

Poster Abstract

A cryo-EM structure to unravel the unexpected promiscuity between IL-6 and IL-11R α .

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Interleukin-6 (IL-6) and interleukin-11 (IL-11) are two cytokines in the IL-6 family of cytokines. As the only two cytokines in this family utilizing a homodimer of gp130, IL-6 and IL-11 form higher-order, hexameric signalling complexes. The hexameric complexes consist of two cytokine molecules, two molecules of gp130, and two molecules of the respective alpha receptor, IL-11R α or IL-6R α . Studies suggest that IL-6 and IL-11 have overlapping but distinct biological activities. The functional differences can be partially explained by expression of IL-6R α and IL-11R α on different cell types; by targeting their specific alpha receptor, cytokines can selectively activate specific cell types. Our preliminary data challenge this assumption, suggesting that IL-6 may promiscuously recognize IL-11R α -expressing cells by forming a hexameric complex with IL-11R α and gp130. Our analytical ultracentrifugation (AUC) data demonstrated that IL-6 may interact with gp130 first as an unstable tetrameric complex. This tetramer is further stabilized by two molecules of IL-11R α , resulting in a chimeric IL-6/ IL-11R α /gp130 complex. We present a cryo-EM density map of the hexameric IL-6/ IL-11R α /gp130 complex at 3.26 Å resolution, and the strategies used to overcome orientation preference and particle flexibility. Further modelling will be conducted to obtain an atomic model of the IL-6 chimeric complex. Structural comparison between the IL-6 complex, IL-11 complex, and IL-6 chimeric complex will provide mechanistic understanding of the promiscuity between IL-6 and IL-11R α .