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Feeling energetic? New strategies to prevent metabolic reprogramming in melanoma

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Commentary

The development of small molecule BRAF kinase inhibitors has proven revolutionary in the treatment of cutaneous melanomas that harbor activating *BRAF* mutations (s1). Despite this, resistance is commonplace and durable responses are lacking for the majority of patients. Escape from BRAF inhibitor therapy is complex, involving both a period of adaptation and reprogramming, before the acquisition of acquired resistance that is largely mediated through the recovery of MAPK pathway signaling (s2, s3). Reactivation of the MAPK pathway frequently has a genetic basis with mutations in *NRAS, MEK* and BRAF splice-form mutants being implicated (s4-s6). Combined inhibition of MEK with BRAF partially overcomes resistance and improves clinical outcomes (1).

In common with many other cancers, melanomas exhibit a different metabolic state to parental melanocytes, and show increased uptake of glucose and production of lactic acid. The acquisition of oncogenic BRAF contributes to this metabolic phenotype by increasing cellular uptake of glucose. Treatment of melanomas with BRAF inhibitors alters their metabolism, with decreased uptake of ^{18}Fluodeoxyglucose (FDG) by PET imaging being an important biomarker of clinical response (2). The escape of melanoma cells from BRAF inhibitor therapy is associated with metabolic reprogramming characterized by increased oxidative respiration and the recovery of glycolysis upon acquisition of drug resistance, and there is preclinical evidence that inhibitors of metabolism can potentiate the effects of BRAF inhibition(3, 4).

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Conflicts of interest

The authors declare no conflicts of interest.

In this issue of Experimental Dermatology, Livingstone and colleagues discuss the feasibility of targeting the mitochondrial transport chain as a strategy to prevent the metabolic adaptation to BRAF inhibitor therapy (5). One potential approach being explored clinically is the use of mitochondrial electron transport inhibitors, such as the biguanine metformin (NCT01638676 and NCT02143050) (commonly used to treat diabetes). As part of their analysis the authors presented data from the BREAK-3 dabrafenib trial comparing the overall survival, progression-free survival and relative response in patients with and without concomitant metformin use (5). Although the proportion of patients taking metformin was quite small and, thus, statistical power for detecting an association with outcome was weak, there seemed to be little evidence that metformin enhanced BRAF inhibitor responses (5). The likeliest explanation for this lack of activity was that metformin only weakly inhibits mitochondrial bioenergetics. The authors suggest that more potent biguanine inhibitors, such as phenformin, might show better clinical activity and that other metabolic inhibitors such as BZ-423 (which inhibits ATP-synthase activity) and elesclomol (a copper-chelator that disrupts mitochondrial respiration through the formation of reactive oxygen species) should be evaluated (5). In fact, Yuan and colleagues reported the ability of phenformin, but not metformin to overcome BRAF inhibitor resistance (6). The direct targeting of mitochondrial function, while clinically desirable, is likely to be fraught with difficulty and associated with both a narrow therapeutic window (all cells rely upon mitochondrial respiration to varying degrees) and off-target effects (increased lactic acidosis, ROS generation, and general mitochondrial toxicity). Other possible strategies already exist for targeting these metabolic adaptations, with recent work showing the ability of mTORC inhibitors to overcome BRAF inhibitor resistance mediated through PGC1α and oxidative phosphorylation (s7). There is also evidence that inhibition of glycolysis using dichloroacetate (DCA) can prevent and overcome BRAF inhibitor resistance (3).

Direct targeting of glycolysis and the inhibition of mitochondrial function may not be the best strategy for limiting adaptation and therapeutic escape. The emerging evidence suggests that metabolic reprogramming is just one aspect of a broader phenotypic switch that occurs following BRAF inhibition and it is likely that this phenotypic state change may be driven by pathways that are therapeutically tractable. The sum of data published to date suggests that BRAF inhibition leads to phenotypic changes that are associated with increased invasive potential, the expression of mesenchymal markers and a dedifferentiated state (s8-s10). In this regard melanomas may be similar to other cancers such as breast cancer and non-small cell lung cancer where therapeutic escape is frequently associated with loss of differentiation and an epithelial-to-mesenchymal transition (EMT) (s11). The EMT switch has already been associated with metabolic reprogramming in basal-like breast cancer through a mechanism involving the Snail-G9a-Dnmt1 complex (7). The phenomenon of phenotype switching has been well characterized in melanoma, with the melanocyte lineage transcription factor microphthalmia (MITF) being identified as the key regulator of the transition between proliferative ($MITF^{HIGH}$) and invasive states ($MITF^{LOW}$) (8). The process is known to be highly dynamic and reversible, with FACS-sorted populations of invasive or proliferative cells having the capacity to generate tumors that have a heterogeneous pattern of MITF expression and a mix of phenotypic behaviors. Low MITF expression levels and the adoption of the $MITF^{LOW}$ invasive phenotype are highly

correlated with resistance to BRAF inhibition, thus therapeutic escape is linked to both phenotype switching and dedifferentiation (8). MITF also controls the metabolic state of melanoma cells through regulation of the mitochondrial master regulator PGC1α (4). In addition to MITF, other BRAF-regulated transcription factor networks including c-MYC and HIF-1α also regulate glycolysis in melanoma cells (s12-S13). HIF-1α also contributes to the invasive phenotype of melanoma cells through regulation of ROR2 expression, the receptor for Wnt5A (s13). Taken together, these data suggest that metabolic reprogramming is just one aspect of wider adaptive changes that occur following BRAF and BRAF/MEK inhibition. Identification of the drivers of this process may present alternate strategies that allow the metabolically reprogrammed cells to be targeted and eliminated. It is likely that some of the changes in receptor tyrosine kinase signaling (ERBB3, EGFR, IGF-1R, PDGFR, c-MET) and alterations in other pathways (Wnt signaling, STAT3, AKT etc) that have been observed upon BRAF inhibition may be involved in the adaptive, metabolic phenotype (s14-s16). High throughput phenotypic screens could be devised to identify small molecule inhibitors that limit melanoma cell reprogramming and may identify novel combination partners for use with BRAF and BRAF/MEK inhibitors. Further insight into this process could also reveal which aspects of phenotype switching are important to survival, and indeed how many phenotypic states melanoma cells can exist in. Ultimately the goal of these studies would be to identify novel therapeutic 6 strategies that restrict the plasticity of melanoma cells, leading to more durable clinical responses to BRAF and BRAF/MEK inhibitor therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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