TWEAK receptor agonism to increase T cell mediated cancer immunotherapy

A genome-wide CRISPR/Cas9 screen to sensitize IFNγ receptor-deficient tumor cells to CD8 T cell elimination uncovered several hits mapping to the tumor necrosis factor (TNF) pathway. Taking advantage of the genetic screen, investigators in the lab of Daniel Peeper at NKI-AVL demonstrate that ablation of the top hit (TRAF2), lowers the TNF cytotoxicity threshold in tumors by redirecting TNF signaling to favor RIPK1-dependent apoptosis. TRAF2 loss greatly enhanced the therapeutic potential of pharmacologic inhibition of its interaction partner cIAP, another screen hit, thereby cooperating with immune checkpoint blockade (ICB). The investigators’ results suggest that selective reduction of the TNF cytotoxicity threshold increases the susceptibility of tumors to immunotherapy.

Key advantages

- TWEAKr agonism (via nb-clusters or TWEAK-receptor ligand) sensitizes tumor cells to T cell-derived TNF in a TRAF2-dependent manner.
- The interaction partner of TRAF2 (cIAP1/2) can be inhibited by a SMAC-mimetic. Combining birinipant with a TWEAKr agonist generates synthetic lethality for tumor cells, by inactivating TRAF2 and breaking intrinsic T cell resistance.
- The combination targeting TRAF2/cIAP1 increased ICB therapy in a tumor-bearing mouse model.
- Cancers with increased TWEAK expression include melanoma, breast, brain, NSCLC, pancreas, esophageal, colorectal, renal, ovarian and prostate.

Potential impact

Optimal anti-tumor immunity

As no TRAF2 inhibitor is currently available, the investigators took advantage of prior observations that upon ligation of TNFRSF12A (also known as FN14) and the TWEAK-receptor by its ligand TWEAK, TRAF2 was lysosomally degraded and used this knowledge to develop TWEAK-receptor agonists which can be used to reduce TRAF2 levels and sensitize tumor cells to T cell killing. Taken together with their identification that TRAF2 loss greatly enhanced the therapeutic potential of pharmacologic inhibition of its interaction partner cIAP, the investigators have shown in vitro activity in a large tumor cell line panel, comprising human and mouse melanoma, lung and colon cancer lines (Fig 1). As well, in vivo experiments (Fig 2) have shown that the combination of a TWEAK-receptor agonist and cIAP1 inhibitor sensitized tumor cells to T cell killing, reducing tumor volume in a mouse model of LL2 lung cancer.
Single agent TWEAK-ligand or Birinapant (c-IAP1 inhibitor) treatment causes enhanced sensitivity to TNF-α in multiple human and mouse tumour cell lines; combination-treatment shows to be additive, or synergistic, in most - even in some otherwise non-responsive cell lines.

### References

Vredevoogd et al, Augmenting Immunotherapy Impact by Lowering Tumor TNF Cytotoxicity Threshold, Cell 178, p.585-599

### Patent Status


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**Fig. 1 Summary TWEAK in vitro**

- **a. Human melanoma:**
  - FM6
  - BLM
  - ACT7
  - BMES

- **b. Human non-small cell lung cancer:**
  - NCI H441

- **c. Human colon adenocarcinoma:**
  - LCLC-103H

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**Fig. 2. LL2 lung cancer mouse model**

- VEH/VEH
- VEH/Birinapant
- VEH/TWEAK-Fc(DANA)
- Birinapant/TWEAK-Fc(DANA)

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**References**

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