Targeting Tumor Fibrosis with Small Molecule Inhibitors of ROCK2 or DDR1/2 Improves Therapy Response in Preclinical Models of PDAC & TNBC

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Introduction

- The critical role of the tumor-stromal microenvironment (TME) in driving tumor progression and modulating treatment response to chemo-, radio- and immunotherapy is well established.
- Tumor infiltrating stromal cells provide an additional layer of heterogeneity modulating extracellular matrix (ECM) deposition, exerting mechanical forces and secreting a milieu of factors leading to interstitial fibrosis.
- Here, we discuss effects of two anti-fibrotic small molecule inhibitors of Discoidin-domain receptors 1 & 2 (DDR1/2) and ROCKassociated coiled-coil containing protein kinase 2 (ROCK2) respectively, which have both demonstrated anti-fibrotic efficacy in preclinical models of kidney and lung fibrosis (in-house data).
- ROCK2 expression has been shown to be increased in pancreatic cancer¹ and targeting of ROCK using Fasudil has been shown to potentiate response to standard of care (SoC) chemotherapy².
- Discoidin domain receptors 1 and 2 (DDR1/2) are emerging targets in oncology, complete genetic knockout (KO) or knockdown (KD) of either DDR1 or DDR2 in mouse syngeneic models increases anti-tumor immune infiltrate in the TME³.
- Targeting of DDR1/2 using non-selective inhibitors in combination with chemotherapy in genetically engineered mouse models (GEMM) of Lung & Pancreatic cancer increased anti-tumor efficacy and survival⁴-⁶.

The data presented investigates the rationale of targeting interstitial fibrosis through small molecule inhibition that could lead to improved therapy response in combination with SoC chemotherapy or immunotherapy in tumor types characterized by high stromal infiltrate and dense ECM deposition which often prove to be therapy refractive.

ROCK2 inhibition reduces collagen content in a KPC PDAC model

ROCK2 inhibition alters the tumor immune microenvironment in a KPC PDAC model

RXC007 increases survival in combination with Gemcitabine/Abraxane in metastatic and High-ECM patient-derived PDAC

ROCK2 inhibition increases survival in FOLIRINOX resistant patient-derived PDAC model

Conclusions

Highly selective small molecule inhibitors of Discoidin-domain receptors 1 & 2 (DDR1/2) and ROCK-associated coiled-coil containing protein kinase 2 (ROCK2) have been developed in house at Redx.

The ROCK2 inhibitor REDX10616, a close analogue of ROCK2, altered both the stromal and immune compartments in the KPC PDAC model, REDX15016 monotherapy led to significant decreases in tumor fibroblast collagen content, an increase in desmin positive myofibroblasts and a reduction in CD8+ T-cell infiltrate, a reduction in TRegs and allowing of macrophage polarization was observed upon REDX15016 monotherapy.

In a high-ECM and highly metastatic patient derived orthotopic model of PDAC the combination of ROCK2 inhibition with RXC007 and SGC chemotherapy (GA) lead to a dose dependent increase in survival when compared to chemotherapy alone.

In a chemo-resistant patient derived model, in which an increase in tumor collagen content is observed upon development of resistance, the addition of REDX15016 in combination with FOLIRINOX re-vitalized the tumor to treatment and led to a striking increase in survival.

Using a tool DDR1/2 inhibitor in combination with anti-PD1 in the TNBC 12771 model led to an increase in survival when compared to the control group, an effect not observed upon single agent treatment. The combination also led to an increase in CD8+ and CD4+ T-cells and a decrease in M2-Mφ's in the tumors, compared to control animals.

The data presented here provides a rationale for clinical investigation of this approach to treatment.

References