THE METABOLIC SENSOR AMPK IS A NEW REGULATOR OF ONCOGENE-DRIVEN ERK SIGNALING IN CANCER CELLS

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Malignant melanoma is an aggressive malignant tumor that rarely responds to standard chemotherapy or radiotherapy. Targeted therapy focuses in particular on the ERK kinase pathway, which is activated in most melanomas by mutations of BRAF or NRAS oncogenes. New BRAF inhibitors manage to slow down the progression of the disease, but the majority of patients develops resistance to the therapy, and alternative treatment options are needed.

Genetic and epigenetic changes that occur during malignant transformation contribute to changes in cell metabolism. Deregulation of metabolic pathways is one of the characteristics of tumor cells, and their metabolism, therefore, appears to be a promising therapeutic target. Several small molecule drugs targeting the energy metabolism of tumor cells have already entered clinical trials.

Our results suggest the existence of a previously unrecognized regulatory mechanism, mediated by proteins from the KSR family and the AMPK kinase, which actively modulates the oncogene-activated ERK pathway under stress induced by energy metabolism inhibitors. In melanoma cells carrying the NRAS mutation, metabolic stress promotes interaction between KSR scaffold proteins and CRAF kinase, resulting in an excessive increase in ERK signaling independently of NRAS and inhibition of cancer cell growth. In BRAF-mutated melanoma cells, metabolic stress also stimulates ERK activity by promoting interactions between the BRAF V600E mutant and KSR proteins. Higher levels of metabolic stress, however, promote the localization of the AMPK energy sensor into the BRAF-KSR complex, followed by the disruption of this complex and inhibition of the ERK pathway. These results indicate that while ERK activity in the melanomas with NRAS and BRAF mutations is affected by metabolic stress differently, the disruption of energy metabolism leads to deregulation of the ERK pathway and inhibition of tumor cell proliferation in both molecular subtypes of melanoma.

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