PUSHING THE ERK PATHWAY ACTIVITY OUT OF THE FITNESS ZONE WITH METABOLIC STRESSORS: NEW TARGETED THERAPY FOR MELANOMA?

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The majority of malignant melanomas are driven by mutations in the MAPK/ERK signaling pathway which dysregulate a number processes, leading to aberrant cell growth and proliferation. The development of mutant BRAF kinase-targeted therapy has prolonged patient survival. However, in most patients, tumor cells acquire resistance after several months of treatment. A new ERK pathway-targeted approach for melanoma therapy has been recently suggested - to push the cancer cells out of their fitness zone by over-activating the ERK signaling to levels that the cancer cell cannot sustain.
We recently demonstrated that melanoma cells respond to metabolic stress induced by inhibitors of cell energy metabolism by enhancing ERK pathway activity. While studying further the mechanisms responsible for this hyperactivation, we identified AMPK as an essential player in this process. We also found a small molecule drug (DRG) that potently enhanced ERK signaling at very low concentrations and inhibited melanoma cell growth and proliferation. The effect of DRG was observed only at the level of ERK, not its upstream signaling, and we propose that the candidate target for DRG is the negative feedback regulator of ERK – dual-specificity phosphatases (DUSPs). Interestingly, when metabolic stressor or AMPK activators were combined with DRG, we observed a robust synergizing effect on the ERK signaling on transcriptional levels. Our results show surprising plasticity of oncogene-driven ERK signaling in cancer cells and suggest new drug combinations that might be suitable for targeting the ERK pathway in melanoma.
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