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Structural insights into the signaling of the human Interleukin-3 receptor

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The interleukin-3 (IL-3), IL-5 and GM-CSF family of cytokines regulates the survival, proliferation, differentiation and functional activation of hematopoietic cells. These same cytokines have also been implicated in multiple pathologies resulting from the excessive or aberrant expression of the cytokine or their receptors, in conditions such as arthritis, asthma, autoimmunity and leukaemia. The receptors for these cytokines are expressed on the cell surface and comprise a cytokine-specific alpha subunit and a beta subunit that is common to all three receptors. The alpha subunit binds cytokine with low affinity forming a complex that is able to recruit the beta subunit, converting the binding to a high affinity state. A detailed molecular understanding of the basis for affinity conversion and signaling of heteromeric cytokine receptors has been hampered by the paucity of crystal structures of both binary and ternary complexes of the same receptor [1].

We have determined the crystal structures of the IL-3 receptor alpha subunit [2], as binary complex with its cytokine and a mutated "superkine" (unpublished), and as a ternary complex with the beta common subunit (unpublished). The ternary complex consisting of the cytokine and both its receptors assembles into a remarkable dodecamer complex. A comparison of the structures reveals numerous major as well as subtle conformational changes in cytokine and receptor chains, including a significant repositioning of the cytokine on assembly of the activated complex. The similarities of the IL-3 receptor to other members of the beta common superfamily [3] suggest the mode of cytokine recognition and conformational changes that accompany affinity conversion and assembly of the activated complex seen in the IL-3 receptor will be applicable to varying degrees to all family members.

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