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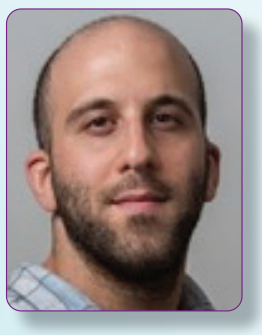

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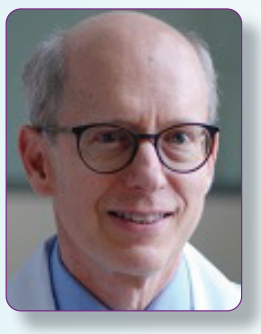

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Peroxisome disruption alters lipid metabolism and potentiates anti-tumor response with MAPK-targeted therapy in melanoma

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Melanoma is the deadliest form of skin cancer that originates from melanocytes. Current treatments for patients with metastatic melanoma include therapies that target the MAPK pathway (i.e., BRAF and MEK inhibitors) and immunotherapies targeting immune checkpoints, such as CTLA-4 and PD-1/PD-L1 axis. However, melanomas reprogram their metabolism to rapidly adapt to therapy-induced stress conditions, allowing them to persist and ultimately develop resistance.

In this study, we sought to investigate the underexplored role of peroxisome-mediated lipid metabolism in melanoma response and resistance to MAPK inhibition.

Our results indicate that inhibiting peroxisome biogenesis uncovers a metabolic vulnerability in melanoma. Specifically, we report that a subpopulation of melanoma cells tolerates MAPK pathway inhibitors (MAPKi) through a concerted metabolic reprogramming mediated by peroxisomes and UDP-glucose ceramide glycosyltransferase (UGCG). We show that compromising peroxisome biogenesis, by repressing PEX3 expression, potentiates the pro-apoptotic effects of MAPKi via an induction of ceramides, an effect limited by UGCG-mediated ceramide metabolism. Co-targeting PEX3 and UGCG selectively eliminates a subset of metabolically active, drug-tolerant CD36+ melanoma persister cells, thereby sensitizing melanoma to MAPKi and delaying resistance. Increased levels of peroxisomal genes and UGCG are found in patient-derived MAPKi-relapsed melanomas, and simultaneously inhibiting PEX3 and UGCG restores MAPKi sensitivity in multiple models of therapy resistance. Finally, triple therapy comprised of a newly identified inhibitor of the PEX3-PEX19 interaction, a UGCG inhibitor and a MAPKi demonstrates potent anti-tumor activity in pre-clinical melanoma models.

Together, our findings open new avenues for therapeutic intervention in augmenting therapeutic responses to MAPKi and overcoming MAPKi resistance via crippling peroxisome function. This study provides a proof-of-concept that dual blockade of peroxisome biogenesis and UGCG, using pharmacological inhibitors of PEX3-PEX19 binding and UGCG, is an effective strategy to sensitize melanoma to MAPK-targeted therapy.

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