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Linear ubiquitin binding via A20 zinc finger7 is involved in the canonical NF- κ B regulation

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Abstract

LUBAC (linear ubiquitin chain assembly complex) composed of HOIL-1L, HOIP, and SHARPIN, regulates the canonical NF- κ B pathway through linear polyubiquitination of NEMO and RIP1. However, deubiquitinase (DUB), which down-regulates LUBAC-mediated NF- κ B activation, remains elusive. We identified that A20 (TNFAIP3) suppresses LUBAC-mediated NF- κ B activation by the specific binding to linear polyubiquitin via the C-terminal seventh zinc finger (ZF7), whereas CYLD suppresses it through DUB activity. We determined the crystal structures of A20 ZF7 in complex with linear diubiquitin at 1.70–1.98 Å resolutions. The crystal structures revealed that A20 ZF7 simultaneously recognizes the Met1-linked proximal and distal ubiquitins with a novel manner. Importantly, genetic mutations associated with B cell lymphomas, such as N772K and E781D, map to the ubiquitin-binding sites, and our functional analysis indicated that the binding of A20 ZF7 to linear polyubiquitin contributes to the recruitment of A20 into a TNF receptor (TNFR) signalling complex containing LUBAC and I κ B kinase (IKK), which results in NF- κ B suppression. These findings provide new insight into the regulation of immune and inflammatory responses, and the linear ubiquitin-binding through A20 ZF7 will provide a novel therapeutic target for B cell lymphomas.