

## RISING DERM STARS

### Inhibition of isoprenoid synthesis synergizes with MAPK blockade to prevent growth in targeted therapy-resistant melanoma

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Though targeted therapy for late-stage BRAF-mutant melanoma patients often produces dramatic initial results, virtually 100% of responders eventually develop drug-resistant disease, usually within 6-11 months (Chapman et al., 2011; Sosman et al., 2012).

As a result, the search for new adjunctive agents continues to be of marked clinical significance. Agents previously approved and broadly-prescribed for other indications are especially attractive given their ease of utilization. HMG-CoA reductase inhibitors, or statins, have previously been postulated to have anti-cancer properties. Nevertheless, significant concern over their toxicity at required doses has limited their evaluation in the past.

Deregulation of the mevalonate pathway, upstream of cholesterol synthesis, has been noted to be important for growth in cancers such as prostate, breast, acute myeloid leukemia, and melanoma (Kang et al., 2015; Santos and Schulze, 2012). Much of this is thought to be due to the aberrantly increased production of farnesyl and geranylgeranyl groups: two types of post-translational isoprenoid moieties that affect the ability of proteins to localize to lipid rich regions such as the interior plasma membrane and the

Golgi apparatus. In our recent work, we provide evidence of marked potentiation of statin-induced growth inhibition in MAPK-driven melanoma, in combination with small molecule MAPK inhibitors. We also present evidence that this effect is mediated by impaired production of isoprenoid farnesyl and geranylgeranyl groups: products of the mevalonate pathway, with downstream effects on both PI3K/AKT and Hippo signaling. These findings were verified by reintroducing metabolites downstream of HMG-CoA reductase, which fully rescues tumor lines' growth phenotypes.

Mouse studies of dual therapy with statins and BRAF inhibitors in the setting of vemurafenib-resistant BRAF-mutant melanoma provide additional in vivo evidence of efficacy, supporting a possible role for trials of statin and MAPK inhibitor combination therapy in human cancer patients. We also used data from The Cancer Genome Atlas to independently analyze correlation of pathway member levels with overall survival. We found that upregulation of farnesyl pyrophosphate synthase (FDPS), Farnesyl-Diphosphate Farnesyltransferase (FDFT1), mevalonate kinase (MVK), and mevalonate dehydrogenase (MVD) were all significantly

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associated with decreased overall survival, highlighting the importance of this pathway to human cancer biology and disease prognosis.

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