Mitochondria on the move: emerging paradigms of organelle trafficking in tumour plasticity and metastasis

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There is now a resurgent interest in the role of mitochondria in cancer. Long considered controversial or outright unimportant, mitochondrial biology is now increasingly recognised as an important tumour driver. The underlying mechanisms remain to be fully elucidated. But recent studies have uncovered a complex landscape where reprogramming of mitochondrial homoeostasis, including organelle dynamics, metabolic output, apoptosis control and redox status converge to promote tumour adaptation to an unfavourable microenvironment and inject new traits of aggressive disease. In particular, mechanisms of subcellular mitochondrial trafficking have unexpectedly emerged as central regulators of metastatic competence in disparate tumours. Some of these pathways are druggable, opening fresh therapeutic opportunities for advanced and disseminated disease.

Among the uniqueness of cancer is a pervasive reprogramming of cellular metabolism, which shifts from oxidative bioenergetics in mitochondria to a process of glycolysis even in the presence of oxygen. As one of the hallmarks of cancer, this ‘Warburg effect’ (Vander Heiden et al, 2009), produces biomass for malignant expansion, introduces new cancer traits and reprograms accessory cells in the microenvironment (Vander Heiden et al, 2009). At least in certain tumours, a glycolysis signature is a strong indicator of worse patient outcome. Against this backdrop, it is not surprising that mitochondrial oxidative metabolism has been viewed as unimportant in cancer, or even dubbed as a ‘tumour suppressor’, at least in certain malignancies.

Recent studies, however, have changed that perspective. In fact, work from several groups have now uncovered a far more complex landscape, where mitochondrial homoeostasis in general and, more specifically, oxidative phosphorylation critically contribute to tumour fitness, promote adaptation to an ever-changing and mostly unfavourable microenvironment, and inject new traits of aggressive disease. For instance, oxidative phosphorylation still accounts for a large portion of ATP generated in tumours (Moreno-Sanchez et al, 2014), supports malignant growth in patients (Sellers et al, 2015) and enables key cancer traits of ‘stemness’ (Janiszewska et al, 2012), drug resistance (Roesch et al, 2013) and metastatic competence (LeBleu et al, 2014).

The present mini-review is not intended to revisit the broad array of mitochondrial functions implicated in cancer. Excellent contributions on this topic have recently appeared in the literature (Vyas et al, 2016; Zong et al, 2016). Instead, we will focus on an emerging role of subcellular mitochondrial trafficking as an unexpected requirement of tumour cell motility, invasion and metastasis. This process and its underlying mechanisms reflect mitochondrial reprogramming to microenvironment stress, and may provide new therapeutic targets in advanced disease (Caino et al, 2013).

Most cancer death are due to metastatic disease: the successful dissemination of tumour cells to distant organs. Available therapeutic options in these settings are scarce, producing only palliative, short-lived clinical responses, if at all. Considerable progress has been made in our mechanistic understanding of the metastatic process. However, a basic question of how tumours that utilise an inefficient glycolytic metabolism (Vander Heiden et al, 2009) accomplish among the most energy-intensive processes of

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membrane-cytoskeletal dynamics, chemotaxis and invasion across basement membrane(s) (Roussos et al, 2011) has remained unanswered.

Recent studies have provided a unique perspective to this question. Exposure of tumour cells to small molecule inhibitors of the phosphatidylinositol-3-kinase (PI3K), a key ‘cancer’ gene and therapeutic target in humans (Frauman and Rommel, 2014), was found to upregulate multiple signalling pathways of cell motility, invasion and metastasis (Caino et al, 2015). These results were confirmed experimentally, as PI3K inhibitors dramatically stimulated membrane-cytoskeletal dynamics, tumour chemotaxis and invasion across basement membranes or in 3D spheroids (Caino et al, 2015). Such a paradoxical response to molecular therapy, where treated cells actually acquire more malignant traits, is not without precedent. For instance, angiogenesis inhibitors (Ebos et al, 2009) or anti-Hsp90 therapy (Yano et al, 2008) have also been associated with increased metastatic propensity in tumour models, in vivo. What was unique in the tumour response to PI3K inhibitors was a dynamic behaviour of mitochondria, which migrated from their polarised and perinuclear localisation to the cortical cytoskeleton of treated cells (Caino et al, 2015), accumulating in physical proximity of focal adhesion complexes, which are effectors of cell motility (Roussos et al, 2011). Functionally, these cortical mitochondria supported membrane lamellipodia dynamics, actin cytoskeleton remodelling and phosphorylation of cell motility kinases, increased focal tumour cell motility and invasion (Caino et al, 2015). This pathway was not an oddity of PI3K therapy: chemotactic stimuli produced the same response, repositioning mitochondria from their perinuclear localisation to the cell periphery to support invasion and metastasis in mouse models (Rivadeneira et al, 2015). One requirement of the pathway was that mitochondria had to be energetically active for successful subcellular trafficking. Tumour cells with poisoned mitochondria or where oxidative phosphorylation was pharmacologically inhibited failed to reposition mitochondria to the cortical cytoskeleton, and had lost the ability to migrate and invade across basement membranes (Caino et al, 2015; Rivadeneira et al, 2015). Independent studies validated the model of mitochondrial trafficking as a requisite of tumour cell movements (Jung et al, 2016), and linked mitochondrial infiltration of polarised lamellipodia protrusions to increased ‘regional’ oxidative metabolism to fuel tumour cell movements (Cunniff et al, 2016).

The concept that mitochondria are highly motile organelles is not new. In fact, we know that mitochondria actively travel along the microtubule network in neurons and accumulate at sites of high energy demands, such as synapses and growth cones (Birs, et al, 2013). We also know that this pathway relies on an elaborate mitochondrial-cytoskeletal machinery of cellular motors, adapter proteins and GTPases that controls both anterograde (from nuclei to periphery) and retrograde (from periphery to nuclei) mitochondrial movements (Sheng, 2014). Although originally considered ‘neuronal specific’, some aspects of this pathway are clearly at work in other cell types. Consistent with recent findings (Caino et al, 2015; Rivadeneira et al, 2015; Jung et al, 2016), mitochondria have been shown to redistribute along the actin and tubulin networks in migrating lymphocytes (Campello et al, 2006), as well as tumour cells (Mills et al, 2016), and localise to membrane protrusions implicated in directional cell movements in both cell types (Desai et al, 2013; Morlino et al, 2014). Some of the signalling requirements of this pathway have also come into better focus. For instance, heightened activity of the energy sensor, AMPK has been associated with increased mitochondrial infiltration of leading edge lamellipodia, resulting in localised increase in mitochondrial mass and ‘regional’ ATP production (Cunniff et al, 2016). So, is a neuronal machinery of mitochondrial trafficking exploited in cancer to control metastatic competence, one of the most deleterious traits of progressive disease?

To answer this question and identify novel regulators of mitochondrial regulated tumour cell invasion, a genome-wide short hairpin RNA screen was recently carried out. Unexpectedly, one of the top hits in the screen was synaptphilin (SNPH) (Caino et al, 2016), a molecule that halts mitochondrial movements in neurons at subcellular sites of high energy demands (Sheng, 2014). Although originally characterised as ‘neuronal specific’, SNPH was in fact expressed in multiple non-neuronal tissues, including cancer (Caino et al, 2016). Functionally, silencing of SNPH in tumour cells was sufficient, in the absence of other stimuli, to cause exaggerated mitochondrial repositioning to the cortical cytoskeleton (Figure 1), increased focal adhesion complex dynamics and heightened tumour cell motility and invasion (Caino et al, 2016). As in neurons, this was due to the ability of SNPH to inhibit mitochondrial movements in tumour cells, decreasing the time that organelles spend in motion, or processivity, compared to stationary mitochondria. These findings had a clear disease-relevance. Analysis of genomic databases as well as primary patient cohorts showed that SNPH became downregulated or even lost during disease progression, correlating with worse patient outcome (Caino et al, 2016). Conversely, re-introduction of SNPH in invasive tumour cells was sufficient to reduce metastatic dissemination in a mouse model, in vivo. So, does this mean that other effectors of ‘neuronal’ mitochondrial trafficking are equally exploited in cancer (Sheng, 2014)? And does SNPH represent a novel class of
Mitochondrial reprogramming in cancer

Metastasis suppressors, shutting off the energy requirements of invasive tumours? More work is required to reach these conclusions. Key questions of what controls the extraneuronal expression of SNPH, how is endogenous SNPH downregulated in advanced tumours, and whether other ‘positive’ regulators of ‘neuronal’ mitochondrial trafficking become upregulated in cancer remain to be experimentally demonstrated. However, it is intriguing that atypical mitochondrial GTPases, Miro-1 or -2, which support mitochondrial trafficking in neurons (Birsas et al, 2013) become prominently upregulated in disparate cancers (Caino et al, 2016), and have been implicated in mitochondrial trafficking (Mills et al, 2016) and directional cell movements in tumour cells (Desai et al, 2013).

Although bioenergetics is critical for cellular functions, mitochondria do more than producing ATP, and it is possible that these additional functions may also contribute to tumour chemotaxis. For instance, changes in SNPH levels in tumour cells have been associated with increased cycles of mitochondrial fusion and fission, i.e., dynamics (Caino et al, 2016). A key regulator of organelle shape and size, recent work has suggested that mitochondrial dynamics is broadly exploited for a host of tumour traits, such as proliferation, invasion, redox balance and ‘stemness’ (Senft and Ronai, 2016). In turn, mitochondrial dynamics couples to mitophagy, a process of organelle quality control that clears damaged or energetically impaired mitochondria (Youle and Narendra, 2011). The role of mitophagy in cancer remains poorly understood, but recent findings suggest an important tumour suppressor function, involving both Parkin-dependent and -independent mechanisms (Bernardini et al, 2017), and there is initial evidence that mitophagy defects may favour disease progression (Chourasia et al, 2015). Whether mitochondrial dynamics (Senft and Ronai, 2016) and/or mitophagy (Youle and Narendra, 2011) contribute to organelle trafficking and tumour cell motility remain to be established. However, it is intriguing that deletion of SNPH significantly increases cycles of both mitochondrial fusion and fission in tumour cells, and that changes in organelle size influence the velocity of mitochondrial repositioning to the cortical cytoskeleton (Caino et al, 2016).

IS IT ONLY ABOUT ‘REGIONAL’ ATP PRODUCTION?

A straightforward interpretation of the data briefly summarised above is that mitochondrial repositioning to the cortical cytoskeleton provides an efficient, ‘regional’ energy source to fuel membrane-cytoskeletal dynamics and lamellipodia formation (Cunliff et al, 2016) that are essential for cell movements (Roussos et al, 2011). Per this model, it may not be the ‘how much’ ATP is generated, but rather the ‘when’ and ‘where’ that are important to support tumour cell invasion, and, therefore, metastasis. But what is the biological context for this response? The fact that molecular therapy stimulates mitochondrial trafficking and cell invasion (Caino et al, 2015) suggests that ‘stress’ conditions in the microenvironment may function as central drivers of this pathway (Gillies et al, 2012). This is consistent with other data that mitochondrial metabolism was required to sustain tumour cell invasion and metastasis under restrictive conditions of the microenvironment, such as glucose or amino acid depletion (Caino et al, 2013). Taken together, in an as yet fanciful scenario, it could be hypothesised that mitochondrial trafficking to the cortical cytoskeleton and the ensuing heightened cell motility constitute an adaptive response to ‘stress’, enabling tumour cells to ‘escape’ from the tumour microenvironment modulate mitochondrial functions in apoptosis inhibition, cell motility and invasion, proliferation, ‘retrograde’ gene expression, metabolic reprogramming and organelle dynamics, including subcellular trafficking. In turn, these mitochondrial functions expand tumour diversity, buffer environmental stress stimuli and introduce new traits of aggressive disease, including drug resistance and metastatic competence.

Figure 2. Mitochondrial reprogramming contributes to tumour plasticity. Stress stimuli of the tumour microenvironment modulate mitochondrial functions in apoptosis inhibition, cell motility and invasion, proliferation, ‘retrograde’ gene expression, metabolic reprogramming and organelle dynamics, including subcellular trafficking. In turn, these mitochondrial functions expand tumour diversity, buffer environmental stress stimuli and introduce new traits of aggressive disease, including drug resistance and metastatic competence.
an unfavourable microenvironment (Caino et al., 2015), no longer able to support their expansion (Gillies et al., 2012). In this context, there is evidence that mitochondrial reprogramming contributes to multiple aspects of tumour adaptation to environmental ‘stress’ stimuli (Figure 2). Published work from several groups suggests that this involves flexible titration of an anti-apoptotic threshold, control of ‘retrograde’ gene expression signalling, modulation of multiple metabolic pathways and redox status and sustained tumour cell proliferation even in noxious conditions (Vyas et al., 2016; Zong et al., 2016; Figure 2). These mechanisms help tumours cope with a rapidly evolving and often unfavourable microenvironment, while conferring new adaptive traits, such as drug resistance and metastatic competence that are key for disease progression in the clinic.

**CONFLICT OF INTEREST**

The author declares no conflict of interest.

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