The structure of IL-11 Mutein suggests a surprising mechanism of inhibition

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The multifunctional cytokine interleukin (IL) 11 has recently been shown to have roles in several diseases, including gastrointestinal cancer, where IL-11 signaling has been shown to be a therapeutic target. We have shown that IL-11 forms a hexameric signaling complex with its two receptors, the IL-11 specific IL-11Rα, and the shared receptor gp130. Preventing the assembly of the IL-11 signalling complex is an obvious strategy for IL-11 signalling inhibition.

We were interested in the structural mechanism of a very potent antagonistic mutant of IL-11, IL-11 Mutein [1]. IL-11 Mutein comprises a mutation in a gp130 binding site ($IL\text{-}11_{W147A}$) which was proposed to prevent the assembly of the hexameric signalling complex, and a second set of mutations ($IL\text{-}11_{PAIDY}$), which were thought to increase affinity for IL-11Rα, enabling Mutein to outcompete IL-11 for IL-11Rα. We have shown that IL-11 and IL-11 Mutein have similar affinity for IL-11Rα, meaning that the suggested mechanism of action is not possible. We have further shown *in vitro*, that IL-11 Mutein abolishes IL-11 signalling, while $IL\text{-}11_{W168A}$ permits limited IL-11 signalling, implying that the $IL\text{-}11_{PAIDY}$ mutations may further decrease affinity for gp130 over $IL\text{-}11_{W147A}$. To understand the structural basis of Mutein antagonism, we have solved the crystal structure of IL-11, IL-11 Mutein and $IL\text{-}11_{W147A}$. These structures show that a loop in the vicinity of a gp130 binding site is displaced in IL-11 Mutein compared to $IL\text{-}11_{W147A}$, suggesting that alteration of loop dynamics form the structural basis for IL-11 Mutein antagonism. We are currently conducting molecular dynamics (MD) simulations of IL-11 and IL-11 mutants, to understand the nature of loop dynamics in both proteins.

Reference:

[1] Chun, G. L., Hartl, D., Matsuura, H., Dunlop, F. M., Scotney, P.D., Fabri, L.J ., Nash, A. D., Chen, N. Y., Tang, C. Y., Chen, Q., Homer, R. J., Baca, M. and Elias J. (2008) "Endogenous IL-11 signaling is essential in Th2- and IL-13-induced inflammation and mucus production", *Am. J. Respir. Cell Mol Biol.* 39:739-746