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

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Abstract

The main abstract text is limited to 300 words but this does not include the information relating to title, author and affiliation.

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 may be driven 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-non-muscle Myosin II (NMII) pathway, which is essential for cancer invasion and metastasis.

NMII activity is decreased shortly after MAPK is blocked. However, persister cells promptly restore NMII activity to increase survival, and this becomes a vulnerability, since survival of MAPKi- and ICB-resistant cells is highly dependent on ROCK-NMII. 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 reducing myeloid- and lymphoid-driven immunosuppression, ultimately overcoming cross-resistance. In human tumours, high ROCK-NMII levels identify MAPKi-, ICB-resistant melanomas, and treatment-naïve melanomas with worse prognosis.

Therefore, a subset of MAPKi- and ICB-resistant melanomas is more susceptible to ROCK-NMII blockade, suggesting clinical opportunities for combination therapies.

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