

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

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TAX1-binding protein 1 (TAX1BP1) is a negative regulator of TNF- α - and IL-1 β -induced NF- κ B activation. TAX1BP1 comprises two C-terminal zinc finger domains that bind to mono- and polyubiquitin, which are needed for TRAF6 (TNF-associated factor-6) or RIP1 (receptor interacting protein-1) association followed by recruitment of A20 deubiquitinase (DUB) resulting in NF- κ B downregulation. To understand the molecular basis for the ubiquitin-mediated function of TAX1BP1, we determined the crystal structure of its C-terminal UBZ 1+2 domain. The structure shows two tandem zinc fingers of the classical type C2H2, 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 the inverted ubiquitin-interacting motif (IUIM). However, based on site-directed mutagenesis and isothermal titration calorimetry analyses, a model is proposed for TAX1BP1 UBZ 2 interaction with ubiquitin, indicating a new mode of interaction between ubiquitin and the UBZ 2 domain of TAX1BP1. This provides an insight into the mechanism of ubiquitin recognition by TAX1BP1, and its function in the NF- κ B pathway.