Structural studies of the ubiquitin binding zinc finger domains of human TAX1-binding protein-1 (TAX1BP1)

Ahmed Rohaim[1,2], Masato Kawasaki[1,2], Ryuichi Kato[1,2], Ivan Dikic[3] and Soichi Wakatsuki[1,2].

[1]Department of Materials Structure Science, The Graduate University for Advanced Studies (SOKENDAI), [2]Structural Biology Research Centre, Photon Factory, High Energy Accelerator Research Organization (KEK), Tsukuba, Japan.
[3]Institute for Biochemistry II, Goethe University Medical School, Frankfurt, Germany.

Nuclear factor kappa B (NF-κB) is a key mediator of innate and adaptive immune response. Incorrect regulation of NF-κB pathway has been linked to immune and inflammatory disease as well as cancers. Tax1-binding protein 1 (TAX1BP1) is a negative regulator of TNF-alpha- and IL-1beta-induced NF-κB activation. TAX1BP1 binds to mono- and polyubiquitin by its C-terminal ubiquitin-binding zinc finger (UBZ) domains, which are needed for TRAF6 (TNF-associated factor-6) or RIP1 (receptor interacting protein-1) association followed by recruitment of A20 deuibiquitinase (DUB) resulting in NF-κB inhibition. In order to acquire a better understanding of the molecular interaction between TAX1BP1 and its counterparts, we have determined the crystal structure of the C-terminal UBZ domains of TAX1BP1 in fusion with Green fluorescence protein (GFP) at 2.8 Å resolution. The crystal structure shows two tandem zinc fingers of the classical type C2H2 owing to the zinc coordinating atoms, both having a β-β-α fold. Other members of the same C2H2 UBZ family are proposed to bind ubiquitin exclusively through the α-helix in a manner similar to inverted ubiquitin-interacting motif (IUIM). Superposition of the α-helix of the UBZ domain of TAX1BP1 to existing structural models indicates similar conformation of the ubiquitin binding surface, proposing similar interaction mechanism and a conserved architecture throughout the UBZ domains.