Published in final edited form as:

Cell Mol Life Sci. 2019 March ; 76(5): 827–835. doi:10.1007/s00018-018-2961-2.

MITOCHONDRIAL DYNAMICS AND METASTASIS

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Abstract

Changes in cellular metabolism are now a recognized hallmark of cancer. Although this process is ripe with therapeutic potential in the clinic, its complexity and extraordinary plasticity have systematically defied dogmas and oversimplifications. Perhaps best exemplifying this intricacy is the role of mitochondria in cancer, which in just a few years has gone from largely unnoticed to pivotal disease driver. The underlying mechanisms are only beginning to emerge. However, there is now clear evidence linking the dynamic nature of mitochondria to the machinery of tumor cell motility and metastatic spreading. These studies may open fresh therapeutic options for patients with disseminated cancer, currently an incurable and mostly lethal condition.

Keywords

Mitochondria; cancer; dynamics; trafficking; tumor cell invasion; metastasis

INTRODUCTION

Although popularly viewed as “factories” for energy production, mitochondria have emerged as central signaling hubs in the eukaryotic cell [1], and key drivers of evolution [2]. Their functions connect to all other organelles [3], influence gene expression, modulate cell cycle transitions, regulate cell death, govern adaptation to an ever-changing cellular environment, and, clearly, control bioenergetics [4]. Whether these activities contribute to cancer has been intensely debated. The re-discovery of the “Warburg effect”, where tumors shift their metabolism from oxidative phosphorylation to glycolysis even in the presence of oxygen [5], has led to a long-held view that mitochondria must either be damaged or unimportant in cancer, perhaps even acting as “tumor suppressors” [6].

However, this perception has recently changed [7]. We now know that oxidative phosphorylation remains a central energy source for most malignancies [8], and mitochondria drive important tumor traits [9, 10], such as tumor repopulation after oncogene ablation [11], drug resistance [12], cancer stem cell maintenance [13] and disease expansion [14]. Another cancer trait consistently associated with mitochondrial function is the

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CONFLICT OF INTEREST

The author declares that no conflict of interest exists

dissemination of tumor cells to distant organs, or metastasis [15], which is responsible for over 90% of cancer deaths [16]. The acquisition of a metastatic phenotype is complex, multifaceted and likely not very efficient. Continuously processing cues from their microenvironment [17], metastatic tumors must reprogram their metabolism, thwart cell death, become migratory, invade across basement membranes and successfully colonize distant anatomical sites [18]. How mitochondria contribute to this process, and to what extent, is only beginning to emerge. On the other hand, there is evidence that signaling pathways that control mitochondrial size, shape, subcellular position and quality control, a process collectively known as mitochondrial dynamics [19], directly influences multiple steps in cancer biology [20], and, in particular, metastatic propensity, in vivo.

The present contribution is not designed to review the various cellular responses associated with mitochondrial dynamics. For that, the reader is directed to many outstanding review articles recently appeared in the literature [21–23].

Cellular effectors of mitochondrial dynamics

Mitochondria continuously adjust their architecture, position and overall fitness in response to cellular and extracellular cues (Figure 1). It is now accepted that this process of mitochondrial dynamics encompasses four different, but interconnected pathways (Figure 1). The control of mitochondrial shape and size, two key aspects of mitochondrial dynamics, depend on alternating cycles of organelle fusion and fission. Collectively, this pathway relies on an evolutionary conserved cellular machinery where classes of GTPases either divide mitochondria by constriction (fission) or promote the coordinated elongation (fusion) of individual mitochondria (Figure 1). The underlying molecular requirements of this process have recently come into better focus [24]. Mammalian cells express two GTPases of the dynamin family called mitofusin 1 and 2 (MFN1, MFN2) that are anchored by their C-termini to the mitochondrial outer membranes. MFNs promote fusion of outer membranes of adjacent organelles via homo- and heterotypic GTP hydrolysis, followed by the cristae-shaping activity of a dynamin-like optic atrophy 1 (Opa1) molecule that fuses the inner membranes and ultimately generates elongated, string-like organelles. Mitochondrial fission begins with receptor-mediated recruitment of cytosolic dynamin-related protein 1 (Drp1), and possibly other dynamins [25], to the outer mitochondrial membrane. Differentially regulated by multiple post-translational modifications, including phosphorylation at activating [26] or inhibitory [27, 28] serine residues, as well as S-nitrosylation [29], Drp1 executes mitochondrial division through the assembly of a ring-like structure around the organelle outer membrane [30] (Figure 1).

A third component of mitochondrial dynamics oversees organelle quality control [23]: a collection of mechanisms that remove unnecessary or damaged mitochondria through mitophagy [31] (Figure 1). One of the best characterized mitophagy pathways involves the stabilization of the PINK1 kinase at the mitochondrial outer membrane. In turn, PINK1 phosphorylates a cytosolic E3 ubiquitin ligase, Parkin, which ubiquitinates proteins at the mitochondrial outer membrane, signaling their subsequent engulfment in autophagosomes [32]. The fourth facet of mitochondrial dynamics refers to subcellular organelle trafficking, as mitochondria continuously move, pause, switch directions and become stationary at

specific subcellular sites [33] (Figure 1). Worked out in detail in neurons, this pathway concentrates a potent energy source where ATP production is most needed [34], such as synapses, growth cones and branches [35]. The machinery for subcellular mitochondrial movements involves outer membrane atypical GTPases RHOT1 and 2 (also called Miro1 and 2) [34], adapter proteins TRAK1 and 2 (also called Milton) [36], and motor proteins that couple mitochondria to polymerized microtubules for anterograde (from nucleus to cell periphery, kinesin Kif5B) or retrograde (from cell periphery to nucleus, dynein) movements [37] (Figure 1).

There is clear evidence that all four aspects of mitochondrial dynamics are often deregulated in cancer. Many tumors exhibit fragmented mitochondria with increased expression of Drp1 and/or downregulation of MFNs [38]. In turn, Drp1 activity has been associated with MAPK-dependent tumor growth [39], Ras-driven tumorigenicity [40], cell cycle transitions [41], and cancer cell stemness [21, 42]. Parkin is frequently inactivated in cancer suggesting that mitophagy may play an important role as a tumor suppressor [43], and changes in mitochondrial dynamics have been implicated in cachexia [44], metabolic reprogramming [45], mTOR-dependent cell survival [46], and modulation of oxidative stress [47] in disparate tumor types. In addition, there is now accumulating evidence that deregulated mitochondrial dynamics is an important driver of metastatic competence and potential therapeutic target.

Mitochondrial proteostasis and metastasis—An early hint that mitochondrial integrity is important for metastasis came from experiments looking at organelle protein folding. Owing to their unique double membrane- enclosed anatomy, perturbations of the protein folding environment is particularly dangerous for mitochondria, coupling to a potentially lethal unfolded protein response (UPR) [48], activation of mitophagy [49], and disease pathogenesis [50]. Within mitochondria, protein folding homeostasis, or proteostasis relies on two complementary branches: the (re)folding activity of mitochondrial-resident chaperones, such as members of the Heat Shock Protein-90 (Hsp90) family, Hsp90 and its homolog TNFR-Associated Protein 1 (TRAP1) [51], and, conversely, the proteolytic function of AAA⁺ proteases, such as ClpP [52, 53], which degrade irretrievably misfolded and aggregated proteins. Both branches of mitochondrial proteostasis are upregulated in cancer, limit the occurrence of a mitochondrial UPR [54, 55] and data from mouse models suggests that they may be important as disease drivers: homozygous deletion of TRAP1 reduces the incidence of age-associated pathologies in mice, including cancer [56], whereas transgenic expression of TRAP1 in Pten^{+/-} prostatic epithelium accelerates prostate cancer onset and progression [57].

Against this backdrop, non-lethal perturbations of mitochondrial proteostasis via pharmacologic or genetic inhibition of mitochondrial Hsp90s potently suppressed tumor chemotaxis [58], shutting off membrane lamellipodia dynamics, phosphorylation of cell motility kinases and impeding tumor cell movements across basement membranes [59]. Silencing of the ClpP protease produced a similar phenotype, inhibiting tumor cell motility and suppressing metastatic dissemination in mice [52]. The molecular basis of this response seemed to reflect insufficient energy production to sustain cell movements. In fact, interference with mitochondrial proteostasis was associated with extensive bioenergetics

defects, including reduced oxygen consumption, decreased ATP generation, and aberrant production of reactive oxygen species (ROS) [52, 59]. A key player in this metabolic phenotype was succinate dehydrogenase B (SDHB). Mutated in certain neuroendocrine cancers [6], SDHB is the iron-sulfur subunit of oxidative phosphorylation Complex II, and was identified in a global proteomics screen as one of ~70 mitochondrial proteins that require Hsp90/TRAP1 for proper folding [60]. Consistent with this, SDHB was especially to perturbation of mitochondrial proteostasis and interference with Hsp90/TRAP1 or ClpP function was sufficient to trigger SDHB misfolding, loss of Complex II activity, and impaired mitochondrial bioenergetics, ultimately culminating with inhibition of tumor cell chemotaxis and invasion [52, 60, 61].

Regional mitochondrial bioenergetics and tumor cell motility—So, is mitochondrial bioenergetics indispensable for tumor cell motility? A clue to this question came from experiments looking at the morphology and subcellular localization of mitochondria during lymphocyte migration [62]. In this study, mitochondria were found to actively redistribute to the polarized cytoskeleton at the leading edge of lymphocyte migration, the so-called uropodial cytoskeleton, correlating with enhanced cell motility [62]. Anticipating an important connection with changes in mitochondrial shape and size, only fragmented mitochondria appeared able to redistribute to the uropodial cytoskeleton, whereas mitochondrial fusion suppressed subcellular organelle trafficking and blocked lymphocyte motility [62].

Outside of neurons with their large cell bodies and axons that can be up to one meter long [63], subcellular mitochondrial movements have not been considered physiologically significant. This is because ATP levels in epithelial cells that are 10–20 μm in diameter have long been thought to remain fairly constant across subcellular microdomains, making it unnecessary to reposition mitochondria in order to optimally fuel specific cellular functions. However, we now know that, in fact, subcellular ATP levels can be highly dishomogeneous in epithelial cells [64, 65], continuously influenced by the adenylate pool, nutrient availability and activity of cytoplasmic ATPases [66]. Consistent with this notion, several independent studies demonstrated that subcellular mitochondrial trafficking is not an oddity of migrating lymphocytes [62], but a phenotype widely seen in tumors, and functionally important to support cell movements. In breast cancer models, increased mitochondrial fragmentation via activated Drp1 or MFN silencing resulted in mitochondrial repositioning to the lamellipodia of the peripheral cytoskeleton, providing a concentrated energy source to power tumor cell motility and invasion [67]. Independent studies reinforced the same model in other epithelial cell types, as mitochondrial redistribution to the leading edge of the peripheral cytoskeleton supported increased velocities of directional tumor cell migration, and this response was dampened by inhibition of mitochondrial fission and fusion [68]. Similarly, mitochondrial infiltration of the lamellipodial cytoskeleton in ovarian cancer locally increased mitochondrial mass and augmented “regional” ATP production via heightened mitochondrial dynamics [69]. Based on these findings the role of mitochondrial protein folding and Complex II-directed bioenergetics in tumor cell motility came into better focus [52, 60, 61]. In fact, both of these pathways were required to support mitochondrial trafficking to the peripheral cytoskeleton, fueling tumor chemotaxis and invasion in prostate

cancer and glioblastoma cell models [52, 61]. Taken together, these results point to a model where epithelial tumors hijack the “neuronal” process of subcellular mitochondrial trafficking to “regionally” power the membrane machinery of cell movements, fueling lamellipodia dynamics, actin cytoskeleton remodeling and turnover of focal adhesion complexes [58]. Consistent with this scenario, lamellipodia assembly has been associated with a local surge in ATP levels, which contributes to cellular shape during cell migration [65]. Conversely, interference with mitochondrial bioenergetics prevents lamellipodia formation, blocks focal adhesion complex dynamics and shuts off tumor cell movements [52, 61, 67].

Mitochondrial trafficking in response to cellular stress—But how is mitochondrial trafficking regulated to fuel cell movements in cancer? One possibility to answer this question is to consider tumor cell migration (and metastasis) as an adaptive response to microenvironment stress. We know that unfavorable conditions of the microenvironment, such as low levels of oxygen or nutrients or high concentrations of radicals drive metastatic behavior [17]. Therefore, acquiring faster, more efficient migratory and invasive properties, even at the expense of cell proliferation or quality control could theoretically produce an important advantage, and endow tumor cells with the ability to “escape” local, unfavorable conditions [15, 70]. Extending this concept, recent studies asked if molecular therapy could be one of the drivers of tumor adaptation, creating noxious environmental conditions that prompt compensatory responses in transformed cells. In line with this possibility, recent studies showed that treatment of tumor cell types with small molecule inhibitors of phosphatidylinositol-3 kinase (PI3K), a key signaling node in cancer, triggered extensive transcriptional and metabolic reprogramming, specifically in mitochondria [71, 72]. Functionally, this was associated with heightened resistance to mitochondrial apoptosis [72], and increased mitochondrial trafficking to the cortical cytoskeleton [71], powering up focal adhesion complex turnover, lamellipodia dynamics and tumor cell motility and invasion [71]. As in previous studies, mitochondria had to be energetically active for this response, as tumor cells devoid of mitochondrial DNA failed to reposition their mitochondria to the cortical cytoskeleton and support tumor cell movements [71].

There may be concrete translational implications for these observations. Despite the promise of personalized therapy, PI3K inhibitors have been disappointing drugs in the clinic, showing modest efficacy, quickly supplanted by disease progression [73]. It is tempting to speculate that adaptive mitochondrial dynamics may play an important role in this poor efficacy, reprogramming tumor responses to promote cell survival [72] and metastatic propensity [71]. Whether other conventional or molecular therapies also adaptively reprogram mitochondrial dynamics to promote aggressive disease is currently unknown. On the other hand, there is evidence that oncogenic signaling pathways may similarly impinge on mitochondrial dynamics. For instance, silencing of the Adenomatous Polyposis Coli (APC) protein, a key regulator of Wnt signaling and disease driver in colorectal cancer caused retrograde mitochondrial trafficking [74]. Mechanistically, this response relied on a direct interaction between the APC carboxyl- terminus and the mitochondrial atypical GTPase, RHOT and the adapter protein, TRAK, which mediate mitochondrial trafficking in neurons [34]. Conversely, loss-of-function mutations in APC disrupted the APC-RHOT-

TRAK complex, inhibiting retrograde mitochondrial redistribution in colorectal cancer cells [74].

Requirements of mitochondrial trafficking for tumor cell motility—So, if the process of mitochondrial trafficking is hijacked in cancer, does it mean that the same machinery that moves mitochondria in neurons [34] is also exploited by tumor cells? A genome-wide shRNA screening designed to identify genes implicated in inhibition of tumor cell invasion after targeting mitochondrial Hsp90s began to address this question [59]. One of the top hits in this study was syntaphilin (SNPH), a molecule that arrests mitochondrial trafficking in neurons [75]. How SNPH does this is not completely clear, but a prevailing model is that SNPH binds to cytoskeletal microtubules at one end and immobilizes mitochondria at the other end by displacing their association with the anterograde motor, Kif5B [76]. In cancer, SNPH seems to serve a similar role. Accordingly, expression of SNPH in glioblastoma or prostate cancer models was sufficient to shut down the speed and distance traveled by individual mitochondria (Figure 2), inhibit tumor cell migration and invasion and attenuate metastatic dissemination in mice. Conversely, loss of SNPH had the reciprocal effect promoting more efficient mitochondrial redistribution to the cortical cytoskeleton with increased focal adhesion dynamics and greater tumor chemotaxis and invasion [77]. This response was associated with major changes in mitochondrial dynamics as loss of SNPH resulted in increased recruitment of Drp1 to the mitochondrial outer membrane, higher expression of MFNs and greater frequency of both mitochondrial fusion and fission cycles [77]. Intriguingly, analysis of public databases suggested that SNPH was often downregulated or lost in advanced tumors, suggesting that it may function as a novel “metastasis suppressor” [77] via modulation of mitochondrial dynamics.

A potential problem with this model is that SNPH was not previously believed to be expressed outside neurons, let alone in cancer [34]. More recent studies addressed this potential discrepancy and demonstrated that processing of a single *SNPH* locus in humans was more complex than anticipated, generating at least two SNPH isoforms by alternative splicing. These included a “long” SNPH isoform corresponding to previously described neuronal SNPH [76] and solely expressed in the CNS, and a novel, “short” SNPH isoform containing a unique mitochondrial-localization sequence and found in both CNS and non-CNS tissues [78]. Consistent with a submitochondrial localization to the organelle inner membrane, “short” SNPH played an important role in buffering ROS production while maintaining Complex II-directed ATP production [78]. Functionally, this was important to fuel continued tumor cell proliferation, while suppressing mitochondrial trafficking to the cortical cytoskeleton and tumor cell migration. Conversely, conditions of hypoxic stress that are frequently seen in the tumor microenvironment acutely downregulated SNPH levels. In turn, this resulted in increased ROS production, lower ATP generation and suppression of cell proliferation with concomitant increase in mitochondrial trafficking to the cortical cytoskeleton and heightened tumor cell motility and metastasis [78].

This dual function of SNPH seems ideally placed to influence what is known as the cell proliferation-motility dichotomy [79], a process also called phenotype switching [80] (Figure 3). Although not universally accepted, and probably more relevant for selected malignancies, the assumption is that tumors must judiciously allocate the limited resources

of an often unfavorable microenvironment [81] to either support cell proliferation, and therefore local expansion, or stimulate cell motility [82] and thus enable metastasis [83], but not both processes at the same time. If one accepts this premise, the dual function of SNPH in mitochondrial bioenergetics or subcellular organelle trafficking may titrate the balance between cell proliferation and cell motility, depending on the conditions of the tumor microenvironment (Figure 3). A key second messenger in this response was the increased production of mitochondrial ROS after SNPH downregulation. Accordingly, ROS levels promoted mitochondrial trafficking and increased tumor cell motility [78] while suppressing cell proliferation in both primary and metastatic tumors (Figure 3). The impact of ROS in cancer has remained largely controversial and likely context-dependent [84]. On the other hand, these data fit well with a role of mild oxidative stress as a mediator of EMT [85] in promoting increased tumor cell migration and invasion [86–88]. A new player in this pathway was recently identified as “family with sequence similarity 49 member B” (FAM49B), a mitochondria-localized protein that, similarly to SNPH, becomes downregulated in pancreatic ductal adenocarcinoma in response to microenvironment cues. In these predominantly K-Ras mutant tumors, loss of FAM49B was associated with increased mitochondrial fragmentation, heightened ROS production and greater tumor cell migration, invasion and metastatic dissemination in mouse models [89].

Finally, recent studies investigated the requirements of SNPH inhibition of mitochondrial trafficking in tumors. Here, a global proteomics screen identified regulators of ubiquitination as the most abundant class of SNPH-associated proteins in prostate cancer models [90]. Experimentally, it was shown that SNPH became ubiquitinated by the E3 ligase C-terminus of Hsc70-interacting protein (CHIP, also called STUB1) on multiple lysine residues, including Lys111 and Lys153 in the microtubule-binding domain, in a reaction reversed by the deubiquitinase, USP7. In these studies, CHIP ubiquitination did not affect protein stability or proteasomal degradation but was required to anchor SNPH on microtubules and thus enable its inhibition of mitochondrial trafficking and tumor cell motility [90]. Reciprocally, expression of ubiquitination-defective SNPH mutant Lys111→Arg or Lys153→Arg was sufficient to recapitulate this pathway, increase the speed and distance traveled by individual mitochondria in tumor cells, reposition mitochondria to the cortical cytoskeleton and support increased tumor cell invasion and metastatic dissemination in mice [90]. Consistent with the earlier results of SNPH knockdown [77], expression of ubiquitination-defective SNPH mutants was also associated with changes in mitochondrial dynamics, and increased rate of both fusion and fission cycles in prostate cancer cells [90]. An as yet unanswered question is whether a similar non-degradative ubiquitination step regulates the function of “long” SNPH in suppressing mitochondrial trafficking in neurons.

Concluding remarks and future directions—The recent explosion of knowledge on the role of mitochondria in cancer has now provided an updated, albeit more complex perspective on metabolic reprogramming in tumor cells. Notwithstanding the switch to aerobic glycolysis of most tumors, mitochondrial biology has now emerged as a pivotal signaling hub exploited by transformed cells to titrate complex adaptive responses to their ever-changing microenvironment.

Clearly, many questions remain. For instance, hypoxic or oxidative stress are excellent drivers of subcellular mitochondrial trafficking and heightened tumor cell motility. But these conditions also damage the mitochondria, reducing their bioenergetics output and lowering the organelle's overall fitness. And yet, these subpar mitochondria manage to escape quality control mechanisms by mitophagy, travel to the lamellipodial cytoskeleton and fuel energy-intensive processes of cell motility and invasion. Does that mean that there is a currently unappreciated link between mitophagy and stress-regulated mitochondrial trafficking? And what other interplay(s) exist between different facets of mitochondrial dynamics? For instance, we know that SNPH suppresses mitochondrial trafficking *and* cycles of fusion and fission. But is this a causative link? And how is it that mitochondrial trafficking and tumor cell invasion seem to involve only small, fragmented mitochondria generated through fission, a condition that has been paradoxically associated with increased cell death? And, finally, can the role of mitochondrial dynamics in tumor cell invasion be exploited therapeutically? For instance, can it be envisioned that shutting off anterograde cellular motor(s) implicated in mitochondrial trafficking may limit metastatic dissemination in patients? Given the fast pace of basic and translational advances in this field, the answers to many of these questions will undoubtedly be forthcoming.

ACKNOWLEDGMENTS

I thank present and past members of my laboratory for their innovative contributions to the studies summarized in this contribution. This work was supported by National Institutes of Health (NIH) grants R01 CA140043 and R35 CA220446.

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Figure 1. Cellular machinery of mitochondrial dynamics.
Schematic diagrams representing modulation of mitochondrial fusion, quality control/mitophagy, fission and subcellular trafficking are shown.

Figure 2. Subcellular mitochondrial trafficking in tumor cells.

Glioblastoma LN229 cells were transfected with control vector or FLAG-syntaphilin cDNA and analyzed for subcellular mitochondrial localization by confocal laser microscopy. 3D rendering of representative images are shown. The individual labeling for FLAG-syntaphilin (SNPH), nuclei, mitochondria or actin is indicated. Reproduced from Caino et al. (2017) Syntaphilin controls a mitochondrial rheostat for proliferation-motility decisions in cancer. *J Clin Invest* 127:3755–3769.

Figure 3. Dual function of syntaphilin (SNPH) in cancer.

In the presence of nutrients and oxygen (O₂) in a *favorable* microenvironment (**A**), high SNPH levels at the inner and outer mitochondrial membranes support tumor cell proliferation via oxidative phosphorylation and reduced ROS, while preventing mitochondrial trafficking to the cortical cytoskeleton and tumor cell movements. In contrast, low nutrients and oxygen (O₂) in an *unfavorable* microenvironment (**B**) decrease SNPH levels resulting in reduced ATP production, greater ROS generation and released inhibition of mitochondrial trafficking, triggering decreased tumor cell proliferation but heightened tumor cell motility and invasion.