AG Tumorbiochemie

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Genetic tumor heterogeneity and its influence on therapy response

Translational research (Comprehensive Cancer Center Mainfranken)

The collaboration with the Comprehensive Cancer Center and the Department of Dermatology, we investigate the genetic setup of melanoma samples from patients under different treatment regimen. We could allocate the resistance-mediating mutations for the majority of melanomas that recurred after BRAF/MEK inhibition and found numerous cancer-predisposing germline mutations in melanoma patients, with impact for their follow-up care as well as their relatives` tumor prevention measures. In addition, we found a growing role for receptor tyrosine kinases (RTKs) in melanoma. On gene level, several RTKs are mutationally activated in BRAF/NRAS wt melanomas (Appenzeller et al., 2019). In response to BRAF/MEK inhibition, the transcriptional upregulation of FGF1 leads to drug resilience in an auto- and paracrine manner (Grimm et al., 2018) (Figure 2).

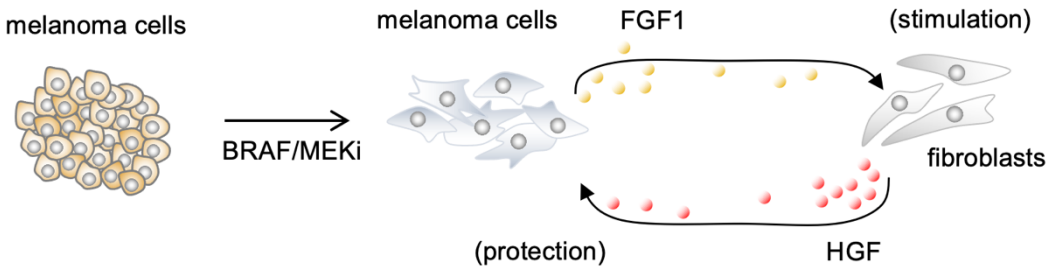

Figure 2: Effect of BRAF/MEK inhibition on melanoma cells.
BRAF/MEK inhibition lead to the secretion of FGF1, which stimulate fibroblasts and lead to their production of HGF, a known growth factor mediating BRAF/MEK inhibitor resistance.

This work is done in the context of the Interdisciplinary Unit for Precision Oncology (IUPO), a structured network of the CCC Mainfranken, the Bavarian Cancer Research Center and the Interdisciplinary Center for Clinical Research. The IUPO focuses on the detailed molecular genetic analyses of various tumors for clinical and research purposes, to enable the execution and development of optimized therapy for cancer patients (Thiem et al., 2019; Maurus et al., 2018). In the future, resistance mechanisms towards immune checkpoint inhibitors in melanoma and in other tumor entities will play a growing role in this project focus.

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Grimm J, Hufnagel A, Wobser M, Borst A, Haferkamp S, Houben R, Meierjohann S: BRAF inhibition causes melanoma cell resilience by secreting FGF1. Oncogenesis 7:71 (2018)

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Thiem A, Hesbacher S, Kneitz H, di Primio T, Heppt MV; Hermanns HM, Goebeler M, Meierjohann S, Houben R, Schrama: IFN-gamma-induced PD-L1 expression in melanoma depends on p53 expression. Journal of Experimental & Clinical Cancer Research 38:397 (2019)