

**IL-27 EXPRESSED IN THE TUMOR MICROENVIRONMENT IS CORRELATED WITH PD-L1 LEVELS AND CAN INDUCE PD-L1 EXPRESSION ON IMMUNE AND TUMOR CELLS**

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**Background** Interleukin (IL)-27 is a heterodimeric cytokine expressed by myeloid cells that is known to reduce the intensity and duration of immune responses. IL-27 signaling via IL-27RA receptor augments the expression of co-inhibitory molecules (PD-L1, LAG-3, TIM-3, and TIGIT) on immune cells and reduces proinflammatory cytokines in the tumor microenvironment. Blocking IL-27 activity by SRF388, a first-in-class monoclonal antibody, enhances immune function and demonstrates monotherapy activity in patients with cancer (NCT04374877). This study further characterizes the expression of IL-27 in primary solid tumors.

**Methods** Gene expression profiles from published datasets were analyzed to identify *IL27* and *IL27RA* transcripts. Immunohistochemistry (IHC) and flow cytometry were used to quantify IL-27, PD-L1, and IL-27RA expression in primary tumors. IL-27 levels were measured in cell culture media of primary tumor cells and activated peripheral blood mononuclear cells (PBMCs) by ELISA.

**Results** Primary tumor samples showed IL-27 expression by IHC within morphologically defined tumor-associated macrophages (TAMs) in several cancers, including lung, liver, renal, gastric, and head and neck. This is consistent with single-cell RNA-seq transcriptional data showing predominant expression in macrophages from several tumor types. Interestingly, IL-27<sup>+</sup> TAMs are localized in the vicinity of PD-L1-expressing cells in gastric, lung, and liver tumors, where the highest IL-27<sup>+</sup> TAM density is associated with the highest expression of PD-L1. Expression of IL-27RA in tumor tissues was also explored by IHC. IL-27RA expression was identified on tumor cells in several cancers and included examples where tumor cell expression of the receptor was maintained at sites of lymph node metastasis. In vitro cultures of activated PBMCs showed that IL-27 increased PD-L1 expression on immune cells, an effect that was further amplified in the presence of dissociated primary tumors co-cultured with activated PBMCs. IL-27 levels were higher in co-cultures of activated PBMCs and dissociated primary tumors than in cultures of PBMCs alone. Finally, IL-27 was shown to upregulate PD-L1 expression on tumor cell lines that express IL-27RA.

**Conclusions** IL-27 is expressed by TAMs and plays a role in immune suppression. IL-27<sup>+</sup> cells are found in close proximity to PD-L1<sup>+</sup> cells in patient tumors, and IL-27 can regulate levels of PD-L1 expression in immune cells and tumor cell lines, suggesting cross-talk between these molecules to diminish immune activation within the tumor microenvironment. Combined blockade of IL-27 and PD-(L)1 to enhance antitumor immune responses is currently being evaluated in clinical trials.

<http://dx.doi.org/10.1136/jitc-2022-SITC2022.1082>