Increased IL-27 is associated with poor prognosis in renal cell carcinoma and supports use of SRF388, a first-in-class IL-27p28 blocking antibody to counteract IL-27-mediated immunosuppression in this setting.

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Orthotopic Renca Model

- IL-27 is a heterodimeric member of the IL-12/IL-23 cytokine family that consists of 2 subunits; IL-27p28 and Epstein-Barr virus-induced gene 3 (EBI3).
- IL-27 signals through a heterodimeric receptor composed of glycoprotein 130 (gp130) and IL-27 receptor subunit alpha (IL27RAW01).
- IL-27 signals through the JAK-STAT pathway to limit the duration and intensity of T cell-mediated immunity.
  - Altered immunoregulatory receptor expression
  - Decreased proinflammatory cytokine secretion (TNFα, IFNγ, and IL-17).
- SRF388 is a first-in-class IL-27p28 antibody that blocks the interaction of IL-27 with IL-27RA and inhibits IL-27 signaling in primary human immune cells.
- Given the immunoregulatory function of IL-27, blockade of IL-27 signaling represents a novel and promising strategy to treat cancer.

IL-27 Signature Genes Are Associated with Poor Outcomes in Renal Cell Carcinoma

- IL-27 is a cytokine involved in resolving T cell-mediated inflammation
- Increased IL-27 is associated with poor prognosis in renal cell carcinoma and supports use of SRF388, a first-in-class IL-27p28 blocking antibody to counteract IL-27-mediated immunosuppression in this setting.

Figure 1. IL-27 is a cytokine involved in resolving T cell-mediated inflammation.

Figure 2. (A) Differential expression of EBI3, IL-27p28, and IL-27RA in tumor and normal kidney in a TCGA cohort. Circulating levels of the EBI3 subunit of IL-27 are elevated in a subset of patients with RCC. (B) Kaplan-Meier curves; patients with poor survival were defined as having lung metastases.

Figure 3. FACS of blood mononuclear cells (PBMCs) from individuals was analyzed with anti-CD3 and treated with IL-27RA antibody or control. Cytokine production was analyzed by cytometric bead array (CBA). Data represent fold change to control (CBA). *P = 0.001 (paired t-test).

Figure 4. (A) EBI3 levels were measured by ELISA in serum or plasma from two cohorts of patients with RCC using a porcine EBI3-specific antibody. (B) EBI3 levels in serum from patients with RCC (n=58) compared with serum from healthy donors. Serum from pregnant donors was included as a positive control. (C) EBI3 levels were measured by ELISA in IL-27 RA antibody or control treated serum from patients with RCC (n=18) and grouped by stage. Dotted line indicates mean of all healthy donors. (D) Lung metastasis survival was available for 20 patients. (E) Overall survival and (D) disease-free survival curves were generated for patients from cohort #2. Statistics were calculated by Log-rank test. HR = Hazard ratio.

Figure 5. Human PBMCs from healthy donors (n=10) and patients with RCC (n=20) were activated with anti-CD3 and treated with IL-27RA or control. Cytokine production was analyzed by cytometric bead array (CBA). Data represent fold change to control (CBA). *P = 0.001 (paired t-test).

EPI3 Plasma Levels in Patients with Renal Cell Carcinoma Predict Poor Outcome

- Genes downstream of IL-27 signaling are coordinately regulated in a subset of patients with RCC and associated with poor prognosis.
- Circulating levels of the EBI3 subunit of IL-27 are associated with poor outcomes in RCC.

Figure 6. Human PBMCs from healthy donors (n=10) and patients with RCC (n=20) were activated with anti-CD3 and treated with IL-27RA or control. Cytokine production was analyzed by cytometric bead array (CBA). Data represent fold change to control (CBA). *P = 0.001 (paired t-test).

Conclusions

- IL-27p28, EBI3, and IL-27RA transcript levels are elevated in tumors from patients with RCC.
- High levels of these genes are associated with poor clinical outcome in patients with RCC.
- EBI3 downstream of IL-27 signaling are coordinately regulated in a subset of patients with RCC and associated with poor prognosis.
- Circulating levels of the EBI3 subunit of IL-27 are elevated in a subset of patients with RCC and inversely correlated with both disease-free and overall survival.
- IL-27 counteracts proinflammatory cytokine production in response to PD-1 blockade—this effect is inhibited by SRF388, a first-in-class IL-27p28 blocking antibody.
- Blockade of IL-27 with SRF388 may represent a promising strategy for patients with RCC who have high levels of circulating EBI3.
- SRF388 is being evaluated in a Phase I clinical trial (NCT04374877) in patients with advanced solid tumors.