MINIREVIEW

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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).

SUBCELLULAR MITOCHONDRIA TRAFFICKING AS A NOVEL REQUIREMENT OF TUMOUR CELL MOTILITY AND METASTASIS

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 (Fruman 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, resulting in increased 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 (Birsa *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?

EXPLOITATION OF A NEURONAL NETWORK OF MITOCHONDRIAL TRAFFICKING FOR METASTASIS

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 syntaphilin (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

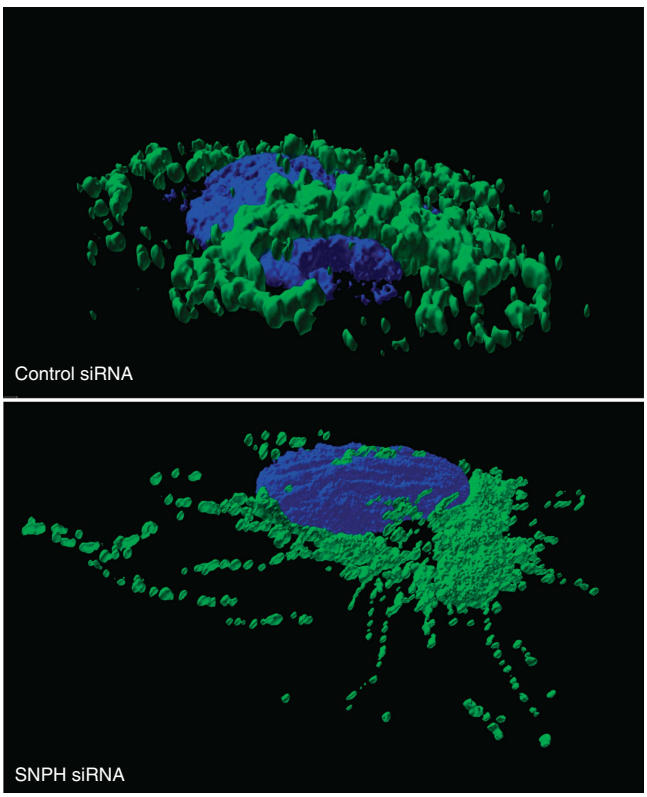

Figure 1. Mitochondrial trafficking to the cortical cytoskeleton. Prostate adenocarcinoma PC3 cells were transfected with control non-targeting siRNA or SNPH-directed siRNA and analysed for mitochondrial repositioning to the cortical cytoskeleton by confocal microscopy. A 3D isosurface rendering of mitochondria was obtained by staining fixed cells with an antibody to mitochondria (green), followed by Alexa Fluor 488-conjugated secondary antibody. DNA (blue) was stained with DAPI.

'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 (Birsa *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).

IS IT ONLY ABOUT 'REGIONAL' ATP PRODUCTION?

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 addition, changes in mitochondrial dynamics have been linked to tumour cell migration and invasion (Zhao *et al*, 2013; Ferreira-da-Silva *et al*, 2015). 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).

MITOCHONDRIAL TRAFFICKING AS PART OF TUMOUR PLASTICITY

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 (Cunniff *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

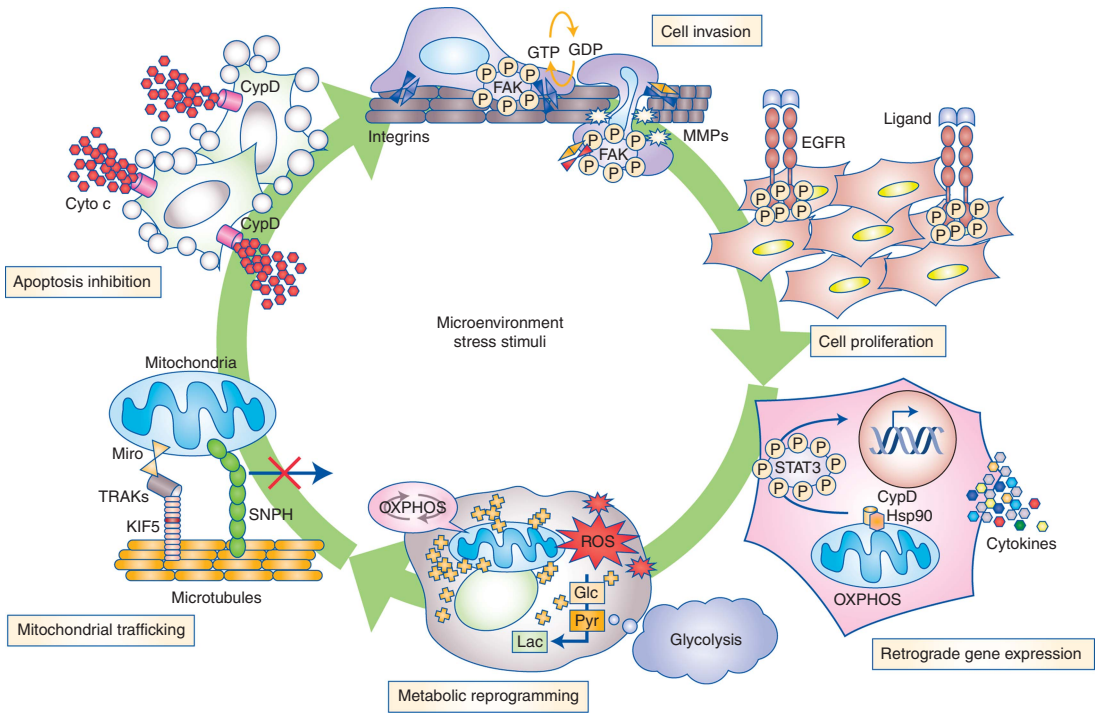

Figure 2. Mitochondrial reprogramming contributes to tumour plasticity. Stress stimuli of the tumour microenvironment modulate mitochondrial functions in apoptosis inhibition, cell motility and invasion, proliferation, 'retrograde' gene expression, metabolic reprogramming and organelle dynamics, including 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.

TRANSLATIONAL IMPLICATIONS – MITOCHONDRIA-DIRECTED CANCER THERAPY?

The impressive technological advances of the past decade have changed the paradigm in cancer therapy and ushered the concept (and hope) of personalised, or precision medicine: that if we sequence the genome of every patient, we will successfully match genetic alterations to specific inhibitor(s) and bring about durable clinical responses, even cures (Carneiro *et al*, 2016). Unfortunately, the reality in the clinic proved different, as all molecularly targeted agents so far produce short-lived responses, quickly supplanted by the emergence of drug-resistant and metastatic disease (Tannock and Hickman, 2016). The data reviewed above point to mitochondrial reprogramming (Vyas *et al*, 2016; Zong *et al*, 2016) in response to environmental 'stress' (Gillies *et al*, 2012) as a novel, key determinant of disease progression (Figure 2). We now know that some of these pathways are druggable, with manageable or minimal toxicity for normal tissues (Fulda *et al*, 2010). Differently from the premise of personalised medicine, targeting mitochondrial reprogramming is expected to simultaneously disable multiple, fundamental mechanisms of disease progression irrespective of driver mutation(s) (Figure 2). This approach may be applicable across a broad spectrum of genetically heterogeneous tumours, and has the potential to bypass the powerful mechanisms of tumour selection that are at work to confer drug resistance in face of single oncogene targeting. Clearly, much work remains to be done, and it is not a foregone conclusion that disabling an entire organelle system, that is, mitochondria, may be sufficiently tolerated in humans. On the other hand, initial proof-of-concept studies have suggested that pharmacological disruption of mitochondrial protein folding quality control (Chae *et al*, 2013; Cole *et al*, 2015) or inhibition of oxidative metabolism (Rivadeneira *et al*, 2015) is feasible in different tumour models, causes irreversible collapse of multiple mitochondrial functions and delivers promising anticancer activity with manageable toxicity, *in vivo*.

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CONFLICT OF INTEREST

The author declares no conflict of interest.

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