NEMO (NF-κB essntial modulator) selectively binds linear ubiquitin chains in NF-κB activation

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Members of the nuclear factor-κB (NF-κB) family are key transcription factors that regulate gene expression during critical cellular processes including inflammation, cell proliferation and apoptosis. In the inactive state binding to inhibitory-κB (IκB) molecules sequesters NF-κB transcription factors in the cytosol. Activation is tightly regulated by a signaling network which integrates stimuli from various sources and requires binding of NF-κB essential modulator (NEMO) to ubiquitylated substrates. Here we report that UBAN (Ubiquitin Binding in ABIN and NEMO) motif of NEMO preferentially binds to linear (head-to-tail) ubiquitin chains. Crystal structures of the UBAN motif alone and in complex with linear diubiquitin chains indicate that UBAN motif forms a parallel coiled-coil homo-dimer which binds to one linear diubiquitin on either side. The UBAN dimer contacts canonical Il44 surface on distal and a novel surface on proximal ubiquitins which provide specificity for linear ubiquitin chain binding. Residues of NEMO involved in interactions with linear ubiquitin chains are essential for NF-κB activation by TNF-α and other agonists, which explains the detrimental effect of NEMO mutations in patients suffering from X-linked ectodermal dysplasia and immunodeficiency.