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Abstract

Implication of Intra-Tumor Heterogeneity on Colorectal Cancer Response to MEK Inhibition †

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Abstract: Intra-tumor heterogeneity (ITH) poses a major obstacle in cancer therapy. In colorectal cancer (CRC), mutations in the transforming growth factor-β/bone morphogenetic protein (TGF-β/BMP) pathway, especially in the SMAD4 gene, have been correlated with decreased overall survival and are suspected to modulate chemoresistance. We have previously shown that SMAD4^{R361H} is associated with differential drug response towards EGFR, MEK and PI3K inhibitors. Here, we analyzed the mechanistic role of SMAD4^{R361H} using oncoproteomics in CRISPR-engineered SMAD4^{R361H} and CRC patient-derived organoids (PD3D®). Utilizing DigiWest® multiplex protein profiling analysis, we confirmed a stronger response to MEK inhibition in organoids harboring SMAD4^{R361H} as compared to SMAD4^{wt} PD3D. After 24 h of incubation with 0.03 µM trametinib, we observed a more pronounced decrease in proliferation markers, such as cyclin B1 and aurora kinase A in SMAD4^{R361H} cells. Interestingly, there was no noticeable accumulation of caspases 3 and 9 in any organoid culture; however, there was a conspicuous trend in the accumulation of Bcl-xL in presence of SMAD4^{R361H}. To understand the underlying mechanism of such a discrepancy, we analyzed the protein levels and phosphorylation status of other SMADs, as SMAD4^{R361H} disrupts TGF-β/BMP signal transduction. Out of all SMADs, only SMAD5 showed significant changes in protein level and phosphorylation status in response to the treatment only in SMAD4^{wt} organoids. As previously published, BMP signaling promotes cancer cell proliferation and tumor growth. It is plausible to assume that functional loss of SMAD4 and thus loss of SMAD5 signaling renders the SMAD4^{R361H} subpopulation of cells more sensitive to MEK inhibitors. Loss of SMAD4 was previously shown to promote chemoresistance and was associated with a higher recurrence rate in colorectal cancer. The heterogenic landscape of mutated SMAD4 within the same tumor, in this light, can give rise to multi-drug resistant disease.

Keywords: intra-tumor heterogeneity; cancer; cellular pathology

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