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Review

Mitochondrial function in melanoma

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ABSTRACT

Melanoma is the most lethal form of skin cancer and its incidence is rapidly rising. Breakthroughs in the understanding of the basic biology of melanoma in the past decade have yielded several new treatments, and advances continue to be made on a variety of fronts. One such area involves the delineation of changes in mitochondria that occur during melanoma formation, and how these changes affect responses to therapy. In this review, we summarize recent developments on the multiple functions that mitochondria play in melanoma, and how these roles are currently being evaluated as new targets for clinical intervention.

Introduction

Malignant melanoma is currently the fifth most common cancer in the US and will cause an estimated 9710 deaths in 2014 alone [24]. Large scale sequencing efforts have defined the signaling pathways that drive melanoma formation [53]. Alterations in the MAPK and PI3K pathways are common and have marked effects on melanoma cell metabolism. Activation of the MAPK pathway is nearly universal in melanoma, including activating mutations in BRAF (50%), NRAS (20%), inactivating mutations in NF1 (10%), or activating mutations in tyrosine kinases including KIT (5–10%) [11,22,30,12]. The microopthalmia transcription factor (MITF)[1] is of particular interest, as it is amplified in a subset of melanomas and directly regulates Peroxisome proliferator-activated receptor Gamma Coactivator 1-alpha (PGC-1α), a master regulator of mitochondrial biogenesis and function regulation [19,47]. The identification of these mutations has helped define how genetic changes in melanoma alter cellular metabolism to permit rapid tumor growth.

Mitochondria integrate and regulate various aspects of cellular metabolism and produce the majority of cellular ATP. Melanoma cells primarily utilize glucose as an energy source, which is metabolized to pyruvate and imported into mitochondria, converted to acetyl-CoA, and utilized by the tricarboxylic acid (TCA) cycle to generate electron donors and create a proton gradient across the inner mitochondrial membrane. The resulting electrochemical gradient is used by ATP synthase to generate ATP [4] or by uncoupling proteins to produce heat [8]. Although this process delivers electron pairs to molecular oxygen, the terminal acceptor of the electron transport chain, molecular oxygen may also become partially reduced by a single electron, forming highly reactive and toxic superoxide anions. The generation of reactive oxygen species (ROS) has a variety of effects, promoting or inhibiting cancer growth in different situations [52].

Recent work has identified a cascade of transcriptional regulators downstream of PGC-1 coactivators involved in mitochondrial biogenesis and energy transduction. These include the peroxisome proliferator-activated receptors (PPARs), estrogen-related receptors (ERRs), and Nuclear Respiratory Factor (NRF) 1 and 2, which regulate expression of TFAM and many components of the respiratory chain and mitochondrial structure [14,25,31,47]. Several of these regulators also act on a broad range of extra-mitochondrial metabolic processes, including gluconeogenesis, glucose transport, and lipogenesis [14].

Mitochondria play a central role in metabolic homeostasis in all cells, including melanoma tumor cells. In this review, we summarize the roles that mitochondria play in melanoma formation and

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[1] *Abbreviations used:* MITF, microopthalmia transcription factor; PGC-1α, peroxisome proliferator-activated receptor Gamma Coactivator 1-alpha; TCA, tricarboxylic acid; ROS, reactive oxygen species; PPARs, peroxisome proliferator-activated receptors; ERRs, estrogen-related receptors; NRF, Nuclear Respiratory Factor; OIS, oncogene-induced senescence; HK, hexokinase; MOMP, mitochondrial outer membrane permiabilization; PPARα, peroxisome proliferator-activated receptor α; ERRα, estrogen-related receptor α, α-MSH, α-melanocyte stimulating hormone, OAA, oxaloacetate; α-KG, α-ketoglutarate; AMPK, AMP kinase.

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progression and highlight how differences in mitochondrial function define melanoma subsets. In addition, the role of mitochondria in the response to therapy and the development of resistance are discussed. Finally, we explore how targeting mitochondrial function may be exploited for clinical benefit. (See Fig. 1).

The Warburg Effect and energy homeostasis

Otto Warburg hypothesized that metabolic changes in the relative balance of glycolysis/fermentation and respiration are a central feature of cancer, however rigorous evaluation of these alterations has been a comparatively recent undertaking [29,57,60]. Warburg observed elevated rates of fermentation even in the presence of normoxia in cancer and hypothesized that this was due to a defect in mitochondrial respiration [29]. In rare cases, mitochondrial dysfunction does appear to contribute to tumorigenesis, however in most cases, tumors exhibit relatively normal levels of oxidative phosphorylation [49]. In fact, rather than decreasing, some studies have shown that TCA cycle flux may be elevated in a subset of melanomas relative to benign epidermal melanocytes [5,49]. However in nearly all melanomas, glucose uptake is increased, and the relative levels of fermentation and lactic acid production increase as well [7,27,37,49]. Melanoma cells also exhibit enhanced metabolic adaptability relative to benign tissue under metabolically-limiting conditions such as hypoxia and low extracellular glucose [13]. Taken together, these findings suggest that the balance between aerobic and anaerobic respiration in melanoma is both highly variable and may be altered to respond to adverse environmental conditions in order to promote tumor growth and survival. (See Fig. 2).

Although glucose is typically the principal source of energy in melanoma cells, mitochondria also utilize glutamine as an alternative anaplerotic substrate for the TCA cycle [49]. Glutamine is required for rapid growth of a number of different cancers and can serve both as a source of ATP and biosynthetic intermediates [40,42]. Notably, glutamine has been shown to play an important role in the response of melanoma to hypoxia, serving as the source

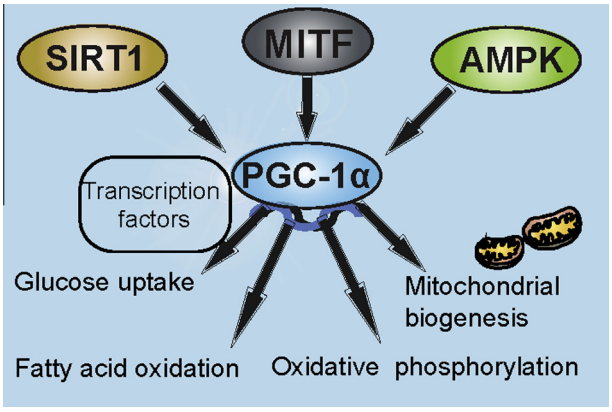

Fig. 2. PGC-1α regulates key metabolic pathways. Activity and expression of PGC-1α is regulated by several signaling pathways including AMP kinase (AMPK), sirtuins and MITF. Through binding with transcription factors, PGC-1α drives expression programs that increase oxidative flux and contribute to oncogenesis.

for over 90% of TCA cycle intermediates under hypoxic conditions [49]. Furthermore, several melanoma studies have described an anaplerotic flux of glutamine carbon in the reverse direction through the TCA cycle, feeding into fatty acid synthesis and serving as a carbon source for lipogenesis [13], underscoring the variety of roles glutamine metabolism can play in maintaining melanoma growth and survival.

Regulation of aerobic versus anaerobic pyruvate utilization in melanoma is of critical importance and has recently been shown to be controlled by the PDK1-PDP2-PDH axis. Oncogene-induced senescence (OIS) induced by constitutive BRAF activation leads to increased activation of PDH through suppression of PDP2. This ultimately funnels a large proportion of glucose into the TCA cycle: an effect that is reversed in malignant cells [26]. The characterization of these control nodes highlights the multiple roles that activation of the MAPK pathway plays in melanoma in regulating glucose metabolism.

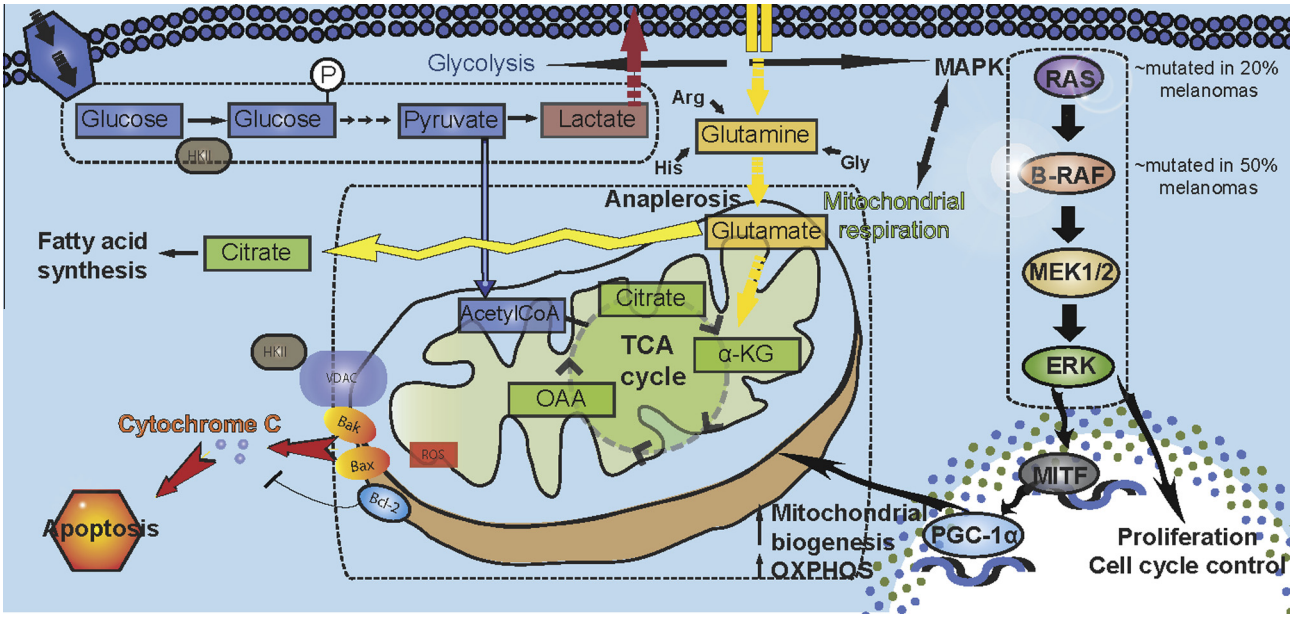

Fig. 1. Mitochondria are at the crossroads of metabolic and cellular signaling changes in melanoma. The MAPK pathway, which is frequently aberrantly activated in melanoma, can dynamically regulate the balance between glycolysis and mitochondrial respiration [27], as well as increase mitochondrial biogenesis via PGC-1α driven transcriptional programs. Interactions between Bcl family proteins, VDAC, and HKII play key roles in controlling cytochrome C release and apoptosis [2]. Glutamine can serve as a carbon source for TCA cycle intermediates as an adaptive response in hypoxia [52]. OAA – oxaloacetate; α-KG – α-ketoglutarate; HKII – Hexokinase II.