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Structural and Functional Characterization of Traf2: Insights into Tnf Signaling and Cancer Therapeutics Traf2 (tnf Receptor-associated Factor 2) Is a Key Adaptor Protein Regulating Inflammation, Immu

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TRAF2 (TNF receptor-associated factor 2) is a key adaptor protein regulating inflammation, immune signaling, and apoptosis. It comprises a RING domain (aa 1–83), five zinc fingers (aa 84–266), a coiled-coil TRAF-N domain (aa 267–328), and a TRAF-C domain (aa 329–501). The TRAF-N domain mediates trimerization and binds downstream effectors in the TNF signaling pathway. The dynamic equilibrium between trimeric and mono/dimeric TRAF2 is critical for its activity. Trimerization enhances binding to TNFRs, while TRAF-C dissociation shifts the equilibrium toward mono/dimeric forms, increasing membrane association. It has been shown that the TRAF-C domain interacts with ganglioside GM1 in lipid rafts, suggesting a role in modulating TRAF2 localization and signaling. To explore the structural basis of these mechanisms, we expressed and purified a TRAF2-N/C construct (aa 267–501) and confirmed stable homotrimer formation by SAXS. Crystallization, NMR spectroscopy, and SAXS-MD simulations are ongoing to solve the structure of the construct. These studies aim to deepen our understanding of TRAF2 signaling and support therapeutic strategies in cancer and inflammation.