IL-27 structural analysis demonstrates similarities with ciliary neurotrophic factor (CNTF) and leads to the identification of antagonistic variants.

Titre	IL-27 structural analysis demonstrates similarities with ciliary neurotrophic factor (CNTF) and leads to the identification of antagonistic variants.
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Résumé en anglais	IL-27, consisting of the subunits IL-27p28 and Epstein-Barr virus-induced gene 3 (EBI3), is a heterodimeric cytokine belonging to the IL-6/IL-12 family of cytokines. IL-27p28 is a four-helical cytokine requiring association with the soluble receptor EBI3 to be efficiently secreted and functionally active. Computational and biological analyses of the IL-27 binding site 1 to its receptor revealed important structural proximities with the ciliary neurotrophic factor group of cytokines and highlighted the contribution of p28 Trp(97), as well as of EBI3 Phe(97), Asp(210), and Glu(159), as key residues in the interactions between both cytokine subunits. WSX-1 (IL-27R) and gp130 compose the IL-27 receptor-signaling complex, recruiting the STAT-1 and STAT-3 pathways. A study of IL-27 binding site 3 showed that Trp(197) was crucial for the cytokine's interaction with gp130, but that the mutated cytokine still recognized IL-27R on the cell surface. IL-27 exerts both pro- and anti-inflammatory functions, promoting proliferation and differentiation of Th1 and inhibiting Th17 differentiation. Our results led us to develop mutated forms of human and mouse IL-27 with antagonistic activities. Using an in vivo mouse model of concanavalin A-induced Th1-cell-mediated hepatitis, we showed that the murine IL-27 antagonist W195A decreased liver inflammation by downregulating the synthesis of CXCR3 ligands and several acute phase proteins. Together, these data suggest that IL-27 antagonism could be of interest in down-modulating acute IL-27-driven Th1-cell-mediated immune response.

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