Poster Presentation

MS16.P12

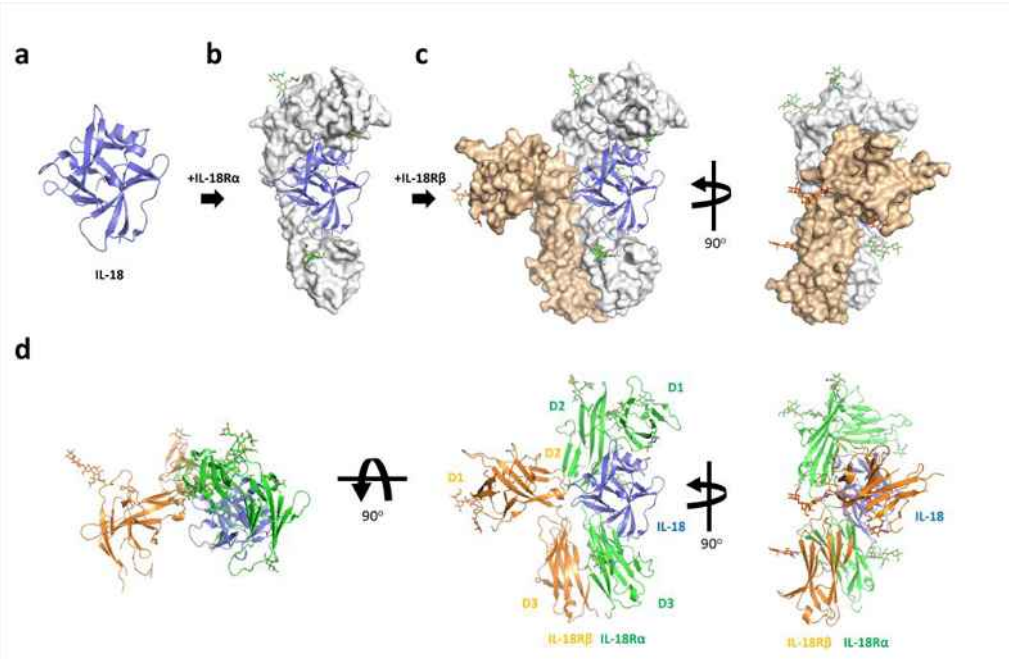
Crystal structure of the extracellular signaling complex of interleukin-18

N. Tsutsumi[1], T. Kimura[2], K. Arita[3], M. Ariyoshi[4], H. Ohnishi[2], T. Yamamoto[2], X. Zuo[5], N. Kondo[2,6], M. Shirakawa[1,7], Z. Kato[2], H. Tochio[1]

[1]Kyoto University, Department of Molecular Engineering, Graduate School of Engineering, Nishikyo-ku, Kyoto, Japan, [2]Gifu University,Department of Pediatrics, Graduate School of Medicine, Gifu, Japan, [3]Yokohama City University, Graduate School of Nanobioscience, Tsurumi-ku, Yokohama, Kanagawa, Japan, [4]Kyoto University, Institute for Integrated Cell-Material Sciences, Kyoto, Japan, [5]Argonne National Laboratory, Chemical and Materials Science Group, X-Ray Science Division, Argonne, USA, [6]Heisei College of Health Sciences,Gifu, Japan, [7]Japan Sciences and Technology Agency, Core Research of Evolution Science (CREST), Tokyo, Japan

Interleukin (IL)-18 [1], a proinflammatory cytokine belonging to the IL-1 superfamily, plays important roles in both innate and adaptive immune system, which is involved in not only the function of host defense mechanism but also allergic reactions. IL-18 is secreted by various types of cells and strongly augments the production of interferon-γ. IL-18 is synthesized as a biologically inactive precursor (proIL-18), which is matured by the action of caspase-1 in the cell upon stimulation. The matured IL-18 is subsequently secreted extracellularly and binds to IL-18 receptor α (Rα) and IL-18 receptor β (Rβ) in a stepwise manner, forming the IL-18/Rα/Rβ ternary complex. The complex initiates the signaling that finally activates NF-κB via the MyD88 dependent pathway [2]. Here, we show the crystal structure of IL-18 (Fig a), the IL-18/Rα binary complex (Fig b) and the IL-18/Rα/Rβ signaling ternary complex (Fig c, d) at 2.33, 3.10 and 3.10 Å resolution, respectively. Overall, the recognition manner of IL-18 by the receptors was similar to that of IL-1β [3], although some remarkable differences such as the orientation of Ig-like domains of IL-18Rβ were revealed. We also demonstrate that carbohydrate chains on IL-18Rα contributes to the recognition of IL-18. Biochemical experiments based on the structure identify amino acid residues that are important in forming the ternary complex and the signal transduction. Our results not only show the common extracellular signaling architecture of IL-1 family cytokines but also unveil unique recognition mechanism of IL-18 with the detailed atomic structures. The structure of the signaling ternary complex of IL-18 would contribute to both understanding the pathogeneses of the IL-18 related diseases and designing new efficient therapeutic agents.

[1] *H. Okamura, H. Tsutsi, T. Komatsu et al. Nature, 1995, 378, 88–91.,* ***[2]*** *O. Adachi, T. Kawai, K. Takeda et al. Immunity, 1998, 9, 143–150.,* ***[3]*** *D. Wang, S. Zhang, L. Li et al. Nat Immunol., 2010, 11, 905-911.*



Keywords: interleukin, cytokine, ternary complex