IDENTIFYING IL-27 DEPENDENT BIOMARKERS IN LYMPHOCYTES, NK CELLS, AND MYELOID CELLS IN PERIPHERAL BLOOD AND THE TUMOR MICROENVIRONMENT

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Background Interleukin (IL)-27 is a heterodimeric cytokine that alters the expression of immunoregulatory receptors and inflammatory cytokines on a variety of lymphoid and myeloid cell types. Inhibition of IL-27 with the anti-IL-27 antibody, CHS-388 (casdozokitug or casdozo; formerly SRF388), has shown monotherapy anti-tumor activity in patients with solid tumors including PD-1 experienced renal cell carcinoma and non-small cell lung cancer (NSCLC). We previously characterized an IL-27-induced gene signature that is enriched in interferon (IFN)-responsive genes and known to associate with cancer therapy resistance. Here we directly compared IL-27-induced gene transcription to those of type 1 (IFNα/IFNβ) and type 2 (IFNγ) IFNs.

Methods Anti-CD3 activated human PBMCs treated with IL-27 or IFNs were analyzed by single-cell RNA sequencing. Immunohistochemistry on sequential samples was used to assess co-localization of IL-27 and its receptor IL-27RA, PD-L1, and GBP5 in human tumors. GBP5 and IRF1 levels were measured by flow cytometry and cytokines were quantified by ELISA.

Results Immune cell subpopulations from PBMCs were found to differentially express and respond to IL-27 and IFNs. After activation, pDCs transiently express IFNα/IFNβ, T and NK cells produce IFNγ, and myeloid cells express IL-27. Although many canonical IFN-responsive genes were induced by both IFNs and IL-27 treatment, biased gene expression was observed in different cell types. For example, IL-27 stimulation led to differential expression of GBP5 and IRF1 in T and NK cells; IFNβ led to IFIT1 and MX2 expression in T cells; NK cells, and monocytes; while IFNγ led to SOCS1 and CXCL9 upregulation in monocytes. IL-27 and IFNα/IFNβ share a similar ability to inhibit pro-inflammatory cytokine secretion and increase expression of PD-L1 on T cells, functions not evident with IFNγ stimulation. Interestingly, although GBP5 and IRF1 are elevated by IL-27 in T/NK cells, these genes are augmented by IFNγ in myeloid cells. Finally, immunohistochemistry on treatment-naïve NSCLC patient samples showed that IL-27+ macrophages are co-localized with GBP5+ T-cell-rich areas in the TME along with PD-L1+ immune cells, suggestive of IL-27-dependent signaling in the NSCLC tumor microenvironment (TME).

Conclusions These studies lend insights into the immune interplay between IFNs and IL-27 signaling across different immune cells and within the TME. In contrast to IFNγ, IL-27 shares with type 1 IFNs the ability to modulate T cells and NK cells, an activity ascribed to mechanisms of effector cell regulation and exhaustion. These observations will help inform the immune suppressive mechanisms of IL-27 in tumors and biomarker exploration in patients treated with the anti-IL-27 antibody CHS-388 (casdozokitug).

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