IFNγ Helps CBLB-Deficient CD8$^+$ T Cells to Put Up Resistance to Tregs

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In this issue, Han and colleagues demonstrate in preclinical cancer models that genetic deletion of the E3 ubiquitin ligase Cbl proto-oncogene B (CBLB) in adoptively transferred CD8$^+$ T cells induces resistance to regulatory T cells. CBLB deletion induces IFNγ and downmodulates TGFβ/SMAD signaling. This ultimately enforces these cells to be way more effective against various cancers.

See related article by Han et al., p. 437 (4).

Avoiding immune destruction is a hallmark of cancer (1) and is mediated by a plethora of cancer cell–intrinsic as well as environmental cues, including local expansion of immune-suppressive regulatory T cells (Treg; ref. 2). Strategies to reenforce effector T cells in the clinical setting (e.g., when aiming for activation of local T cells by immune checkpoint blockade or via cellular therapies, such as chimeric antigen receptor T cells) could be further optimized by depriving the cells from local immunosuppressive cues. Preclinical reports demonstrate that Treg depletion induces strong anticancer immunity (2). In the setting of cellular therapies, it would be of great help to enhance resistance of the cellular (i.e., T cell) product to Treg by extrinsic pharmacologic intervention or intrinsic genetic modification.

The E3 ubiquitin ligase Cbl proto-oncogene B (CBLB) is expressed in many human organs and cells, including those of the hematopoietic and immune system, particularly T, B, and natural killer cells. CBLB functions as a potent negative regulator of ligand-induced T-cell receptor, B-cell receptor, and Tyro3, Axl, and Mer tyrosine kinase receptors. Loss of CBLB uncouples activated T cells from the requirement for CD28 costimulation (3) and overcomes negative milieu signals induced by TGFβ. Mechanistically, CBLB ubiquitinates and subsequently degrades SMAD7, a key negative regulator of the canonical TGFβ receptor signaling pathways. CBLB critically regulates effector T-cell activation and cytokine secretion upon antigen-receptor stimulation in mouse and human. Consistently, studies have shown that transient lymphocytic CBLB silencing prior to adoptive cell transfer reduces tumor growth and increases survival.

In this issue, Han and colleagues show that genetic deletion of lymphocytic CBLB in adoptively transferred model tumor antigen–specific CD8$^+$ T cells leads to robust anticancer effects in murine cancer models, and these effects are mediated by the secretion of excessive levels of IFNγ, which in turn induce autocrine and/or paracrine CD8$^+$ CTL resistance toward Treg suppression (4). This effect cannot be further boosted by Treg depletion and depends on IFN receptor expression on the adoptively transferred CTLs. Interestingly, this effect can also not be boosted by PD-1/PD-L1 blockade, as PD-1 is markedly downmodulated in CBLB-deficient CTLs. This is of relevance as IFNγ is known to induce PD-L1 expression on cancer cells, which is, however, not synergizing with CBLB targeting in the presented models. Mechanistically, RNA-sequencing data of wild type, CBLB-knockout (KO), and CBLB/IFNγ double KO CD8$^+$ T cells revealed that IFNγ selectively upregulates IFN-stimulated genes (ISG) and that genes involved in TGFβ receptor/SMAD3 pathway are differentially expressed upon CBLB deficiency. The data support recent developments in early interventional clinical trials testing pharmacologic (NX-1607; ClinicalTrials.gov Identifier: NCT05107674) or siRNA-mediated CBLB targeting (APN401; ClinicalTrials.gov Identifier: NCT03087591) in adoptively transferred cell products.

Taken together, the new data mechanistically define the reduced sensitivity of CBLB-inhibited CTL to Treg and imply IFNγ hyperproduction as a way to antagonize TGFβ-mediated effects. Although the precise molecular mechanism defining the role of ISGs in Treg resistance is worth further investigation in relevant murine models and in cancer patient biopsies, the current data strongly imply a functional link between IFNγ secretion levels and canonical TGFβ receptor signaling pathway output. Identifying the key contribution of CBLB as a *bona fide* immune checkpoint in adoptive cancer immunotherapy strongly validates the concept of reducing CBLB expression and/or activity as a compelling and unique strategy to reverse Treg-mediated immunosuppression of effector CD8$^+$ T cells at the tumor site.

Authors' Disclosures

No disclosures were reported.

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