Understanding how to reduce drug resistance of metastatic melanoma

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Abstract

Targeted therapy with BRAF and MEK inhibitors has significantly improved the outcomes of patients with BRAF-mutated metastatic melanoma. Unfortunately, a combination of genetic and epigenetic events can create resistance to such treatment, causing most patients to relapse. A new study suggests that this resistance could be due to dysregulation of the miR-146a-5p-regulated NFκB signaling network. Initial experiments showed the gene COX2 to be largely regulated by miR-146a-5p and NFκB. Further experiments involved manipulating miR-146a-5p/COX2 in vitro and in 3D cultures of treatment-resistant tumors explanted from patients undergoing therapy, which demonstrated that miR-146a-5p expression increased drug sensitivity and reduced COX2 expression. Tumor cells' susceptibility to therapy could be significantly enhanced by decreasing COX2 expression through forced miR-146a-5p expression or by inhibiting COX2 expression with the drug celecoxib. Targeting the miR-146a-5p/COX2 axis could therefore constitute a new form of defense that fortifies treatment for patients with drug-resistant melanoma.