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TRIM protein domain topology and implications for antiviral immunity

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The tripartite motif (TRIM) proteins are a large family of >100 members, several of which have important roles in antiviral immunity and innate immune signaling. TRIM5α associates with incoming HIV-1 capsids, interfering with controlled disassembly and targeting them for degradation by the proteasome. TRIM21 is a cytosolic antibody receptor, which also targets incoming viral capsids for proteasomal degradation. TRIM25 is also involved in innate immunity, being essential for the ubiquitination of RIG-I. Recent positive selection analysis has predicted another 10 TRIM proteins with antiviral activity. Despite the fact that TRIM5α, 21 and 25 play key roles in antiviral protection, their mechanism of action is incompletely understood. All three proteins share a similar domain architecture, comprising a RING, B Box, coiled coil and PRYSPRY domains. The RING domains are responsible for ubiquitin ligase activity, while the PRYSPRY domains determine target specificity. We have used a combination of crystallography and SAXS to generate the first complete model for a TRIM protein structure. Crystallographic studies of TRIM25 reveal a central elongated coiled-coil domain with an unusual right-handed twist. The dimer formed by the coiled-coil is antiparallel but is followed by additional helices that reverse the direction of the protein chain. This structure suggests that the N-terminal domains of each monomer are separated but the C terminal domains are maintained in proximity. Multi-angle light scattering (MALS), isothermal titration calorimetry (ITC) and SAXS analysis confirms that this dimer structure is present in solution. Furthermore, scattering studies on the tripartite motif of TRIM21, comprising RING, B Box and coiled-coil, demonstrate that the first two domains of each monomer are held 150-200 Å apart. Finally, SAXS measurement of a complex between intact TRIM21 and its ligand, IgG Fc, provides the first empirical structure of a complete TRIM protein.

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