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.[1,2] 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.[3] HDIL2 treatment is, however, associated with severe toxic side effects such as vascular leak syndrome (VLS), liver dysfunction, and neurological disorders.[4]

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.[5]

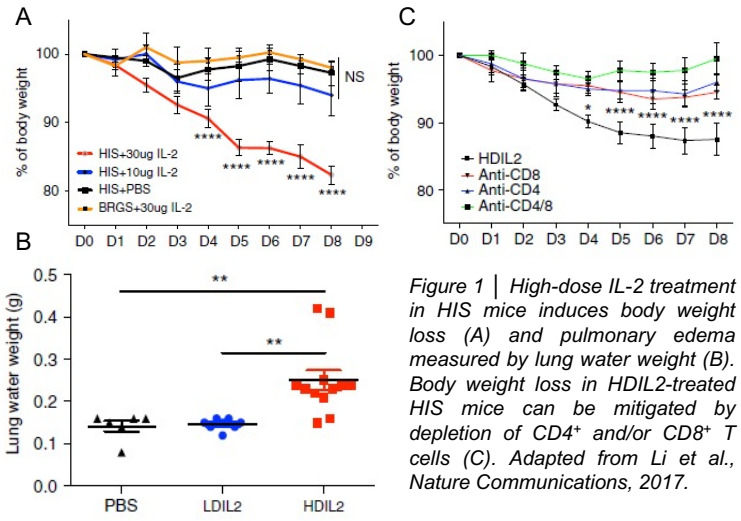

Figure 1 | High-dose IL-2 treatment in HIS mice induces body weight loss (A) and pulmonary edema measured by lung water weight (B). Body weight loss in HDIL2-treated HIS mice can be mitigated by depletion of CD4⁺ and/or CD8⁺ T cells (C). Adapted from Li et al., Nature Communications, 2017.

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.[6] 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.

To better understand HDIL2 toxicity's mechanism of action, the effect of IL-2 treatment on human immune sub-populations was investi-gated. 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 (Fig. 1C).

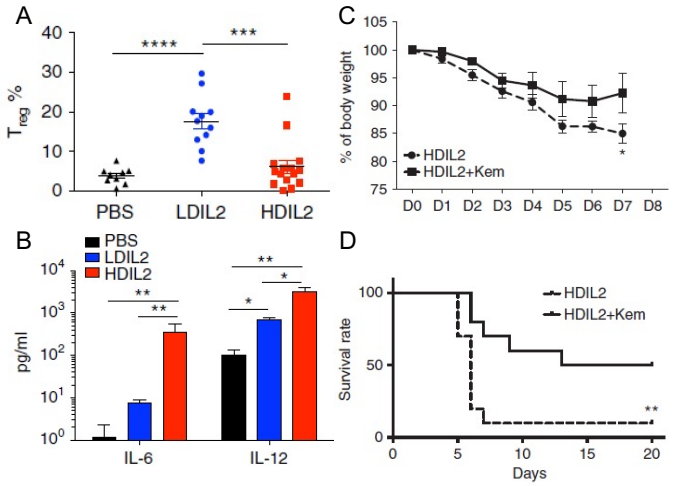

Figure 2 | Treg relative proportion is increased in LDIL2 treated HIS mice (A), but reduced as IL-2 is increased (HDIL2). Serum levels of inflammatory cytokines IL-6 and IL-12 are increased in HDIL2-treated mice (B). Treatment of HDIL2-treated mice with Kaempferol (Kem) reduces weight loss (C) and improves survival (D). Adapted from Li et al., Nature Communications, 2017.

As HDIL2 side effects have been correlated with the Treg number in patients, the authors focused on this subpopulation in IL-2-treated HIS mice, and found that LDIL2 therapy increases Treg percentage, whereas HDIL2 therapy decreases the relative proportion of Treg (Fig. 2A). This decrease was associated with an increase in the number of effector cells (Foxp3$^-$), an increase in IL-6 and IL-12 serum levels—known reducers of Treg function (Fig. 2B)—and a lower Treg-suppressive activity. To confirm the involvement of the observed compromised Treg homeostasis in HDIL2 toxicity, HDIL2-treated HIS mice were administered Kaempferol (Kem), an anti-inflammatory agent preserving Treg-suppressive function. Upon Kem treatment, Treg absolute numbers were increased, body weight loss was mitigated (Fig. 2C), and survival was improved (Fig. 2D). Additionally, serum levels of TNF and IFNɣ 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:

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