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Invited perspective

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.

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,

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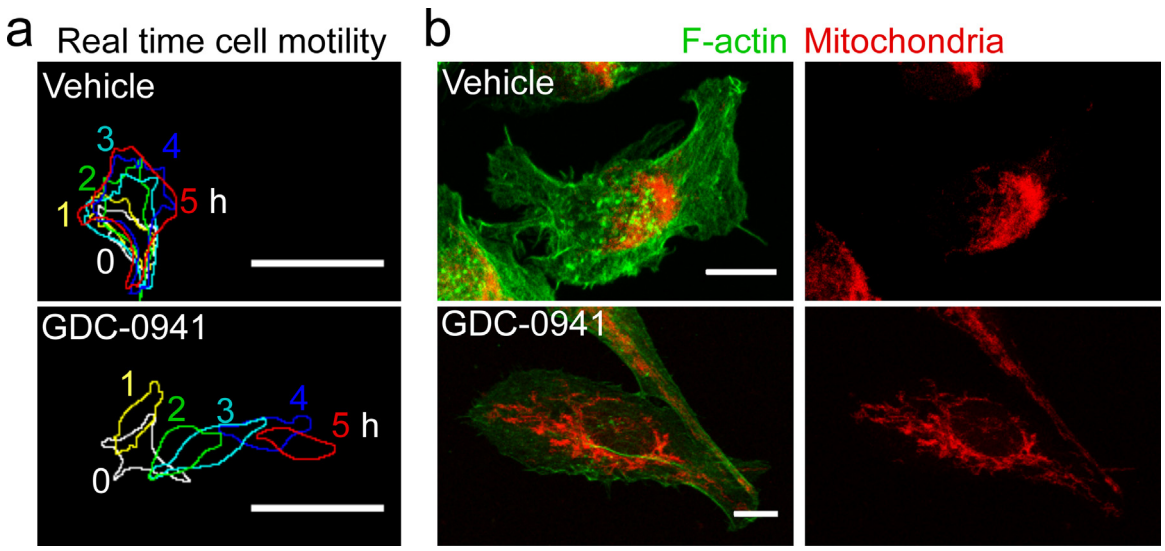

Fig. 1. PI3K therapy stimulates cell motility and induces mitochondrial repositioning. (a) Tumor cells treated with Vehicle or 2 μM GDC-0941 were seeded in 2D chemotaxis chambers and analyzed by phase contrast microscopy for 5 h. Representative cell morphologies and position respect to initial (0 h) is provided. Scale bar, 50 μm. (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 μm.

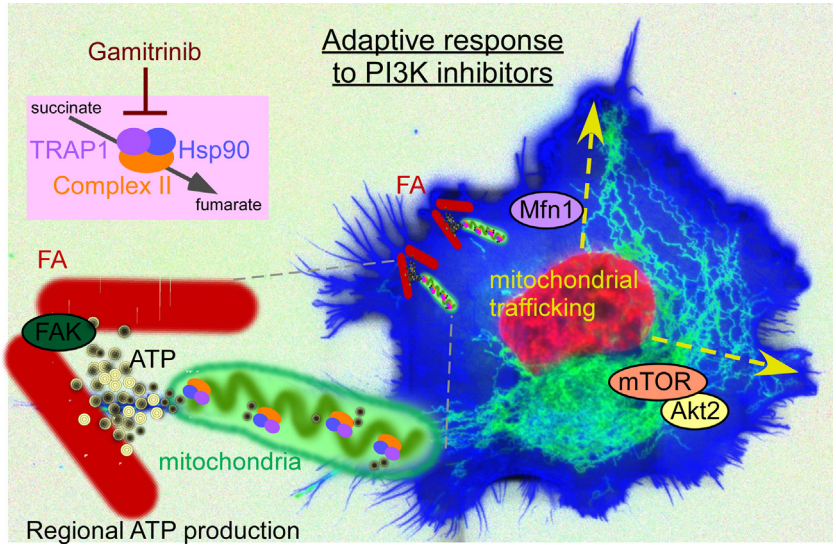

Fig. 2. PI3K therapy triggers an adaptive pro-metastatic switch. Shematic representation of the key molecular events that mediate PI3Ki induced mitochondrial trafficking and tumor cell invasion. Akt2, serine/threonine kinase Akt isoform 2; FA, focal adhesion; FAK, focal adhesion kinase; Hsp90, heat shock protein of 90 kDa; Mfn1, mitofusin 1; mTOR, mammalian target of rapamyicin; 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).

Compound	PubChem CID	Class	Mito trafficking	FA dynamics	Cell motility	Cell invasion
PX-866	9849735	p110α inhibitor	(+++)	(+++)	(+++)	(++)
GDC-0941	17755052	PI3Kα/δ inhibitor	(+++)	na	(+++)	(+++)
AZD6482	44137675	PI3Kβ inhibitor	(++)	na	(+++)	(+++)
BKM120	16654980	p110α/β/δ/γ inhibitor	na	na	(++)	(++)

Note: Na, not assayed; (++), mild stimulatory effect; (+++), strong stimulatory effect.

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] (Fig. 1a). Mechanis-