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Vertical inhibition of the mTORC1/mTORC2/PI3K pathway shows synergistic effects against melanoma *in vitro* and *in vivo*

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Background

The phosphatidyl inositol 3-kinase/mammalian target of rapamycin (PI3K/mTOR) pathway has been shown to be involved in the development of melanoma. PI-103 is a novel kinase inhibitor blocking PI3K class IA and mTOR complex 1 and 2. Here, we studied the effect of targeting the PI3K/mTORC1/mTORC2 pathway by PI-103 and rapamycin in melanoma cells and a melanoma mouse model.

Materials and methods

Human melanoma cell lines (518A2, 607B, A375, Mel-Juso, SKMel-28) were treated with PI-103 and assessed for cell viability, apoptosis and cell cycle distribution. PI3K/mTOR protein target modulation was measured by Western-blotting. For siRNA experiments, cells were transfected with 50 nmol/L Silencer® Select siRNA against PIK3CA (p110α catalytic subunit of PI3K). For *in vivo* studies athymic nude mice were inoculated with 518A2 cells and treated daily with PI-103 (20 mg/kg/d) and sirolimus (1 mg/kg/d). Paraffin-embedded xenograft sections were stained for p-AKT (Ser473) and p-S6 (Ser240+244).

Results

Dual targeting of PI3K and mTOR by PI-103 induced apoptosis and cell cycle arrest, and inhibited viability of melanoma cells *in vitro*. Combined treatment with PI-103 and the prototypic mTORC1 inhibitor rapamycin led to synergistic suppression of AKT and ribosomal S6 protein phosphorylation and to induction of apoptosis. *In vivo*, PI-103 and rapamycin displayed only modest single agent activity but the combination significantly reduced tumor growth compared to both single agents.

Conclusions

Taken together, our study underscores the importance of the PI3K/mTORC1/mTORC2 pathway in melanoma and demonstrates that rational combination of compounds that lead to an optimal blockade of a critical pathway ("vertical inhibition") may provide an effective strategy for future treatment of melanoma.

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