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Interleukin-2 deprived state of regulatory T cells and their recovery by low-dose interleukin-2 in patients with inflammatory myopathies

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Abstract

Objective: Regeneration and expansion of regulatory T cells (Treg) by low-dose interleukin-2 (IL-2) therapy is considered a potential treatment strategy for a wide range of autoimmune diseases. To provide a pathophysiologically-based rationale for low-dose IL-2 therapy, we investigated whether reversible defects in the Treg-IL-2 axis emerge in inflammatory myopathies.

Methods: CD4+ T cell subsets from patients with polymyositis (PM) or dermatomyositis (DM) (n=20) and healthy controls (HC; n=19), and PBMC from 8 patients, that were stimulated in vitro for 24 hours with different concentrations of recombinant human IL-2, were analyzed by multicolor flow cytometry. mRNA expression of IL2RA, IL2RB, IL2RB, ENTPD1, IKZF2, and CTLA4 was quantified by real-time PCR in IL-2 stimulated PBMC (n=6). Two patients with refractory PM/DM were treated with low-dose IL-2 therapy for 8 weeks and monitored for clinical responses and changes in Treg subsets.

Results: Frequencies of Treg expressing CD25 at high levels (CD25hi Treg) and of CXCR5+ Treg were reduced in PM/DM patients compared to HC (p=0.0052; p=0.0661), particularly in active myositis (p=0.0036; p=0.0335). Stimulation with low doses of IL-2 selectively enhanced expression of CD25 molecules by Treg, leading to an increase in the CD25hi Treg subset ($p<0.05$), and augmented mRNA expression of several immunoregulatory molecules ($p<0.05$). Low-dose IL-2 therapy induced decreases in muscle enzymes that were accompanied by a sustained expansion of CD25+ Treg.

Conclusion: Our data suggest that shortage of IL-2 is pathophysiologically relevant in PM/DM. Recovery and expansion of Treg by low-dose IL-2 therapy could thus be a promising targeted treatment option.

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