Deciphering High-Dose IL-2 Toxicity in Reconstituted HIS Mice

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Immunotherapy, particularly checkpoint inhibitors, represents a promising and efficient treatment for a broad range of tumors. However, it displays a major limitation: the onset of immune-related adverse effects. Similarly, high-dose IL-2 (HDIL2) administration has been used as treatment for patients with late-stage metastatic melanoma and carcinoma for almost 25 years. The overall response rate to this treatment can be considered low, about 15%, but its efficiency has been proven in about half of the patients responding to HDIL-2 treatment, with years-long responses. HDIL2 treatment is, however, associated with severe toxic side effects such as vascular leak syndrome (VLS), liver dysfunction, and neurological disorders.

Interestingly, and unfortunately, these side effects correlate with treatment success, and lower IL-2 doses induce fewer side effects and fewer responses. Lots of effort has been focused on understanding the mechanism of HDIL2 toxicity to uncouple its efficiency from its toxicity. In 2017, Li et al. investigated the mechanism of action and adverse events associated with IL-2 immunotherapy in an immunodeficient mouse model reconstituted with a human immune system: BRGS-HIS.

To better understand HDIL2 toxicity’s mechanism of action, the effect of IL-2 treatment on human immune sub-populations was investigated. It was shown that IL-2 expands the absolute number of hCD45+ and T cells, and the percentage of a number of sub-populations including CD8+ and CD4+CD8+ T cells. Interestingly, depleting CD4+ and/or CD8+ T cells in HDIL2-HIS mice inhibited the induced body weight loss, suggesting that CD4+ and CD8+ T cells are critical mediators of IL-2-induced toxicity.

To attempt to model IL-2 induced toxicity, reconstituted HIS mice were injected with low (LDIL2) and high (HDIL2) doses of IL-2 plasmid. HDIL2-treated HIS mice showed clinical signs of IL-2 toxicity, such as body weight loss (Fig. 1A), and pulmonary edema representative of VLS (Fig. 1B). Notably, these clinical signs were not observed in non-reconstituted immunodeficient mice. HDIL2 treatment in HIS mice also triggered a cytokine storm, similar to what was reported in patients. These data show that IL-2 toxicity can be modeled in reconstituted HIS mice, and mirrors the clinical signs observed in patients receiving IL-2 immunotherapy.
Absolute numbers were increased, body weight loss was mitigated (Fig. 2C), and survival was improved (Fig. 2D). Additionally, serum levels of TNF and IFNγ were decreased in Kem-treated HDIL2-HIS mice. These data suggest that Treg function is important to prevent immune system activation and the associated toxic side effects of IL-2 immunotherapy.

This study shows that reconstituted HIS mice represent a useful and workable system to study and decipher human immune cell interactions in IL-2 immunotherapy.

Of note, the reconstituted mouse preclinical model used in this study is available at genOway, designer and provider of multiple preclinical models in immuno-oncology.

References: