

**882 USING ONCOGENIC PATHWAY AGONISM TO SENSITIZE RAS MUTANT CANCERS TO IMMUNOTHERAPY**

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**Background** Overall, 30% of human cancers are driven by mutant RAS proteins. While immunotherapy is effective for NRAS-mutant melanoma, no options exist for resistant disease, and mutant KRAS-driven lung and pancreatic carcinomas are much less responsive. Oncogenic pathways are key targets for inhibition. However, pathway agonism has not been explored as a therapeutic approach. BRAF-mutant melanomas respond to BRAF inhibitors (BRAFi) due to decreased ERK signaling. They can recover signaling by acquiring activating RAS/MEK mutations, but exhibit decreased proliferation in the absence of inhibitor, suggesting that supraphysiologic ERK signaling also compromises fitness. Therefore, we observed that increasing ERK hyperactivation in RAS-mutant cancers might elevate ERK signaling, inducing senescence, and creating an inflammatory tumor microenvironment (TME)

**Methods** BRAFi have been used to study senescence by different assays. *In vivo* assays were performed in C57/Bl6 treated with BRAFi with/without anti-PD1 therapy to study tumor progression. Tumors single cell suspension was used for immunophenotyping by Flow Cytometry and scRNASeq data

**Results** We have shown that 15/21 RAS-mutant cancer cell lines undergo senescence following exposure to all FDA-approved BRAF inhibitors. Simultaneous MEK or ERK inhibition allows the cells to recover proliferation, and a BRAFi which does not induce ERK activation fails to have any effect, showing that ERK hyperactivation is the key driver of this response. Furthermore, our extensive preliminary data in two novel genomically-characterized, high TMB immunocompetent models of NRAS-mutant melanoma and KRAS-mutant pancreatic adenocarcinoma support our *in vitro* findings. Both murine models have shown that anti-PD1 therapy is more efficacious when mice are additionally treated with BRAFi. Molecular profiling of the TME reveals the expression of cytokines related to senescence and marked infiltration of activated CD8+ T-cells. To implement effective immunotherapies, we have analyzed the expression of different immune-checkpoint molecules and we have observed a high expression of LAG3 and TIM3 in the melanoma NRAS-mutant model treated with BRAFi. We will further analyze the effect of those checkpoints in combination with BRAFi to potentiate the anti-tumoral responses and tumor regression

**Conclusions** Oncogenic pathway agonism is a novel, effective, and untested strategy to induce proliferation arrest and sensitization to immunotherapy. The impact of this data is in the ability to broadly sensitize RAS-mutant cancers to immunotherapy in the settings of de-novo and acquired resistance. The direct connection between a tumor cell signaling vulnerability to immunotherapy response is a major point of novelty and provides a clear rationale for pursuing combined targeted and immunotherapy

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