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**Genetic and epigenetic regulations in malignant melanoma**

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Genetic and epigenetic regulations play a significant role in melanomagenesis. In this study, we investigated the role of the histone methyltransferase SETDB1 (SET domain, bifurcated 1), which catalyzes the addition of methyl groups to histone H3 at lysine 9 (H3K9), in the development and progression of melanoma. Furthermore, we investigated genetic alterations in the components of the mitogen-activated protein kinase (MAPK) pathway.

In the present study, it was shown that the SETDB1 gene was highly amplified in melanoma tissues of patients with poor prognosis. The amplification of the gene was correlated with increased expression of the protein. Functional studies revealed that an increased SETDB1 expression was associated with a more proliferative, invasive and migratory phenotype as well as larger tumors in xenograft mouse models. In human primary melanomas, SETDB1 expression was elevated at the invasive borders. The activity of SETDB1 could be blocked by small molecules, which led to reduced cell growth even in melanoma cell lines that were resistant towards BRAF and MEK inhibitors. These findings support SETDB1 as a major driver of melanoma development and progression. We therefore suggest SETDB1 as a potential future target for the treatment of melanoma.

Our study has also shown that gene copy numbers of members of the MAPK signaling pathway varied in different melanoma subgroups. NRAS<sup>wild-type</sup>/BRAF<sup>wild-type</sup> melanoma metastases were characterized by significant gains of MAP2K1 (MEK1) and MAPK3 (ERK1) gene loci. These additional gene copies could lead to an activation of the MAPK signaling pathway via a gene-dosage effect. Our results suggest that downstream analyses of the pMEK and pERK levels in NRAS<sup>wild-type</sup>/BRAF<sup>wild-type</sup> melanoma patients might help identify patients that could benefit from targeted therapies with MEK and ERK inhibitors.