Review

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Molecular drivers of cellular metabolic reprogramming in melanoma

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The development of metastatic melanoma is accompanied by distinct changes in cellular metabolism, most notably a change in strategy for energy production from mitochondrial oxidative phosphorylation to cytoplasmic aerobic glycolysis. This bioenergetic switch occurs at the expense of less-efficient utilization of glucose, but is required for melanoma cells to meet their bioenergetic and biosynthetic demands. Recent work has implicated well-established melanoma drivers such as *BRAF, PTEN, MITF,* and *ARF* in the regulation of cellular energy metabolism. The metabolic changes in melanoma cells offer new opportunities for therapeutic intervention. However, inter- and intratumor bioenergetic heterogeneity caused by variation in genetic driver profiles and mitochondrial performance may impact on the effectiveness of treatment.

Melanoma: a metabolic disease

Metastatic melanoma is a life-threatening condition for patients and is a major clinical challenge for oncologists. While early-stage melanomas can usually be effectively treated with surgery, more advanced tumors have a high metastatic potential and are notoriously resistant to conventional cancer therapies such as radiation and chemotherapy [1]. Despite significant advances in our understanding of melanoma biology and pathogenesis [2,3], and the recent success in developing targeted therapies for melanoma [2,4], the prognosis of the disease remains poor.

Much of the research on melanoma has focused on the genes and molecular processes that drive tumor development. Intensive efforts over several decades have identified the key melanoma-driving genetic changes and have shown how they interact in biochemical and cellular pathways. Recent work has suggested that many melanoma driver genes control cellular metabolism, and that mutations in these genes allow melanoma cells to generate sufficient energy and building blocks to sustain viability and tumor growth. We review current knowledge on the molecular mechanisms of metabolic reprogramming in melanoma and discuss novel therapeutic strategies that may inhibit tumor growth and prevent the development of resistance to existing therapies.

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Driver genes and pathways in melanoma

Melanoma arises from melanocytes, the pigment-generating cells of the skin, hair, and eyes. In a simplistic model, the development and progression of melanoma can be viewed as a stepwise process of clonal succession driven by the acquisition of genomic alterations (Figure 1). Genome-wide sequencing approaches have revealed the enormous genetic complexity of melanoma, with thousands of mutations, deletions, amplifications, translocations, and DNA methylation changes being present in the genomes of individual tumors [5–9]. Only a small minority of these alterations are required for melanoma genesis and maintenance – the so-called 'driver' mutations. The major known melanoma drivers are listed in Table 1, together with current knowledge about the regulatory pathways in which they operate. For recent comprehensive reviews on driver mutations and signaling pathways in melanoma see [2,3].

One of the best-studied oncogenic events in melanoma is mutation of *BRAF* (v-Raf murine sarcoma viral oncogene homolog), a protein kinase acting in the RAS–RAF–MEK–ERK mitogen-activated protein kinase (MAPK) signal transduction pathway (Figure 2). First identified in 2002 [10], *BRAF* mutations have been found in more than 50% of melanomas, most commonly a valine-to-glutamic acid substitution at residue 600 (p.V600E). Melanomas with wild type *BRAF* usually carry oncogenic mutations in upstream components of the MAPK pathway, such as *NRAS* (neuroblastoma RAS viral oncogene homolog), *KIT* (v-Kit Hardy–Zuckerman 4 feline sarcoma viral oncogene homolog), *GNAQ* (guanine nucleotide-binding protein, q polypeptide) and *GNA11* (guanine nucleotide-binding protein, α11) [11–14]. Mutations in *BRAF* have also been found at high frequencies in benign and dysplastic naevi [15–17], and hence have been implicated as an early event during neoplastic transformation of melanocytes (Figure 1). The development of naevi in response to activation of BRAF is a classic example of oncogene-induced senescence (OIS) [18], a cellular fail-safe mechanism that prevents malignant transformation of normal cells by inducing growth arrest [19,20].

Expression of oncogenic $BRAF^{V600E}$ in melanocytes induces expression of $p16^{INK4A}$, a key negative regulator of the cell cycle [15]. $p16^{INK4A}$ is encoded by the *CDKN2A* locus, which is mutated in about 25% of melanoma families [21] and inactivated by mutation, deletion, or promoter hypermethylation in 50–80% of sporadic melanoma cases [22,23]. Genetic alterations in components of the $p16^{INK4A}$–cyclin D/CDK4–RB cell cycle checkpoint are found in virtually all melanoma cell lines in a mutually

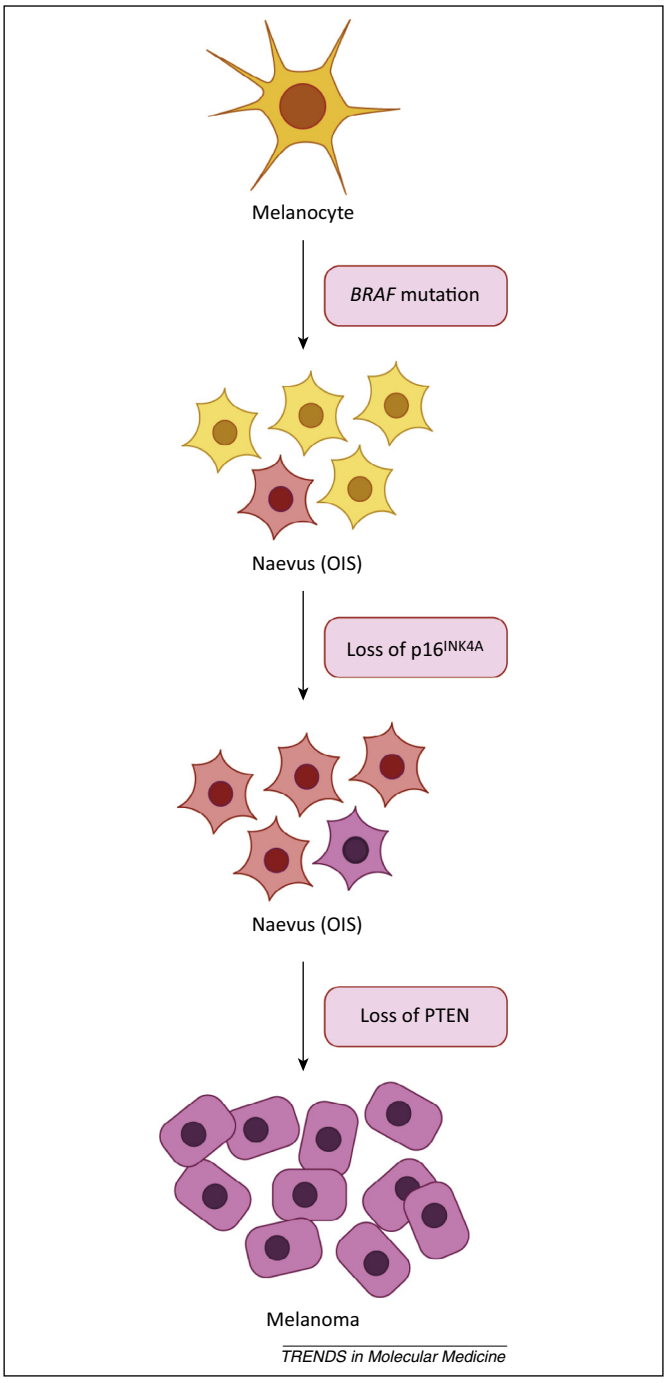

Figure 1. Model for the development and progression of melanoma. The *BRAF*^{V600E} oncogene induces senescence (OIS) in melanocytes and leads to the formation of naevi. Mutations in *CDKN2A* leading to loss of p16^{INK4A} are necessary but not sufficient to bypass OIS. Additional loss of PTEN (phosphatase and tensin homolog) leads to bypass of OIS and progression to melanoma.

exclusive fashion, underlining the importance of this checkpoint in preventing melanoma development [22,23]. While p16^{INK4A} has been shown to be a component of the replicative senescence barrier of human melanocytes [24,25], its role in BRAF-induced senescence is less clear, and several lines of evidence suggest that bypass of a p16^{INK4A}-independent senescence barrier is required for melanoma progression [15,17].

A cooperating event in BRAF-initiated melanomagenesis is constitutive activation of the PI3K (phosphoinositide 3-kinase)–AKT–mTOR (mammalian target of rapamycin) signaling pathway. Hyperactive PI3K–AKT–mTOR signaling in melanomas can often be ascribed to inactivating events in *PTEN* (phosphatase and tensin homolog), a negative regulator of this pathway [26,27]. *NRAS* and *PTEN* mutations are mutually exclusive in melanomas, consistent with the ability of oncogenic RAS to also activate the PI3K–AKT–mTOR pathway (Figure 2) [28]. By contrast, activating mutations in *PIK3CA*, which encodes the catalytic subunit of PI3K, or in *AKT1, AKT2*, and *AKT3*, are rare in melanoma [29,30], suggesting that these alterations do not cover equivalent functions. Gain of AKT3 immunopositivity has been described as a common event in melanoma, and was suggested as an alternative mechanism for PI3K–AKT–mTOR activation in *PTEN* wild type tumors [17,31], but the genetic basis for AKT3 overexpression remains elusive. Furthermore, the role of AKT as an effector of PI3K signaling in melanoma cells has been questioned by a study showing that PI3K inhibition blocks downstream signaling and proliferation better than AKT inhibition [32]. Several studies have demonstrated non-random coexistence of activating *BRAF* mutations and inactivating *PTEN* events in the same melanomas, suggesting that they collaborate during melanomagenesis [23,33]. These findings have been further corroborated by functional studies showing that inactivation of PTEN abrogates BRAF^{V600E}-induced senescence in p16^{INK4A}-deficient melanocytes [17].

Cellular metabolism in melanoma

The pattern of metabolism in normal cells depends on the availability of substrates and oxygen. The major substrate for cellular energy production, glucose, is catabolized to pyruvate through glycolysis in the cytoplasm, yielding two molecules of ATP for each molecule of glucose consumed. In the presence of oxygen, pyruvate enters the mitochondria and is converted into acetyl-CoA by pyruvate dehydrogenase (PDH). Acetyl-CoA is then further catabolized by the tricarboxylic acid (TCA) cycle and oxidative phosphorylation (OXPHOS), increasing the yield of energy to more than 30 ATP molecules per molecule of glucose (Figure 3). Fatty acids decomposed through β-oxidation are another source of acetyl-CoA that can be utilized for energy production in mitochondria. When oxygen is scarce, mitochondrial energy production is restricted, rendering cells more dependent on glycolysis. Pyruvate is then converted into lactate to regenerate the electron acceptor, NAD^+, a cofactor required for sustaining glycolysis during anaerobic conditions. When nutrients are scarce and the AMP/ATP ratio increases, the energy-sensor liver kinase B1 (LKB1) mediates activation of AMP-activated protein kinase (AMPK), and this drives the cell into a state favoring recovery of energy production over growth. Inhibition of the master stimulator of cell growth, mTOR, is central for mediating this response. Thus the balance between catabolic and anabolic processes is controlled by the relative levels of AMPK and mTOR activation.

The regulation of metabolic pathways in cancer cells is dramatically altered from that in normal cells. One of the most fundamental changes is upregulation of glycolysis and elevated production of lactate from pyruvate, even in the presence of abundant oxygen, diverting pyruvate away from oxidation in the mitochondria. This phenotype was

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