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Structure determination of NEMO(NF-; κ B essential modulator) UBAN domain

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NF-κB(nuclearfactor-κB)is a family of trascription factors which play essential roles in regulation of the gene expression in innate or adaptive immune responses. NF-κB proteins are kept inactive in the cytoplasm by binding of inhibitory molecules, IκBs, in the resting cells. Inducing stimuli trigger phosphorylation of the IκBs by a kinase complex (IKK) which leads to their ubiquitylation and degradation. NEMO (also called IKKγ) as a regulatory component of the IKK complex is required for the NF-κB activation in most circumstances. The activation mechanism by NEMO remains unclear, although, its ubiquitylation and oligomerization are proposed to be involved in this process. The minimum ubiquitin binding domain is highly conserved among NEMO and ABIN proteins and is named as UBAN (Ubiquitin Binding domain in ABIN proteins and NEMO). This domain corresponds to the coil-Zipper (CoZi) region in NEMO which is known as the minimum oligomerization domain, as well. Here we report the X-ray crystallographic structure of the COZi domain of NEMO at 2.8 Å resolution. The structure reveals a parallel, highly interacting coiled-coil, homo-dimer all through the CoZi domain.

Keywords: protein X-ray crystallography, NF-κB, NFκB essential modulator

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A structural basis for MHC class I associated susceptibility to multiple sclerosis

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Multiple sclerosis (MS) is an autoimmune disease affecting the central nervous system with characteristic symptoms including motor dysfunction, ataxia and visual and sensory impairment. The events leading to disease initiation remain incompletely understood but it is thought that disease develops in genetically susceptible individuals and requires additional environmental triggers [1]. Linkage studies consistently reveal the MHC region to harbour susceptibility loci and the DR2 haplotype (HLA-DR2a, HLA-DR2b and HLA-DQ6) remains the strongest genetic risk identified to date. However linkage studies stratified for DR2 indicate additional susceptibility loci within the MHC region. In particular, the MHC class I allele HLA-A*0301 has been found to double the risk of developing MS, independently of DR2, whilst individuals positive for both the HLA-A*0301 and DR2 alleles exhibit an enhanced disease risk exceeding the sum of the individual contributions. Here we report the crystal structure of HLA-A*0301 in complex with a candidate autoantigen from proteolipid protein (PLP 45-53). Comparison of this structure to that of the MHC class I molecule HLA-A*0201, which exerts a dominant protective effect from disease and approximately halves the relative risk of disease development [2, 3], offers insight into the structural basis of MHC class I associated susceptibility to multiple sclerosis.

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Crystal structure of the human IL-15/IL-15R α complex

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Interleukin (IL)-15 contributes to CD8$^+$ T-cell memory acquisition and natural killer cell generation, whereas IL-2 has a pivotal role in the expansion and functions of regulatory and activated effector T cells. The IL-15 and IL-2 receptors belong to the common γ (γ c) cytokine receptor family and share signal-transducing β and γc subunits. Within the γc-chain family, the IL-15 and IL-2 receptors are unique insofar as specificity is provided by a third, higher affinity "private" receptor α-subunit. Whereas the private IL-2Rα subunit is co-expressed with β and γc on T- and B-cells ostensibly to allow cell-autonomous signaling, IL-15Rα is expressed *in trans* on antigen-presenting cells. The 1.85 Å crystal structure of the human IL-15/IL-15Rα complex accounts for the specificity of cytokine recognition, highlighting the high degree of electrostatic and geometric complementarity between the acidic receptor-binding surface of IL-15 and the basic ligand-binding region of IL-15Rα, and the essential role of binding-site waters in forming this very high affinity complex (Kd = 38 pM) [1]. In spite of very low IL-15/IL-2 sequence homology and the distinct architectures of the cytokine-binding "sushi" domains of each receptor, the receptor binding foot-prints of each cytokine, and therefore the topologies of both the IL-15/IL-15Rα and IL-2/IL-2Rα complexes, are remarkably similar. Overall, there appear to be no structural obstacles to the transpresentation of either cytokine. Our findings suggest that antigen-experienced IL-2Rα^+ T cells could, in principle, enhance IL-2Rα^- T cells responses *via* the direct presentation of IL-2.

[1] Chirifu, M., et al. (2007) *Nature Immunology* 8, 1001-1007

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Hematopoietic protein tyrosine phosphatase (HePTP): Molecular determinants of substrate specificity

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