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Title

The Myosin II cytoskeleton as a new vulnerability in therapy-resistant melanoma

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Abstract
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MAPK-targeted therapies (MAPKi) and immune checkpoint blockers (ICB) improve survival of subsets of melanoma patients. However, therapy resistance is a persistent problem. Cross-resistance to MAPKi and ICB has been suggested to be driven, in part, by common transcriptomic alterations in pathways controlling invasion and metastasis. We find that adaptation to treatment and acquisition of resistance to MAPKi involve cytoskeletal remodelling and changes in expression levels in the ROCK-Myosin II pathway, which plays a key role in cancer invasion and metastasis.

Myosin II activity is decreased shortly after MAPK is blocked. However, resistant cells promptly restore Myosin II activity to increase survival, and this becomes a vulnerability, since survival of MAPKi- and ICB-resistant cells is highly dependent on ROCK-Myosin II. Efficacy of MAPKi and ICB can be improved by combination with ROCK inhibitors, which have a dual action by impairing melanoma cell survival (through induction of lethal reactive oxygen species and unresolved DNA damage) and myeloid- and lymphoid-driven immunosuppression, overcoming cross-resistance. In human tumours, high ROCK-Myosin II activity and their associated transcriptome identify MAPKi-, ICB-resistant melanomas, and treatment-naïve melanomas with worse prognosis.

Therefore, a subset of MAPKi- and ICB-resistant melanomas is intrinsically more susceptible to ROCK-Myosin II inhibition, suggesting clinical opportunities for combination therapies.