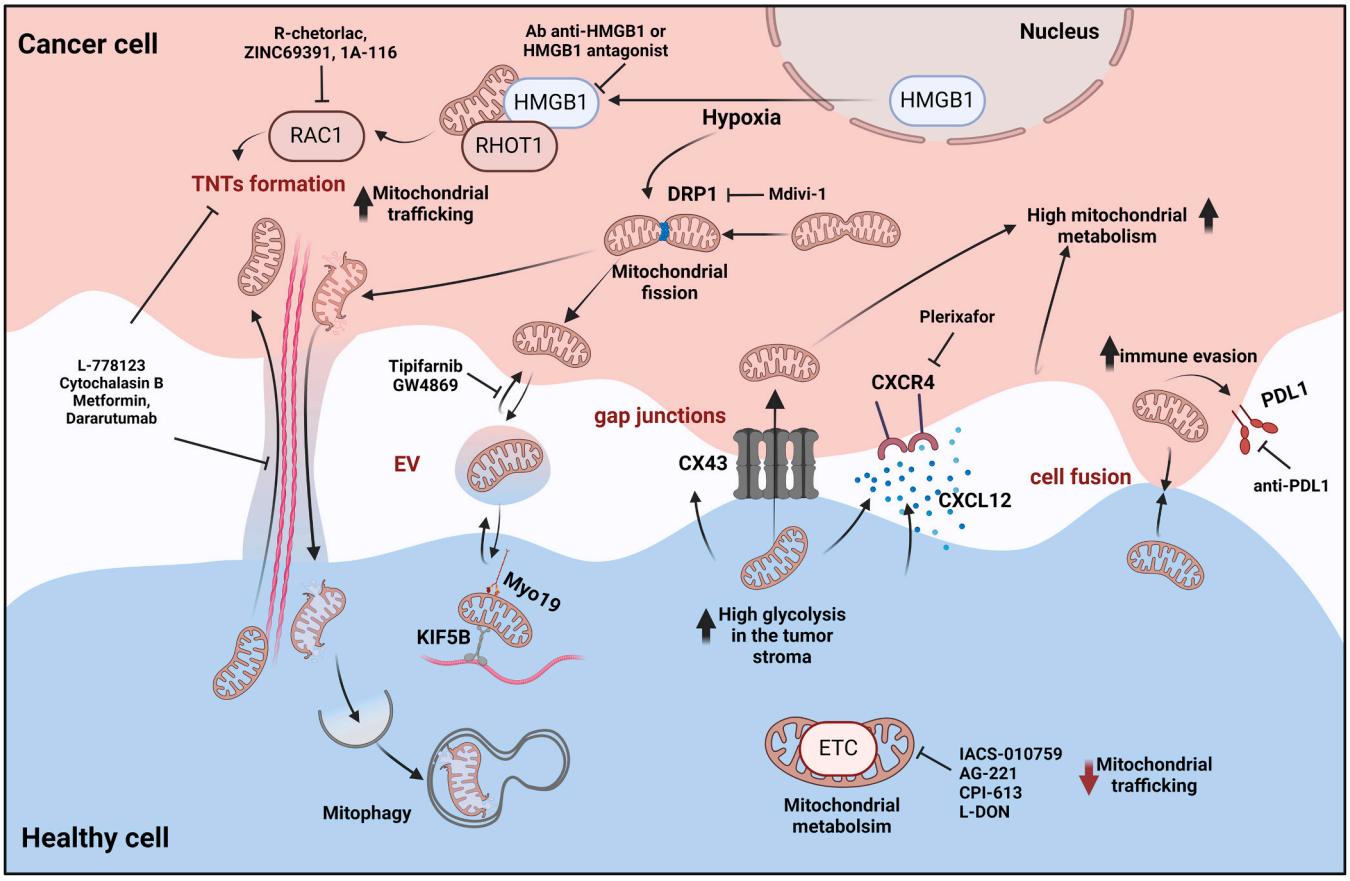

Fig. 3. Targeting horizontal mitochondrial transfer (HMT) in the TME. Transfer of mitochondria in the TME is coordinated by multiple tumor-specific intracellular and extracellular processes that can exploit diverse routes to either acquire healthy mitochondria from non-malignant cells, or to deliver their damaged mitochondria to maintain their own homeostasis. Targeting those processes to block the exchange of mitochondria could improve the effectiveness of cancer therapy. The upper part of the figure depicts the existing drugs that could target the cytoplasmic translocation of the nuclear factor HMGB1 induced by tumor hypoxia, which stimulates mitochondrial trafficking and TNTs formation. TNT formation can be blocked also by different indicated compounds interfering with actin polymerization, with players involved in the organization of microfilaments, as well as, with proteins that drive the mitochondrial dynamics. As shown in the lower part of the figure, targeting the metabolic state of non-malignant cells, which dictates their propensity to export their mitochondria to tumor cells, could efficiently block mitochondrial delivery. Created with BioRender.com.

inhibition through a small brain-permeable molecule suppressed the growth of latent metastatic cells and reduced brain metastatic burden in preclinical models. Inhibiting mitochondrial fission might simultaneously block mitophagy and mitochondrial transfer, offering a dual approach to hinder tumor growth [138]. Moreover, tumor hypoxia can also boost Drp1-dependent mitochondrial fission, leading to the generation of fragmented mitochondria that can be encapsulated and exchanged via EVs or can be delivered to healthy cells via TNT. Thus, specific inhibition of Drp1 in cancer cells could prevent mito-EV trafficking, as well as increase the amount of mitochondrial damage, thereby inducing tumor cell death [137–139].

6. Conclusions

Despite these advances, current inhibitors have limited specificity and efficacy, underscoring the need for further research. Developing precise inhibitors that specifically target TNTs and mitochondrial transfer mechanisms, without affecting normal cellular functions, is essential. Understanding the detailed molecular pathways and identifying specific druggable targets within these pathways could lead to more effective and less toxic cancer therapies. In summary, targeting mitochondrial transfer in cancer therapy offers a multifaceted approach to counteract tumor growth, chemoresistance, and metastasis. It might be possible to enhance the effectiveness of existing treatments and develop new therapeutic strategies, by disrupting the mechanisms that enable tumor cells to acquire mitochondria and energy from their microenvironment. As research progresses, the identification of specific and potent inhibitors will be critical to translate these insights into clinical practice, potentially leading to significant advancements in cancer treatment.

Author's contributions

VM and EV wrote the manuscript. VM prepared figures. VM, EV, FN and SC edited the work. All authors read and approved the final manuscript.

Funding

FN's lab is supported by the "Associazione Italiana Ricerca sul Cancro" (My First Airc Grant -Ref. 27019), by "CureSearch Young Investigator Awards in Pediatric Oncology Drug Development", by "Fondazione Roche per la Ricerca Indipendente", by the Italian Ministry of University and Research (PRIN PNRR P2022JLHZZ); SC' lab is supported by the Italian Ministry of University and Research (PRIN 2022 Prot. 20222Y9X43 and PRIN PNRR 2022 Prot. P2022NMJEC), by #NEXTGENERATIONEU (NGEU) and funded by the Ministry of University and Research (MUR), National Recovery and Resilience Plan (NRRP), project MNESYS (PE00000012), by the Italian Ministry of Health (RF-2019–12369700).

CRediT authorship contribution statement

Veronica Marabitti: Writing – original draft, Conceptualization. **Elisabetta Vulpis:** Writing – original draft, Conceptualization. **Francesca Nazio:** Writing – review & editing, Supervision, Funding acquisition, Data curation, Conceptualization. **Silvia Campello:** Writing – review & editing, Supervision, Funding acquisition, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

References

[1] O. Warburg, On the origin of cancer cells, Science 123 (1956) 309–314, https://doi.org/10.1126/SCIENCE.123.3191.309.
[2] B. Faubert, A. Solmonson, R.J. DeBerardinis, Metabolic reprogramming and cancer progression, Science 368 (2020), https://doi.org/10.1126/SCIENCE.AAW5473.
[3] S. Vyas, E. Zaganjor, M.C. Haigis, Mitochondria and cancer, Cell 166 (2016) 555–566, https://doi.org/10.1016/J.CELL.2016.07.002.
[4] H. Chen, D.C. Chan, Mitochondrial dynamics in regulating the unique phenotypes of cancer and stem cells, Cell Metab. 26 (2017) 39–48, https://doi.org/10.1016/J.CMET.2017.05.016.
[5] Z. Al Amir Dache, A.R. Thierry, Mitochondria-derived cell-to-cell communication, Cell Rep. 42 (2023), https://doi.org/10.1016/J.CELREP.2023.112728.
[6] A. Suomalainen, Mitochondrial DNA inheritance in humans: mix, match, and survival of the fittest, Cell Metab. 30 (2019) 231–232, https://doi.org/10.1016/J.CMET.2019.07.009.
[7] N. Borcherding, J.R. Brestoff, The power and potential of mitochondria transfer, Nature 623 (2023) 283–291, https://doi.org/10.1038/S41586-023-06537-Z.
[8] L.F. Dong, J. Rohlena, R. Zobalova, Z. Nahacka, A.M. Rodriguez, M.V. Berridge, J. Neuzil, Mitochondria on the move: horizontal mitochondrial transfer in disease and health, J. Cell Biol. 222 (2023), https://doi.org/10.1083/JCB.202211044.
[9] L.X. Zampieri, C. Silva-Almeida, J.D. Rondeau, P. Sonveaux, Mitochondrial transfer in cancer: a comprehensive review, Int J. Mol. Sci. 22 (2021), https://doi.org/10.3390/IJMS22063245.
[10] A. Rustom, R. Saffrich, I. Markovic, P. Walther, H.H. Gerdes, Nanotubular highways for intercellular organelle transport, Science 303 (2004) 1007–1010, https://doi.org/10.1126/SCIENCE.1093133.
[11] F. Guan, X. Wu, J. Zhou, Y. Lin, Y. He, C. Fan, Z. Zeng, W. Xiong, Mitochondrial transfer in tunneling nanotubes—a new target for cancer therapy, J. Exp. Clin. Cancer Res. 43 (2024), https://doi.org/10.1186/s13046-024-03069-w.
[12] V. Thayanithy, E.L. Dickson, C. Steer, S. Subramanian, E. Lou, Tumor-stromal cross talk: direct cell-to-cell transfer of oncogenic microRNAs via tunneling nanotubes, Transl. Res. 164 (2014) 359–365, https://doi.org/10.1016/j.trsl.2014.05.011.
[13] S. Desir, E.L. Dickson, R.I. Vogel, V. Thayanithy, P. Wong, D. Teoh, M.A. Geller, C. J. Steer, S. Subramanian, E. Lou, Tunneling nanotube formation is stimulated by hypoxia in ovarian cancer cells, 2016. https://doi.org/10.18632/oncotarget.9504.
[14] D. Cordero Cervantes, C. Zurzolo, Peering into tunneling nanotubes-The path forward, EMBO J. 40 (2021), https://doi.org/10.15252/EMBJ.2020105789.
[15] K. Gousset, L. Marzo, P.H. Commere, C. Zurzolo, Myo10 is a key regulator of TNT formation in neuronal cells, J. Cell Sci. 126 (2013) 4424–4435, https://doi.org/10.1242/JCS.129239.
[16] H. Halász, V. Tárnai, J. Matkó, M. Nyitrai, E. Szabó-Meleg, Cooperation of various cytoskeletal components orchestrates intercellular spread of mitochondria between b-lymphoma cells through tunnelling nanotubes, Cells 13 (2024), https://doi.org/10.3390/CELLS13070607.
[17] X. Wang, H.H. Gerdes, Transfer of mitochondria via tunneling nanotubes rescues apoptotic PC12 cells, Cell Death Differ. 22 (2015) 1181–1191, https://doi.org/10.1038/CDD.2014.211.
[18] J. Shen, J.H. Zhang, H. Xiao, J.M. Wu, K.M. He, Z.Z. Lv, Z.J. Li, M. Xu, Y.Y. Zhang, Mitochondria are transported along microtubules in membrane nanotubes to rescue distressed cardiomyocytes from apoptosis, Cell Death Dis. 9 (2018), https://doi.org/10.1038/S41419-017-0145-X.
[19] N. Resnik, D. Baraga, P. Glažar, Š. Jokhadar Zemljič, J. Derganc, K. Sepčić, P. Veranič, M.E. Kreft, Molecular, morphological and functional properties of tunnelling nanotubes between normal and cancer urothelial cells: new insights from the in vitro model mimicking the situation after surgical removal of the urothelial tumor, Front Cell Dev. Biol. 10 (2022), https://doi.org/10.3389/FCELL.2022.934684.
[20] A. Sartori-Rupp, D. Cordero Cervantes, A. Pepe, K. Gousset, E. Delage, S. Corroyer-Dulmont, C. Schmitt, J. Krijnse-Locker, C. Zurzolo, Correlative cryo-electron microscopy reveals the structure of TNTs in neuronal cells, Nat. Commun. 10 (2019), https://doi.org/10.1038/S41467-018-08178-7.
[21] Y. Zhang, Z. Yu, D. Jiang, X. Liang, S. Liao, Z. Zhang, W. Yue, X. Li, S.M. Chiu, Y. H. Chai, Y. Liang, Y. Chow, S. Han, A. Xu, H.F. Tse, Q. Lian, iPSC-MSCs with High Intrinsic MIRO1 and sensitivity to TNF-α yield efficacious mitochondrial transfer to rescue anthracycline-induced cardiomyopathy, Stem Cell Rep. 7 (2016) 749–763, https://doi.org/10.1016/J.STEMCR.2016.08.009.
[22] M.H. Schuler, A. Lewandowska, G.Di Caprio, W. Skillern, S. Upadhyayula, T. Kirchhausen, J.M. Shaw, B. Cunniff, Miro1-mediated mitochondrial positioning shapes intracellular energy gradients required for cell migration, Mol. Biol. Cell 28 (2017) 2159–2169, https://doi.org/10.1091/MBC.E16-10-0741.
[23] D. Grossmann, C. Berenguer-Escuder, A. Chemla, G. Arena, R. Krüger, The Emerging Role of RHOT1/Miro1 in the pathogenesis of parkinson's disease, Front Neurol. 11 (2020), https://doi.org/10.3389/FNEUR.2020.00587.
[24] E.L. Wilson, E. Metzakopian, ER-mitochondria contact sites in neurodegeneration: genetic screening approaches to investigate novel disease mechanisms, Cell Death Differ. 28 (2021) 1804–1821, https://doi.org/10.1038/S41418-020-00705-8.
[25] L. Kay, I.S. Pienaar, R. Cooray, G. Black, M. Soundararajan, Understanding Miro GTPases: Implications in the Treatment of Neurodegenerative Disorders, Mol. Neurobiol. 55 (2018) 7352–7365, https://doi.org/10.1007/S12035-018-0927-X.
[26] G. López-Doménech, J.H. Howden, C. Covill-Cooke, C. Morfill, J.V. Patel, R. Bürli, D. Crowther, N. Birsa, N.J. Brandon, J.T. Kittler, Loss of neuronal Miro1 disrupts

mitophagy and induces hyperactivation of the integrated stress response, EMBO J. 40 (2021), https://doi.org/10.15252/EMBJ.2018100715.
[27] H. Alshaabi, N. Shannon, R. Gravelle, S. Milczarek, T. Messier, B. Cunniff, Miro1-mediated mitochondrial positioning supports subcellular redox status, Redox Biol. 38 (2021), https://doi.org/10.1016/J.REDOX.2020.101818.
[28] Z. Nahacka, J. Novak, R. Zobalova, J. Neuzil, Miro proteins and their role in mitochondrial transfer in cancer and beyond, Front Cell Dev. Biol. 10 (2022), https://doi.org/10.3389/FCELL.2022.937753.
[29] L.T. Brinton, H.S. Sloane, M. Kester, K.A. Kelly, Formation and role of exosomes in cancer, Cell Mol. Life Sci. 72 (2015) 659–671, https://doi.org/10.1007/S00018-014-1764-3.
[30] A.C. Dixson, T.R. Dawson, D. Di Vizio, A.M. Weaver, Context-specific regulation of extracellular vesicle biogenesis and cargo selection, Nat. Rev. Mol. Cell Biol. 24 (2023) 454–476, https://doi.org/10.1038/S41580-023-00576-0.
[31] Q. Zhang, J.N. Higginbotham, D.K. Jeppesen, Y.P. Yang, W. Li, E.T. McKinley, R. Graves-Deal, J. Ping, C.M. Britain, K.A. Dorsett, C.L. Hartman, D.A. Ford, R. M. Allen, K.C. Vickers, Q. Liu, J.L. Franklin, S.L. Bellis, R.J. Coffey, Transfer of Functional Cargo in Exomeres, Cell Rep. 27 (2019) 940–954.e6, https://doi.org/10.1016/J.CELREP.2019.01.009.
[32] L. Ma, Y. Li, J. Peng, D. Wu, X. Zhao, Y. Cui, L. Chen, X. Yan, Y. Du, L. Yu, Discovery of the migrasome, an organelle mediating release of cytoplasmic contents during cell migration, Cell Res 25 (2015) 24–38, https://doi.org/10.1038/CR.2014.135.
[33] A. Llorente, T. Skotland, T. Sylvänne, D. Kauhanen, T. Róg, A. Orłowski, I. Vattulainen, K. Ekroos, K. Sandvig, Molecular lipidomics of exosomes released by PC-3 prostate cancer cells, Biochim Biophys. Acta 1831 (2013) 1302–1309, https://doi.org/10.1016/J.BBALIP.2013.04.011.
[34] C. Théry, M. Boussac, P. Véron, P. Ricciardi-Castagnoli, G. Raposo, J. Garin, S. Amigorena, Proteomic analysis of dendritic cell-derived exosomes: a secreted subcellular compartment distinct from apoptotic vesicles, J. Immunol. 166 (2001) 7309–7318, https://doi.org/10.4049/JIMMUNOL.166.12.7309.
[35] F. Momen-Heravi, S.J. Getting, S.A. Moschos, Extracellular vesicles and their nucleic acids for biomarker discovery, Pharm. Ther. 192 (2018) 170–187, https://doi.org/10.1016/J.PHARMTHERA.2018.08.002.
[36] W. Liang, S. Sagar, R. Ravindran, R.H. Najor, J.M. Quiles, L. Chi, R.Y. Diao, B. P. Woodall, L.J. Leon, E. Zumaya, J. Duran, D.M. Cauvi, A. De Maio, E.D. Adler, Å.B. Gustafsson, Mitochondria are secreted in extracellular vesicles when lysosomal function is impaired, Nat. Commun. 14 (2023), https://doi.org/10.1038/S41467-023-40680-5.
[37] X. Zhou, S. Liu, Y. Lu, M. Wan, J. Cheng, J. Liu, MitoEVs: A new player in multiple disease pathology and treatment, J. Extra Vesicles 12 (2023), https://doi.org/10.1002/JEV2.12320.
[38] A. Rai, H. Fang, B. Claridge, R.J. Simpson, D.W. Greening, Proteomic dissection of large extracellular vesicle surfaceome unravels interactive surface platform, J. Extra Vesicles 10 (2021), https://doi.org/10.1002/JEV2.12164.
[39] D. Valenti, R.A. Vacca, L. Moro, A. Atlante, Mitochondria Can Cross Cell Boundaries: An Overview of the Biological Relevance, Pathophysiological Implications and Therapeutic Perspectives of Intercellular Mitochondrial Transfer, Int J. Mol. Sci. 22 (2021), https://doi.org/10.3390/IJMS22158312.
[40] X. Wang, I. Weidling, S. Koppel, B. Menta, J. Perez Ortiz, A. Kalani, H.M. Wilkins, R.H. Swerdlow, Detection of mitochondria-pertinent components in exosomes, Mitochondrion 55 (2020) 100–110, https://doi.org/10.1016/J.MITO.2020.09.006.
[41] B. Zhang, S. Asadi, Z. Weng, N. Sismanopoulos, T.C. Theoharides, Stimulated human mast cells secrete mitochondrial components that have autocrine and paracrine inflammatory actions, PLoS One 7 (2012), https://doi.org/10.1371/JOURNAL.PONE.0049767.
[42] M.V. Berridge, J. Neuzil, The mobility of mitochondria: Intercellular trafficking in health and disease, Clin. Exp. Pharm. Physiol. 44 (Suppl 1) (2017) 15–20, https://doi.org/10.1111/1440-1681.12764.
[43] P. Sansone, C. Savini, I. Kurelac, Q. Chang, L.B. Amato, A. Strillacci, A. Stepanova, L. Iommarini, C. Mastroleo, L. Daly, A. Galkin, B.K. Thakur, N. Soplop, K. Uryu, A. Hoshinob, L. Norton, M. Bonafé, M. Cricca, G. Gasparre, D. Lyden, J. Bromberg, Packaging and transfer of mitochondrial DNA via exosomes regulate escape from dormancy in hormonal therapy-resistant breast cancer, Proc. Natl. Acad. Sci. USA 114 (2017) E9066–E9075, https://doi.org/10.1073/PNAS.1704862114.
[44] S.M. Johnson, C. Dempsey, C. Parker, A. Mironov, H. Bradley, V. Saha, Acute lymphoblastic leukaemia cells produce large extracellular vesicles containing organelles and an active cytoskeleton, J. Extra Vesicles 6 (2017), https://doi.org/10.1080/20013078.2017.1294339.
[45] H. Jiao, D. Jiang, X. Hu, W. Du, L. Ji, Y. Yang, X. Li, T. Sho, X. Wang, Y. Li, Y. T. Wu, Y.H. Wei, L. Yu, Mitocytosis, a migrasome-mediated mitochondrial quality-control process, Cell 184 (2021) 2896–2910.e13, https://doi.org/10.1016/J.CELL.2021.04.027.
[46] Y. Tanaka, Y. Kanai, Y. Okada, S. Nonaka, S. Takeda, A. Harada, N. Hirokawa, Targeted disruption of mouse conventional kinesin heavy chain, kif5B, results in abnormal perinuclear clustering of mitochondria, Cell 93 (1998) 1147–1158, https://doi.org/10.1016/S0092-8674(00)81459-2.
[47] S. Yu, L. Yu, Migrasome biogenesis and functions, FEBS J. 289 (2022) 7246–7254, https://doi.org/10.1111/FEBS.16183.
[48] B.I. Shneyer, M. Ušaj, A. Henn, Myo19 is an outer mitochondrial membrane motor and effector of starvation-induced filopodia, J. Cell Sci. 129 (2016) 543–556, https://doi.org/10.1242/JCS.175349.
[49] B.I. Shneyer, M. Ušaj, N. Wiesel-Motiuk, R. Regev, A. Henn, ROS induced distribution of mitochondria to filopodia by Myo19 depends on a class specific tryptophan in the motor domain, Sci. Rep. 7 (2017), https://doi.org/10.1038/S41598-017-11002-9.
[50] O.A. Quintero, M.M. DiVito, R.C. Adikes, M.B. Kortan, L.B. Case, A.J. Lier, N. S. Panaretos, S.Q. Slater, M. Rengarajan, M. Feliu, R.E. Cheney, Human Myo19 is a novel myosin that associates with mitochondria, Curr. Biol. 19 (2009) 2008–2013, https://doi.org/10.1016/J.CUB.2009.10.026.
[51] M. Mathieu, L. Martin-Jaular, G. Lavieu, C. Théry, Specificities of secretion and uptake of exosomes and other extracellular vesicles for cell-to-cell communication, Nat. Cell Biol. 21 (2019) 9–17, https://doi.org/10.1038/S41556-018-0250-9.
[52] L.A. Mulcahy, R.C. Pink, D.R.F. Carter, Routes and mechanisms of extracellular vesicle uptake, J. Extra Vesicles 3 (2014), https://doi.org/10.3402/JEV.V3.24641.
[53] D.A. Goodenough, D.L. Paul, Gap junctions, Cold Spring Harb. Perspect. Biol. 1 (2009), https://doi.org/10.1101/CSHPERSPECT.A002576.
[54] J.C. Sáez, V.M. Berthoud, M.C. Brañes, A.D. Martínez, E.C. Beyer, Plasma membrane channels formed by connexins: their regulation and functions, Physiol. Rev. 83 (2003) 1359–1400, https://doi.org/10.1152/PHYSREV.00007.2003.
[55] I. Antanavičiute, K. Rysevaite, V. Liutkevičius, A. Marandykina, L. Rimkute, R. Sveikatiene, V. Uloza, V.A. Skeberdis, Long-distance communication between laryngeal carcinoma cells, PLoS One 9 (2014), https://doi.org/10.1371/JOURNAL.PONE.0099196.
[56] M.N. Islam, S.R. Das, M.T. Emin, M. Wei, L. Sun, K. Westphalen, D.J. Rowlands, S. K. Quadri, S. Bhattacharya, J. Bhattacharya, Mitochondrial transfer from bone-marrow-derived stromal cells to pulmonary alveoli protects against acute lung injury, Nat. Med 18 (2012) 759–765, https://doi.org/10.1038/NM.2736.
[57] R. Schulz, P.M. Görge, A. Görbe, P. Ferdinandy, P.D. Lampe, L. Leybaert, Connexin 43 is an emerging therapeutic target in ischemia/reperfusion injury, cardioprotection and neuroprotection, Pharm. Ther. 153 (2015) 90–106, https://doi.org/10.1016/J.PHARMTHERA.2015.06.005.
[58] R.P. Norris, M. Terasaki, Gap junction internalization and processing in vivo: a 3D immuno-electron microscopy study, (2021). https://doi.org/10.1242/jcs.252726.
[59] Y. Qin, X. Jiang, Q. Yang, J. Zhao, Q. Zhou, Y. Zhou, The Functions, Methods, and Mobility of Mitochondrial Transfer Between Cells, Front Oncol. 11 (2021), https://doi.org/10.3389/fonc.2021.672781.
[60] K. Golan, A.K. Singh, O. Kollet, M. Bertagna, M.J. Althoff, E. Khatib-Massalha, E. Petrovich-Kopitman, A.M. Wellendorf, H. Massalha, S. Levin-Zaidman, T. Dadosh, B. Bohan, M. V. Gawali, B. Dasgupta, T. Lapidot, J.A. Cancelas, Bone marrow regeneration requires mitochondrial transfer from donor Cx43-expressing hematopoietic progenitors to stroma, Blood 136 (2020) 2607–2619, https://doi.org/10.1182/BLOOD.2020005399.
[61] Y. Yao, X.L. Fan, D. Jiang, Y. Zhang, X. Li, Z.Bin Xu, S.Bin Fang, S. Chiu, H.F. Tse, Q. Lian, Q.L. Fu, Connexin 43-Mediated Mitochondrial Transfer of iPSC-MSCs Alleviates Asthma Inflammation, Stem Cell Rep. 11 (2018) 1120–1135, https://doi.org/10.1016/J.STEMCR.2018.09.012.
[62] G. Okafo, L. Prevedel, E. Eugenin, Tunneling nanotubes (TNT) mediate long-range gap junctional communication: Implications for HIV cell to cell spread, Sci. Rep. 2017 7:1 7 (2017) 1–9, https://doi.org/10.1038/s41598-017-16600-1.
[63] E. Griessinger, R. Moschoi, G. Biondani, J.F. Peyron, Mitochondrial Transfer in the Leukemia Microenvironment, Trends Cancer 3 (2017) 828–839, https://doi.org/10.1016/J.TRECAN.2017.10.003.
[64] H.S. Bagheri, F. Bani, S. Tasoglu, A. Zarebkohan, R. Rahbarghazi, E. Sokullu, Mitochondrial donation in translational medicine; from imagination to reality, J. Transl. Med 18 (2020) 1–18, https://doi.org/10.1186/S12967-020-02529-Z/TABLES/1.
[65] P.S. Aguilar, M.K. Baylies, A. Fleissner, L. Helming, N. Inoue, B. Podbilewicz, H. Wang, M. Wong, Genetic basis of cell-cell fusion mechanisms, Trends Genet 29 (2013) 427–437, https://doi.org/10.1016/J.TIG.2013.01.011.
[66] M.O. Gomzikova, V. James, A.A. Rizvanov, Mitochondria Donation by Mesenchymal Stem Cells: Current Understanding and Mitochondria Transplantation Strategies, Front Cell Dev. Biol. 9 (2021), https://doi.org/10.3389/fcell.2021.653322.
[67] C. Sun, D. Zhao, X. Dai, J. Chen, X. Rong, H. Wang, A. Wang, M. Li, J. Dong, Q. Huang, Q. Lan, Fusion of cancer stem cells and mesenchymal stem cells contributes to glioma neovascularization, Oncol. Rep. 34 (2015) 2022–2030, https://doi.org/10.3892/OR.2015.4135.
[68] H.J. Wei, J.A. Nickoloff, W.H. Chen, H.Y. Liu, W.C. Lo, Y.T. Chang, P.C. Yang, C. W. Wu, D.F. Williams, J.G. Gelovani, W.P. Deng, FOXF1 mediates mesenchymal stem cell fusion-induced reprogramming of lung cancer cells, Oncotarget 5 (2014) 9514–9529, https://doi.org/10.18632/ONCOTARGET.2413.
[69] C. Melzer, J. von der Ohe, R. Hass, In Vitro Fusion of Normal and Neoplastic Breast Epithelial Cells with Human Mesenchymal Stroma/Stem Cells Partially Involves Tumor Necrosis Factor Receptor Signaling, Stem Cells 36 (2018) 977–989, https://doi.org/10.1002/STEM.2819.
[70] G.A. Clawson, G.L. Matters, P. Xin, Y. Imamura-Kawasawa, Z. Du, D. M. Thiboutot, K.F. Helm, R.I. Neves, T. Abraham, Macrophage-tumor cell fusions from peripheral blood of melanoma patients, PLoS One 10 (2015), https://doi.org/10.1371/JOURNAL.PONE.0134320.
[71] C.E. Gast, A.D. Silk, L. Zarour, L. Riegler, J.G. Burkhart, K.T. Gustafson, M. S. Parappilly, M. Roh-Johnson, J.R. Goodman, B. Olson, M. Schmidt, J.R. Swain, P.S. Davies, V. Shasthri, S. Iizuka, P. Flynn, S. Watson, J. Korkola, S. A. Courtneidge, J.M. Fischer, J. Jaboin, K.G. Billingsley, C.D. Lopez, J. Burchard, J. Gray, L.M. Coussens, B.C. Sheppard, M.H. Wong, Cell fusion potentiates tumor heterogeneity and reveals circulating hybrid cells that correlate with stage and survival, Sci. Adv. 4 (2018), https://doi.org/10.1126/SCIADV.AAT7828.

[72] V.V. Boras, A. Fucic, M. Virag, D. Gabric, I. Blivajs, C. Tomasovic-Loncaric, Z. Rakusic, V. Bisof, N.Le Novere, D.V. Vrdoljak, Significance of stroma in biology of oral squamous cell carcinoma, Tumori 104 (2018) 9–14, https://doi.org/10.5301/TJ.5000673.

[73] R. Wang, X. Sun, C.Y. Wang, P. Hu, C.Y. Chu, S. Liu, H.E. Zhau, L.W.K. Chung, Spontaneous cancer-stromal cell fusion as a mechanism of prostate cancer androgen-independent progression, PLoS One 7 (2012), https://doi.org/10.1371/JOURNAL.PONE.0042653.

[74] L. Lartigue, C. Merle, P. Lagarde, L. Delespaul, T. Lesluyes, S. Le Guellec, G. Pérot, L. Leroy, J.M. Coindre, F. Chibon, Genome remodeling upon mesenchymal tumor cell fusion contributes to tumor progression and metastatic spread, Oncogene 39 (2020) 4198–4211, https://doi.org/10.1038/S41388-020-1276-6.

[75] K. Mortensen, J. Lichtenberg, P.D. Thomsen, L.I. Larsson, Spontaneous fusion between cancer cells and endothelial cells, Cell Mol. Life Sci. 61 (2004) 2125–2131, https://doi.org/10.1007/S00018-004-4200-2.

[76] L. Yin, P. Hu, X. Shi, W. Qian, H.E. Zhau, S.J. Pandol, M.S. Lewis, L.W.K. Chung, R. Wang, Cancer cell's neuroendocrine feature can be acquired through cell-cell fusion during cancer-neural stem cell interaction, Sci. Rep. 10 (2020), https://doi.org/10.1038/S41598-020-58118-Z.

[77] X. Lu, Y. Kang, Cell fusion as a hidden force in tumor progression, Cancer Res 69 (2009) 8536–8539, https://doi.org/10.1158/0008-5472.CAN-09-2159.

[78] C. Salaud, A. Alvarez-Arenas, F. Geraldo, J. Belmonte-Beitia, G.F. Calvo, C. Gratas, C. Pecqueur, D. Garnier, V. Pérez-Garcià, F.M. Vallette, L. Oliver, Mitochondria transfer from tumor-activated stromal cells (TASC) to primary Glioblastoma cells, Biochem Biophys. Res Commun. 533 (2020) 139–147, https://doi.org/10.1016/J.BBRC.2020.08.101.

[79] T. Dittmar, R. Hass, Intrinsic signalling factors associated with cancer cell-cell fusion, Cell Commun. Signal 21 (2023), https://doi.org/10.1186/S12964-023-01085-5.

[80] S. Zheng, F. Qin, J. Yin, D. Li, Y. Huang, L. Hu, L. He, C. Lv, X. Li, S. Li, W. Hu, Role and mechanism of actin-related protein 2/3 complex signaling in cancer invasion and metastasis: A review, Medicine 102 (2023) E33158, https://doi.org/10.1097/MD.0000000000033158.

[81] T.N. Seyfried, L.M. Shelton, Cancer as a metabolic disease, Nutr. Metab. (Lond.) 7 (2010), https://doi.org/10.1186/1743-7075-7-7.

[82] M. Sieler, J. Weiler, T. Dittmar, Cell-Cell Fusion and the Roads to Novel Properties of Tumor Hybrid Cells, Cells 10 (2021), https://doi.org/10.3390/CELLS10061465.

[83] H.F. Wang, W. Xiang, B.Z. Xue, Y.H. Wang, D.Y. Yi, X.B. Jiang, H.Y. Zhao, P. Fu, Cell fusion in cancer hallmarks: Current research status and future indications, Oncol. Lett. 22 (2021), https://doi.org/10.3892/OL.2021.12791.

[84] T. Dittmar, M. Sieler, R. Hass, Why do certain cancer cells alter functionality and fuse? Biol. Chem. 404 (2023) 951–960, https://doi.org/10.1515/hsz-2023-0162.

[85] A.S. Tan, J.W. Baty, L.F. Dong, A. Bezawork-Geleta, B. Endaya, J. Goodwin, M. Bajzikova, J. Kovarova, M. Peterka, B. Yan, E.A. Pesdar, M. Sobol, A. Filimonenko, S. Stuart, M. Vondrusova, K. Kluckova, K. Sachaphibulkij, J. Rohlena, P. Hozak, J. Truksa, D. Eccles, L.M. Haupt, L.R. Griffiths, J. Neuzil, M. V. Berridge, Mitochondrial genome acquisition restores respiratory function and tumorigenic potential of cancer cells without mitochondrial DNA, Cell Metab. 21 (2015) 81–94, https://doi.org/10.1016/J.CMET.2014.12.003.

[86] M. Bajzikova, J. Kovarova, A.R. Coelho, S. Boukalova, S. Oh, K. Rohlenova, D. Svec, S. Hubackova, B. Endaya, K. Judasova, A. Bezawork-Geleta, K. Kluckova, L. Chatre, R. Zobalova, A. Novakova, K. Vanova, Z. Ezrova, G.J. Maghzal, S. Magalhaes Novais, M. Olsinova, L. Krobova, Y.J. An, E. Davidova, Z. Nahacka, M. Sobol, T. Cunha-Oliveira, C. Sandoval-Acuña, H. Strnad, T. Zhang, T. Huynh, T.L. Serafim, P. Hozak, V.A. Sardao, W.J.H. Koopman, M. Ricchetti, P.J. Oliveira, F. Kolar, M. Kubista, J. Truksa, K. Dvorakova-Hortova, K. Pacak, R. Gurlich, R. Stocker, Y. Zhou, M.V. Berridge, S. Park, L. Dong, J. Rohlena, J. Neuzil, Reactivation of Dihydroorotate Dehydrogenase-Driven Pyrimidine Biosynthesis Restores Tumor Growth of Respiration-Deficient Cancer Cells, Cell Metab. 29 (2019) 399–416.e10, https://doi.org/10.1016/J.CMET.2018.10.014.

[87] L.F. Dong, J. Kovarova, M. Bajzikova, A. Bezawork-Geleta, D. Svec, B. Endaya, K. Sachaphibulkij, A.R. Coelho, N. Sebkova, A. Ruzickova, A.S. Tan, K. Kluckova, K. Judasova, K. Zamecnikova, Z. Rychtarcikova, V. Gopalan, L. Andera, M. Sobol, B. Yan, B. Pattnaik, N. Bhatraju, J. Truksa, P. Stopka, P. Hozak, A.K. Lam, R. Sedlacek, P.J. Oliveira, M. Kubista, A. Agrawal, K. Dvorakova-Hortova, J. Rohlena, M.V. Berridge, J. Neuzil, Horizontal transfer of whole mitochondria restores tumorigenic potential in mitochondrial DNA-deficient cancer cells, Elife 6 (2017), https://doi.org/10.7554/ELIFE.22187.

[88] L. Ippolito, A. Morandi, M.L. Taddei, M. Parri, G. Comito, A. Iscaro, M. R. Raspollini, F. Magherini, E. Rapizzi, J. Masquelier, G.G. Muccioli, P. Sonveaux, P. Chiarugi, E. Giannoni, Cancer-associated fibroblasts promote prostate cancer malignancy via metabolic rewiring and mitochondrial transfer, Oncogene 38 (2019) 5339–5355, https://doi.org/10.1038/S41388-019-0805-7.

[89] M. Jing, X. Xiong, X. Mao, Q. Song, L. Zhang, Y. Ouyang, Y. Pang, Y. Fu, W. Yan, HMGB1 promotes mitochondrial transfer between hepatocellular carcinoma cells through RHOT1 and RAC1 under hypoxia, Cell Death Dis. 15 (2024), https://doi.org/10.1038/S41419-024-06536-6.

[90] J. Lu, X. Zheng, F. Li, Y. Yu, Z. Chen, Z. Liu, Z. Wang, H. Xu, W. Yang, Tunneling nanotubes promote intercellular mitochondria transfer followed by increased invasiveness in bladder cancer cells, Oncotarget 8 (2017) 15539–15552, https://doi.org/10.18632/ONCOTARGET.14695.

[91] E.L. Eberhardt, A.V. Ludlam, Z. Tan, M.A. Cianfrocco, Miro: A molecular switch at the center of mitochondrial regulation, Protein Sci. 29 (2020) 1269–1284, https://doi.org/10.1002/PRO.3839.

[92] W. Zhang, H. Zhou, H. Li, H. Mou, E. Yinwang, Y. Xue, S. Wang, Y. Zhang, Z. Wang, T. Chen, H. Sun, F. Wang, J. Zhang, X. Chai, S. Chen, B. Li, C. Zhang, J. Gao, Z. Ye, Cancer cells reprogram to metastatic state through the acquisition of platelet mitochondria, Cell Rep. 42 (2023), https://doi.org/10.1016/J.CELREP.2023.113147.

[93] H. Li, W. Sun, W. Gong, Y. Han, Transfer and fates of damaged mitochondria: role in health and disease, FEBS J. (2024), https://doi.org/10.1111/FEBS.17119.

[94] C.H.O. Davis, K.Y. Kim, E.A. Bushong, E.A. Mills, D. Boassa, T. Shih, M. Kinebuchi, S. Phan, Y. Zhou, N.A. Bihlmeyer, J.V. Nguyen, Y. Jin, M. H. Ellisman, N. Marsh-Armstrong, Transcellular degradation of axonal mitochondria, Proc. Natl. Acad. Sci. USA 111 (2014) 9633–9638, https://doi.org/10.1073/PNAS.1404651111/-/DCSUPPLEMENTAL/PNAS.201404651SI.PDF.

[95] R. Lampinen, I. Belaya, L. Saveleva, J.R. Liddell, D. Rait, M.T. Huuskonen, R. Giniatullina, A. Sorvari, L. Soppela, N. Mikhailov, I. Boccuni, R. Giniatullin, M. Cruz-Haces, J. Konovalova, M. Koskuvi, A. Domanskyi, R.H. Hämäläinen, G. Goldsteins, J. Koistinaho, T. Malm, S. Chew, K. Rilla, A.R. White, N. Marsh-Armstrong, K.M. Kanninen, Neuron-astrocyte transmitophagy is altered in Alzheimer's disease, Neurobiol. Dis. 170 (2022), https://doi.org/10.1016/j.nbd.2022.105753.

[96] J. Wang, X. Liu, Y. Qiu, Y. Shi, J. Cai, B. Wang, X. Wei, Q. Ke, X. Sui, Y. Wang, Y. Huang, H. Li, T. Wang, R. Lin, Q. Liu, A.P. Xiang, Cell adhesion-mediated mitochondria transfer contributes to mesenchymal stem cell-induced chemoresistance on T cell acute lymphoblastic leukemia cells, J. Hematol. Oncol. 11 (2018), https://doi.org/10.1186/S13045-018-0554-Z.

[97] S. Valdebenito, A. Audia, K.P.L. Bhat, G. Okafo, E.A. Eugenin, Tunneling Nanotubes Mediate Adaptation of Glioblastoma Cells to Temozolomide and Ionizing Radiation Treatment, IScience 23 (2020), https://doi.org/10.1016/J.ISCI.2020.101450.

[98] T. Saha, C. Dash, R. Jayabalan, S. Khiste, A. Kulkarni, K. Kurmi, J. Mondal, P. K. Majumder, A. Bardia, H.L. Jang, S. Sengupta, Intercellular nanotubes mediate mitochondrial trafficking between cancer and immune cells, Nat. Nanotechnol. 17 (2022) 98–106, https://doi.org/10.1038/S41565-021-01000-4.

[99] J.C. Chang, H.S. Chang, Y.C. Wu, W.L. Cheng, T.T. Lin, H.J. Chang, S.J. Kuo, S. T. Chen, C.S. Liu, Mitochondrial transplantation regulates antitumour activity, chemoresistance and mitochondrial dynamics in breast cancer, J. Exp. Clin. Cancer Res 38 (2019), https://doi.org/10.1186/S13046-019-1028-Z.

[100] J.S. Riley, S.W. Tait, Mitochondrial DNA in inflammation and immunity, EMBO Rep. 21 (2020), https://doi.org/10.15252/EMBR.201949799.

[101] K. Shimada, T.R. Crother, J. Karlin, J. Dagvadorj, N. Chiba, S. Chen, V. K. Ramanujan, A.J. Wolf, L. Vergnes, D.M. Ojcius, A. Rentsendorj, M. Vargas, C. Guerrero, Y. Wang, K.A. Fitzgerald, D.M. Underhill, T. Town, M. Arditi, Oxidized mitochondrial DNA activates the NLRP3 inflammasome during apoptosis, Immunity 36 (2012) 401–414, https://doi.org/10.1016/J.IMMUNI.2012.01.009.

[102] A.N. Cheng, L.C. Cheng, C.L. Kuo, Y.K. Lo, H.Y. Chou, C.H. Chen, Y.H. Wang, T. H. Chuang, S.J. Cheng, A.Y.L. Lee, Mitochondrial Lon-induced mtDNA leakage contributes to PD-L1-mediated immunoescape via STING-IFN signaling and extracellular vesicles, J. Immunother. Cancer 8 (2020), https://doi.org/10.1136/JITC-2020-001372.

[103] S. Wang, B. Liu, J. Huang, H. He, L. Li, A. Tao, Cell-in-cell promotes lung cancer malignancy by enhancing glucose metabolism through mitochondria transfer, Exp. Cell Res 429 (2023), https://doi.org/10.1016/J.YEXCR.2023.113665.

[104] H. Zhang, X. Yu, J. Ye, H. Li, J. Hu, Y. Tan, Y. Fang, E. Akbay, F. Yu, C. Weng, V. G. Sankaran, R.M. Bachoo, E. Maher, J. Minna, A. Zhang, B. Li, Systematic investigation of mitochondrial transfer between cancer cells and T cells at single-cell resolution, Cancer Cell 41 (2023) 1788–1802.e10, https://doi.org/10.1016/J.CCELL.2023.09.003.

[105] C.R. Marlein, R.E. Piddock, J.J. Mistry, L. Zaitseva, C. Hellmich, R.H. Horton, Z. Zhou, M.J. Auger, K.M. Bowles, S.A. Rushworth, CD38-Driven Mitochondrial Trafficking Promotes Bioenergetic Plasticity in Multiple Myeloma, Cancer Res 79 (2019) 2285–2297, https://doi.org/10.1158/0008-5472.CAN-18-0773.

[106] Z. Ren, H. Lantermans, A. Kuil, W. Kraan, F. Arenzana-Seisdedos, M.J. Kersten, M. Spaargaren, S.T. Pals, The CXCL12gamma chemokine immobilized by heparan sulfate on stromal niche cells controls adhesion and mediates drug resistance in multiple myeloma, J. Hematol. Oncol. 14 (2021), https://doi.org/10.1186/S13045-021-01031-3.

[107] C. Giallongo, I. Dulcamare, D. Tibullo, V. Del Fabro, N. Vicario, N. Parrinello, A. Romano, G. Scandura, G. Lazzarino, C. Conticello, G. Li Volti, A.M. Amorini, G. Musumeci, M. Di Rosa, F. Polito, R. Oteri, M. Aguennouz, R. Parenti, F. Di Raimondo, G.A. Palumbo, CXCL12/CXCR4 axis supports mitochondrial trafficking in tumor myeloma microenvironment, Oncogenesis 11 (2022), https://doi.org/10.1038/S41389-022-00380-Z.

[108] Z. Matula, G. Mikala, S. Lukácsi, J. Matkó, T. Kovács, É. Monostori, F. Uher, I. Vályi-Nagy, Stromal Cells Serve Drug Resistance for Multiple Myeloma via Mitochondrial Transfer: A Study on Primary Myeloma and Stromal Cells, Cancers (Basel) 13 (2021), https://doi.org/10.3390/CANCERS13143461.

[109] C.R. Marlein, L. Zaitseva, R.E. Piddock, S.D. Robinson, D.R. Edwards, M.S. Shafat, Z. Zhou, M. Lawes, K.M. Bowles, S.A. Rushworth, NADPH oxidase-2 derived superoxide drives mitochondrial transfer from bone marrow stromal cells to leukemic blasts, Blood 130 (2017) 1649–1660, https://doi.org/10.1182/BLOOD-2017-03-772939.

[110] R. Moschoi, V. Imbert, M. Nebout, J. Chiche, D. Mary, T. Prebet, E. Saland, R. Castellano, L. Pouyet, Y. Collette, N. Vey, C. Chabannon, C. Recher, J.E. Sarry, D. Alcor, J.F. Peyron, E. Griessinger, Protective mitochondrial transfer from bone marrow stromal cells to acute myeloid leukemic cells during chemotherapy, Blood 128 (2016) 253–264, https://doi.org/10.1182/BLOOD-2015-07-655860.

[111] K. Saito, Q. Zhang, H. Yang, K. Yamatani, T. Ai, V. Ruvolo, N. Baran, T. Cai, H. Ma, R. Jacamo, V. Kuruvilla, J. Imoto, S. Kinjo, K. Ikeo, K. Moriya, K. Suzuki, T. Miida, Y.M. Kim, C.P. Vellano, M. Andreeff, J.R. Marszalek, Y. Tabe, M. Konopleva, Exogenous mitochondrial transfer and endogenous mitochondrial fission facilitate AML resistance to OxPhos inhibition, Blood Adv. 5 (2021) 4233–4255, https://doi.org/10.1182/BLOODADVANCES.2020003661.

[112] R. You, B. Wang, P. Chen, X. Zheng, D. Hou, X. Wang, B. Zhang, L. Chen, D. Li, X. Lin, H. Huang, Metformin sensitizes AML cells to chemotherapy through blocking mitochondrial transfer from stromal cells to AML cells, Cancer Lett. 532 (2022), https://doi.org/10.1016/J.CANLET.2022.215582.

[113] X. Guo, C. Can, W. Liu, Y. Wei, X. Yang, J. Liu, H. Jia, W. Jia, H. Wu, D. Ma, Mitochondrial transfer in hematological malignancies, Biomark. Res 11 (2023), https://doi.org/10.1186/S40364-023-00529-X.

[114] M.D. Kolba, W. Dudka, M. Zaręba-Kozioł, A. Kominek, P. Ronchi, L. Turos, P. Chroscicki, J. Wlodarczyk, Y. Schwab, A. Klejman, D. Cysewski, K. Srpan, D. M. Davis, K. Piwocka, Tunneling nanotube-mediated intercellular vesicle and protein transfer in the stroma-provided imatinib resistance in chronic myeloid leukemia cells, Cell Death Dis. 10 (2019), https://doi.org/10.1038/S41419-019-2045-8.

[115] R. Burt, A. Dey, S. Aref, M. Aguiar, A. Akarca, K. Bailey, W. Day, S. Hooper, A. Kirkwood, K. Kirschner, S.W. Lee, C. Lo Celso, J. Manji, M.R. Mansour, T. Marafioti, R.J. Mitchell, R.C. Muirhead, K.C.Y. Ng, C. Pospori, I. Puccio, K. Zuborne-Alapi, E. Sahai, A.K. Fielding, Activated stromal cells transfer mitochondria to rescue acute lymphoblastic leukemia cells from oxidative stress, Blood 134 (2019) 1415–1429, https://doi.org/10.1182/BLOOD.2019001398.

[116] H. Sahinbegovic, T. Jelinek, M. Hrdinka, J.R. Bago, M. Turi, T. Sevcikova, A. Kurtovic-Kozaric, R. Hajek, M. Simicek, Intercellular Mitochondrial Transfer in the Tumor Microenvironment, Cancers (Basel) 12 (2020) 1–12, https://doi.org/10.3390/CANCERS12071787.

[117] J.L. Spees, S.D. Olson, M.J. Whitney, D.J. Prockop, Mitochondrial transfer between cells can rescue aerobic respiration, Proc. Natl. Acad. Sci. USA 103 (2006) 1283–1288, https://doi.org/10.1073/PNAS.0510511103.

[118] J. Pasquier, B.S. Guerrouahen, H. Al Thawadi, P. Ghiabi, M. Maleki, N. Abu-Kaoud, A. Jacob, M. Mirshahi, L. Galas, S. Rafii, F. Le Foll, A. Rafii, Preferential transfer of mitochondria from endothelial to cancer cells through tunneling nanotubes modulates chemoresistance, J. Transl. Med 11 (2013), https://doi.org/10.1186/1479-5876-11-94.

[119] K.F. Goliwas, S. Libring, E. Berestesky, S. Gholizadeh, S.C. Schwager, A.R. Frost, T.R. Gaborski, J. Zhang, C.A. Reinhart-King, Mitochondrial transfer from cancer-associated fibroblasts increases migration in aggressive breast cancer, J. Cell Sci. 136 (2023), https://doi.org/10.1242/JCS.260419.

[120] R.L. Elliott, X.P. Jiang, J.F. Head, Mitochondria organelle transplantation: Introduction of normal epithelial mitochondria into human cancer cells inhibits proliferation and increases drug sensitivity, Breast Cancer Res Treat. 136 (2012) 347–354.

[121] J.C. Chang, H.S. Chang, Y.C. Wu, W.L. Cheng, T.T. Lin, H.J. Chang, S.T. Chen, C. S. Liu, Antitumor Actions of Intratumoral Delivery of Membrane-Fused Mitochondria in a Mouse Model of Triple-Negative Breast Cancers, Onco Targets Ther. 13 (2020) 5241–5255, https://doi.org/10.2147/OTT.S238143.

[122] M. Osswald, E. Jung, F. Sahm, G. Solecki, V. Venkataramani, J. Blaes, S. Weil, H. Horstmann, B. Wiestler, M. Syed, L. Huang, M. Ratliff, K. Karimian Jazi, F. T. Kurz, T. Schmenger, D. Lemke, M. Gömmel, M. Pauli, Y. Liao, P. Häring, S. Pusch, V. Herl, C. Steinhäuser, D. Krunic, M. Jarahian, H. Miletic, A.S. Berghoff, O. Griesbeck, G. Kalamakis, O. Garaschuk, M. Preusser, S. Weiss, H. Liu, S. Heiland, M. Platten, P.E. Huber, T. Kuner, A. Von Deimling, W. Wick, F. Winkler, Brain tumour cells interconnect to a functional and resistant network, Nature 528 (2015) 93–98, https://doi.org/10.1038/NATURE16071.

[123] X. Wang, J. Liang, H. Sun, The Network of Tumor Microtubes: An Improperly Reactivated Neural Cell Network With Stemness Feature for Resistance and Recurrence in Gliomas, Front Oncol. 12 (2022), https://doi.org/10.3389/FONC.2022.921975.

[124] S. Weil, M. Osswald, G. Solecki, J. Grosch, E. Jung, D. Lemke, M. Ratliff, D. Hänggi, W. Wick, F. Winkler, Tumor microtubes convey resistance to surgical lesions and chemotherapy in gliomas, Neuro Oncol. 19 (2017) 1316–1326, https://doi.org/10.1093/NEUONC/NOX070.

[125] D.C. Watson, D. Bayik, S. Storevik, S.S. Moreino, S.A. Sprowls, J. Han, M. T. Augustsson, A. Lauko, P. Sravya, G.V. Røsland, K. Troike, K.J. Tronstad, S. Wang, K. Sarnow, K. Kay, T.R. Lunavat, D.J. Silver, S. Dayal, J.V. Joseph, E. Mulkearns-Hubert, L.A.R. Ystaas, G. Deshpande, J. Guyon, Y. Zhou, C. R. Magaut, J. Seder, L. Neises, S.E. Williford, J. Meiser, A.J. Scott, P. Sajjakulnukit, J.A. Mears, R. Bjerkvig, A. Chakraborty, T. Daubon, F. Cheng, C. A. Lyssiotis, D.R. Wahl, A.B. Hjelmeland, J.A. Hossain, H. Miletic, J.D. Lathia, GAP43-dependent mitochondria transfer from astrocytes enhances glioblastoma tumorigenicity, Nat. Cancer 4 (2023) 648–664, https://doi.org/10.1038/S43018-023-00556-5.

[126] J. Nakhle, K. Khattar, T. Özkan, A. Boughlita, D. Abba Moussa, A. Darlix, F. Lorcy, V. Rigau, L. Bauchet, S. Gerbal-Chaloin, M. Daujat-Chavanieu, F. Bellvert, L. Turchi, T. Virolle, J.-P. Hugnot, N. Buisine, M. Galloni, V. Dardalhon, A.-M. Rodriguez, M.-L. Vignais, Mitochondria Transfer from Mesenchymal Stem Cells Confers Chemoresistance to Glioblastoma Stem Cells through Metabolic Rewiring, Cancer Res. Commun. 3 (2023) 1041–1056, https://doi.org/10.1158/2767-9764.CRC-23-0144.

[127] S. Zhang, L. Hu, J. Jiang, H. Li, Q. Wu, K. Ooi, J. Wang, Y. Feng, D. Zhu, C. Xia, HMGB1/RAGE axis mediates stress-induced RVLM neuroinflammation in mice via impairing mitophagy flux in microglia, J. Neuroinflamm. 17 (2020), https://doi.org/10.1186/S12974-019-1673-3.

[128] L. Yang, F. Ye, L. Zeng, Y. Li, W. Chai, Knockdown of HMGB1 Suppresses Hypoxia-Induced Mitochondrial Biogenesis in Pancreatic Cancer Cells, Onco Targets Ther. 13 (2020) 1187–1198, https://doi.org/10.2147/OTT.S234530.

[129] Y. Liu, W. Yan, S. Tohme, M. Chen, Y. Fu, D. Tian, M. Lotze, D. Tang, A. Tsung, Hypoxia induced HMGB1 and mitochondrial DNA interactions mediate tumor growth in hepatocellular carcinoma through Toll-like receptor 9, J. Hepatol. 63 (2015) 114–121, https://doi.org/10.1016/J.JHEP.2015.02.009.

[130] S. Desir, P. O'Hare, R.I. Vogel, W. Sperduto, A. Sarkari, E.L. Dickson, P. Wong, A. C. Nelson, Y. Fong, C.J. Steer, S. Subramanian, E. Lou, Chemotherapy-Induced Tunneling Nanotubes Mediate Intercellular Drug Efflux in Pancreatic Cancer, Sci. Rep. 8 (2018), https://doi.org/10.1038/S41598-018-27649-X.

[131] V.J. Clemente-Suárez, A. Martín-Rodríguez, R. Yáñez-Sepúlveda, J.F. Tornero-Aguilera, Mitochondrial Transfer as a Novel Therapeutic Approach in Disease Diagnosis and Treatment, Int J. Mol. Sci. 24 (2023), https://doi.org/10.3390/IJMS24108848.

[132] S.J. Hanna, K. McCoy-Simandle, V. Miskolci, P. Guo, M. Cammer, L. Hodgson, D. Cox, The Role of Rho-GTPases and actin polymerization during Macrophage Tunneling Nanotube Biogenesis, Sci. Rep. 7 (2017), https://doi.org/10.1038/S41598-017-08950-7.

[133] Y. Qian, M. Zhao, Q. Han, J. Wang, L. Liao, H. Yang, D. Liu, P. Tu, H. Liang, K. Zeng, Pharmacologically targeting molecular motor promotes mitochondrial fission for anti-cancer, Acta Pharm. Sin. B 11 (2021) 1853–1866, https://doi.org/10.1016/J.APSB.2021.01.011.

[134] S. Harada, D. Hashimoto, H. Senjo, K. Yoneda, Z. Zhang, X. Chen, R. Kikuchi, M. Chiba, H. Ohigashi, T. Ara, M. Nakagawa, M. Suganuma, R.C. Tsai, T. Teshima, Intercellular Mitochondrial Transfer Enhances Metabolic Fitness and Anti-Tumor Effects of CAR T Cells, Blood 140 (2022) 2356–2357, https://doi.org/10.1182/BLOOD-2022-162535.

[135] S.F. Murphy, R.T. Varghese, S. Lamouille, S. Guo, K.J. Pridham, P. Kanabur, A. M. Osimani, S. Sharma, J. Jourdan, C.M. Rodgers, G.R. Simonds, R.G. Gourdie, Z. Sheng, Connexin 43 Inhibition Sensitizes Chemoresistant Glioblastoma Cells to Temozolomide, Cancer Res 76 (2016) 139–149, https://doi.org/10.1158/0008-5472.CAN-15-1286.

[136] M.C. Pietanza, S.N. Waqar, L.M. Krug, A. Dowlati, C.L. Hann, A. Chiappori, T. K. Owonikoko, K.M. Woo, R.J. Cardnell, J. Fujimoto, L. Long, L. Diao, J. Wang, Y. Bensman, B. Hurtado, P. de Groot, E.P. Sulman, I.I. Wistuba, A. Chen, M. Fleisher, J.V. Heymach, M.G. Kris, C.M. Rudin, L.A. Byers, Randomized, Double-Blind, Phase II Study of Temozolomide in Combination With Either Veliparib or Placebo in Patients With Relapsed-Sensitive or Refractory Small-Cell Lung Cancer, J. Clin. Oncol. 36 (2018) 2386–2394, https://doi.org/10.1200/JCO.2018.77.7672.

[137] Q. Xie, Q. Wu, C.M. Horbinski, W.A. Flavahan, K. Yang, W. Zhou, S. M. Dombrowski, Z. Huang, X. Fang, Y. Shi, A.N. Ferguson, D.F. Kashatus, S. Bao, J.N. Rich, Mitochondrial control by DRP1 in brain tumor initiating cells, Nat. Neurosci. 18 (2015) 501–510, https://doi.org/10.1038/nn.3960.

[138] P.K. Parida, M. Marquez-Palencia, S. Ghosh, N. Khandelwal, K. Kim, V. Nair, X.-Z. Liu, H.S. Vu, L.G. Zacharias, P.I. Gonzalez-Ericsson, M.E. Sanders, B.C. Mobley, J.G. McDonald, A. Lemoff, Y. Peng, C. Lewis, G. Vale, N. Halberg, C.L. Arteaga, A. B. Hanker, R.J. DeBerardinis, S. Malladi, Limiting mitochondrial plasticity by targeting DRP1 induces metabolic reprogramming and reduces breast cancer brain metastases, Nat. Cancer 4 (2023) 893–907, https://doi.org/10.1038/s43018-023-00563-6.

[139] X.H. Lin, B.Q. Qiu, M. Ma, R. Zhang, S.J. Hsu, H.H. Liu, J. Chen, D.M. Gao, J. F. Cui, Z.G. Ren, R.X. Chen, Suppressing DRP1-mediated mitochondrial fission and mitophagy increases mitochondrial apoptosis of hepatocellular carcinoma cells in the setting of hypoxia, Oncogenesis 9 (2020), https://doi.org/10.1038/S41389-020-00251-5.