Rigosertib turns up the heat on melanoma cells to enhance response to immune checkpoint inhibitors

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Abstract

Activating mutations in BRAF or NRAS are present in ~60% and ~20% of melanoma patients, respectively, leading to enhanced tumor cell proliferation and survival. Rigosertib (RGS) is a non-ATP-competitive small molecule RAS mimetic that has the potential to block RAS-RAC-MEK-ERK and PI3K-AKT-mTOR signaling pathways and to interfere with CRAF interaction with PLK1, resulting in alteration of its centrosomal localization. Here, we demonstrate that treatment of human and murine melanoma cell lines in vitro with µM levels of RGS reduced tumor cell viability, elevated the production of mitochondrial reactive oxygen species, promoted tumor cell death, and suppressed mitosis. Using multiple murine melanoma xenograft models (BrafV600E and BrafWT), we identified the optimal in vivo dose of RGS (300mg/kg), resulted in >50% inhibition of tumor volume and weight and was well tolerated in mice. RGS-treated tumors exhibited an inflammatory tumor microenvironment with enrichment of dendritic cells and CD45/4MHCI+ cells, as well as elevation in frequency and activation of T cells and NK cells. Notably, treatment with RGS + aPD1/nCTLA4 immune checkpoint blockade (ICB) inhibited tumor growth by ~70%. RGS monotherapy and the combined RGS + ICB therapy upregulated cytokimulatory signals (e.g., CD40/CD80/4MHCI-L) on melanoma cells in vitro, while knockdown of CD40 in melanoma tumors resulted in resistance to RGS treatment. Analysis of human cBioportal and Oncomine databases indicates that the gain of CD40/CD80/4MHCI-L copy number in melanoma patients is associated with significantly better survival and the tumor CD40 level is prognostic for response to RAF inhibitor treatment. This combination of RGS + ICB therapy warrants a clinical study.

Rigosertib blocks Ras binding and pathway activation

RGS inhibits melanoma cell viability in vitro

RGS turns the cold tumor/LN hot (immunogenic)

RGS induces T-cell responses in the TME

RGS-induced anti-tumor immunity is CD40-dependent

Prognostic value of CD40/CD80/ICOS-L in human melanoma

Conclusions

- Our work reveals a novel role of RGS in immuneogenic cell death via promoting CD40 expression on melanoma cells.
- Combining RGS and aPD1/nCTLA4-immune therapy offers considerable promise for melanoma treatment.

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