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Disabling mitochondrial reprogramming in cancer

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Abstract

Recent studies have demonstrated that tumor cells exposed to molecular therapy with PI3K antagonists redistribute their mitochondria to the peripheral cytoskeleton, fueling membrane dynamics, turnover of focal adhesion complexes and increased tumor cell motility and invasion. Although this process paradoxically increases metastatic propensity during molecular therapy, it also emphasizes a critical role of *regional* mitochondrial bioenergetics in tumor metabolic reprogramming and may offer prime therapeutic opportunities to prevent disseminated disease.

Graphical Abstract

Keywords

Mitochondria; drug resistance; PI3K; Hsp90; metastasis

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Disclosure of potential conflicts of interest

The authors declare that no conflicts of interest exist.

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1. Mitochondria rewiring in cancer

Tumors extensively reprogram their metabolism to meet the increased demand of macromolecules for biomass expansion and to support cell division. This involves a general shift from oxidative phosphorylation (OxPhos) to glycolysis, even under conditions of oxygen availability (the “Warburg effect”), oxidation of glutamine by glutaminolysis and a truncated tricarboxylic acid (TCA) cycle [1]. It is generally believed that metabolic rewiring is critical to afford survival and proliferative advantages in a tumor microenvironment typically characterized by nutrient and oxygen deprivation [2]. A transcriptional program initiated by the hypoxia-inducible factors (HIF) triggers increased expression of glycolytic enzymes, glucose transporters, inhibitors of mitochondrial metabolism and pro-angiogenic factors [3]. In addition to HIF, activation of the Ras [4], Akt [5] and Myc [6] oncogenes has been associated with key features of the Warburg effect. Although shutting off the OxPhos is a hallmark of tumor metabolism, mitochondria remain active in cancer cells and contribute to metabolic reprogramming through glutaminolysis and a partial TCA [7].

In this context, a mitochondrial pool of chaperones of the heat shock proteins of 90 KDa (mtHsp90) is essential for transformed cells to buffer proteotoxic stress, and ensure the stability and folding of various bioenergetics effectors, including the OxPhos iron-sulfur Complex II subunit, succinate dehydrogenase B (SDHB) [8]. In addition, mtHsp90s have been shown to sustain tumor cell invasion and metastasis by dampening activation of cellular stress mechanisms, in particular autophagy and the unfolded protein response [9].

Mitochondria of tumor cells continuously undergo dynamic changes in number, intracellular location and structure [10]. These processes of division, fusion and transport are collectively known as “mitochondrial dynamics” and may be important for tumor progression traits, including malignant growth, drug resistance and invasiveness [11]. Although mitochondrial dynamics is key to organelle function, its impact for metabolic reprogramming and tumor progression is not well understood. Fresh experimental evidence indicates that mitochondrial dynamics are modulated in response to hyperactive growth factor signaling [12–15], tumor microenvironment stress [16–18] and therapy resistance [17, 19, 20].

2. The paradox: a PI3K therapy adaptive pro-metastatic switch is mediated by mitochondrial dynamics

Together, phosphoinositide-3 kinases (PI3K) and downstream serine/threonine protein kinases Akt and mTOR constitute one of the most commonly altered pathways in human cancer and important therapeutic target [21]. Despite enormous efforts to develop high-affinity PI3K-targeting drugs, these agents have shown limited activity in the clinic, and significant toxicity [22, 23]. The molecular basis of resistance mechanisms to PI3K antagonists has not been completely elucidated, but it is possible that the activation of compensatory signals in treated tumor cells through RTKs, ERK, MYC, Notch/Wnt; as well as Akt/mTOR [24] may play critical roles in these responses.

In two recent studies, we demonstrated that PI3K-directed therapy induces extensive bioenergetics and transcriptional reprogramming in tumors [20, 25]. This involved global

changes in the secretory profile and activation of growth factor receptor pathways, culminating with the recruitment of Akt2 to mitochondria. In turn, mitochondrial Akt2 preserved organelle bioenergetics, opposed permeability transition and prevented tumor cell death [25]. Unexpectedly, these studies uncovered an additional adaptive mechanism associated with PI3K therapy: the induction of a highly migratory and invasive phenotype [20] (Figure 1a). Mechanistically, this was associated with increased mitochondrial fusion, and resulted in the active redistribution of mitochondria to cellular protrusions of the peripheral cytoskeleton of tumor cells [20] (Figure 1b). In turn, the repositioned mitochondria fueled membrane lamellipodia dynamics, phosphorylation of cell motility kinases, most notably focal adhesion kinase (FAK) and increased turnover of focal adhesion complexes (Table 1). In terms of signals, suppression of mitochondrial OxPhos or silencing Akt or FAK prevented mitochondrial repositioning to the peripheral cytoskeleton in response to PI3K therapy, and blocked tumor cell invasion [20] (Figure 2).

3. The promise: targeting mitochondrial bioenergetics and dynamics salvages PI3K therapy

From a translational and disease-relevant perspective, the results above caution against the use of single-agent PI3K therapy in cancer patients. On the other hand, it may be speculated that the combination of PI3K antagonists with agents that prevent mitochondrial reprogramming may provide better anticancer approaches in the clinic. Indeed, our studies showed that tumor cells deficient in OxPhos were unable to switch to a pro-metastatic phenotype upon treatment with PI3Ki [20]. Furthermore, pharmacological blockade of mitochondrial respiration (Table 1) prevented mitochondrial dynamics and suppressed tumor cell invasion in response to PI3Ki. This pathway was contributed by mtHsp90, which maintain the stability and folding of electron transport chain (ETC) effectors, and accordingly, siRNA silencing of mtHsp90 chaperones prevented mitochondrial trafficking and suppressed tumor cell invasion [20]. Consistent with these findings, treatment of tumor cells with Gamitrinib, a small molecule Hsp90 inhibitor engineered to selectively accumulate in mitochondria also suppressed mitochondrial repositioning to the cortical cytoskeleton and abolished tumor cell invasion in response to PI3K therapy.[26]. Accordingly, preclinical studies confirmed a promised anti-cancer activity of Gamitrinib in localized and disseminated xenograft and genetic tumor models [27, 28], alone or in combination with other molecular therapies.

In addition to antagonists of mitochondrial bioenergetics, inhibition of kinase-dependent signaling effectively prevented the pro-metastatic effects of PI3Ki (Table 3). Accordingly, siRNA depletion of FAK, mTOR and Akt2 blocked PI3Ki-induced mitochondria trafficking and tumor cell invasion [20]. Based on these findings, it is possible that the combination of antagonists for FAK, Akt2, or mTOR plus PI3Ki may generate potent and synergistic anticancer activity (Table 3).

Finally, manipulation of mitochondrial dynamics reduced the pro-metastatic effects of PI3K antagonists (Table 3). In these studies, depletion of the effector of mitochondrial fusion, Mitofusin 1 was sufficient to prevent mitochondrial trafficking and tumor cell invasion induced by PI3Ki [20]. Although pharmacologic modulators of mitochondrial dynamics

suitable for clinical practice are still in infancy, the prediction is that the combination of PI3Ki therapy plus an inhibitor of mitochondrial fusion directed against Mitofusins or Opa (or, alternatively, an activator of mitochondrial fission, for instance Drp1) may also provide synergistic anticancer activity. In proof-of-concept studies, Drp1 inhibitors successfully improved cardiac function and ameliorated the clinical picture of Huntington's disease in mice [29–31].

Finally, although the cytoskeletal requirements that support mitochondrial relocation to cellular protrusions of cell motility have not yet been identified, it could be speculated that inhibition of these mechanisms could also interfere with metastatic competency (Table 3). At least in neurons, there is an elaborate machinery that enables mitochondrial trafficking along the microtubule cytoskeleton and their concentration at strategic subcellular sites of high energy demands, including synapses and growth cones. These molecules include mitochondrial Rho GTPases (RhoT1/2), trafficking adapter proteins that bridge RhoTs to motors (Trak1/2), and the molecular motors kinesin-1 and dynein [32]. Recent evidence suggests that part of this pathway might be conserved in other cell types, including lymphocytes [33, 34] and tumor cells [35, 36]. Importantly, mitochondrial trafficking has also been observed during tumor chemotaxis, with redistribution of organelles at the leading edge of migration [35]. Whether the same cytoskeletal machinery involved in mitochondrial trafficking in neurons mediates a similar response in tumors, and may provide a therapeutic target for anti-metastatic strategies is currently not known. In addition, pharmacologic agents that selectively target a mitochondrial trafficking machinery, including the mitochondria receptors RhoT1 and RhoT2[37, 38] have not yet been developed.

4. Conclusions

PI3K inhibitors reprogram tumors and select new cancer phenotypes important for disease progression. This adaptive response involves the trafficking of energetically active mitochondria to subcellular sites of cell motility, where they provide a potent, “regional” energy source to support tumor cell invasion. Although this response may paradoxically increase the risk of metastasis during PI3K therapy, we propose that targeting mitochondrial reprogramming with currently available drugs for FAK, Akt2, mTOR and mtHsp90 is feasible, and could provide a novel therapeutic strategy to limit disease dissemination in patients.

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Figure 1. PI3K therapy stimulates cell motility and induces mitochondrial repositioning
a) Tumor cells treated with Vehicle or 2 μ M GDC-0941 were seeded in 2D chemotaxis chambers and analyzed by phase contrast microscopy for 5 h. Representative cell morphologies and position respect to initial (0h) is provided. Scale bar, 50 μ m. b) Cells treated as in (a) were stained with Mitotracker Red and phalloidin-Alexa 488 (green) and analyzed by confocal microscopy. Full cell stacks were combined to generate 3D maximum intensity projections. Scale bar, 10 μ m.

Figure 2. PI3K therapy triggers an adaptive pro-metastatic switch

Schematic representation of the key molecular events that mediate PI3Ki induced mitochondrial trafficking and tumor cell invasion. Akt2, serine/threonine kinase Akt isoform 2; FA, focal adhesion; FAK, focal adhesion kinase; Hsp90, heat shock protein of 90 kDa; Mfn1, mitofusin 1; mTOR, mammalian target of rapamycin; TRAP1, tumor necrosis factor receptor associated protein 1.

Table 1

PI3K antagonists and associated pro-metastatic phenotypes

The PI3K inhibitors studied in [20] are provided, with their associated phenotype (mitochondrial trafficking, focal adhesion dynamics, cell motility and cell invasion). Na, not assayed; (++) , mild stimulatory effect; (+++), strong stimulatory effect.

Compound	PubChem CID	Class	mito trafficking	FA dynamics	Cell motility	Cell invasion
PX-866	9849735	p110 α inhibitor	(+++)	(+++)	(+++)	(++)
GDC-0941	17755052	PI3K α/δ inhibitor	(+++)	na	(+++)	(+++)
AZD6482	44137675	PI3K β inhibitor	(++)	na	(+++)	(+++)
BKM120	16654980	p110 $\alpha/\beta/\delta/\gamma$ inhibitor	na	na	(++)	(++)

Table 2
Pharmacological inhibitors that disable pro-metastatic effects of PI3K therapy

A summary of the mitochondrial targeting drugs that were tested for their ability to prevent PX-866's pro-metastatic effects is shown [20]. The name, chemical ID, and mechanism of action of each drug is listed. The effect of combination of each drug with PX-866 compared to PX-866 alone in mitochondrial trafficking and cell invasion is shown. Na, not assayed; (–), blocks PX-866 effects; (=), no differences between PX-866 alone and combination of PX-88 + drug.

Name	PubChem CID	class	combination	mito trafficking	cell invasion
Rotenone	6758	ETC inhibitor	PX-866	na	(–)
Antimycin A	16218979	ETC inhibitor	PX-866	na	(–)
Oligomycin A	6364620	ATP synthase inhibitor	PX-866	na	(–)
CCCP	2603	uncoupler	PX-866	na	(–)
NAC	12035	antioxidant	PX-866	(=)	(=)
mitoTEMPO	73504625	superoxide scavenger	PX-866	(=)	(=)
Gamitrinib	na	mtHsp90 inhibitor	PX-866	(–)	(–)

Table 3
Potential targets that disable pro-metastatic effects of PI3K therapy

A summary of the molecular targets tested in [20] is provided. The effect of the combination of siRNA mediated depletion of each target with PX-866 treatment on mitochondrial trafficking and cell invasion is noted. An example of drugs that inhibit the target, with its associated chemical ID, class and clinical status of the drug is provided. n/a, not available.

Target	combination	mito trafficking	cell invasion	Drugs	PubChem CID	class	Clinical status
FAK	siRNA + PX-866	(-)	(-)	Defactinib	25117126	FAK inhibitor	phase 2
mTOR	siRNA + PX-866	(-)	(-)	Torin 1	49836027	mTOR inhibitor	
Akt2	siRNA + PX-866	(-)	(-)	Afuresertib	46843057	Akt2 inhibitor	phase 2
Mitofusin 1	siRNA + PX-866	(-)	(-)	n/a			