

Solution Structure of Mst1 SARAH Domain and its Interaction with Rassf5 and WW45 SARAH Domains for the Apoptosis Pathway

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In eukaryotic cells, apoptosis and cell cycle arrest by the Ras RASSF MST pathway are controlled by the interaction of SARAH (for Salvador/Rassf/Hippo) domains in the C-terminal part of tumor suppressor proteins. The Mst1 SARAH domain interacts with its homologous domain of Rassf1 and Rassf5 (also known as Nore1) by forming a heterodimer that mediates the apoptosis process. Here we describe the homodimeric structure of the human Mst1 SARAH domain, and its heterotypic interaction with the Rassf5 and Salvador (Sav) SARAH domain. The Mst1 SARAH structure forms a homodimer containing two helices per monomer. An anti-parallel arrangement of the long alpha helices (h2/h2') provides an elongated binding interface between the two monomers, and the short 3₁₀ helices (h1/h1') are folded toward that of the other monomer. Chemical shift perturbation experiments identified an elongated, tight binding interface with the Rassf5 SARAH domain, and a 1:1 heterodimer formation. The linker region between the kinase and the SARAH domain is shown to be disordered in the free protein. This implies a novel mode of interaction with RASSF family proteins, and provides insight into the mechanism of apoptosis control by the SARAH domain.

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