

**A-4****Crystal Structure of Human TRAIL, the First Molecule With Selective Antitumor Activity**

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TRAIL (also known as Apo-2L) is a newly identified cytokine belonging to the large tumor necrosis factor (TNF) family. TRAIL is a novel molecule in that it induces apoptosis in a wide variety of tumor cells but not in normal cells. In order to help elucidating its biological roles and designing mutants with improved therapeutic potential, we have determined the crystal structure of human TRAIL. The structure reveals that a novel frame insertion of 12 - 16 amino acids, an unique feature among the known TNF family members, adopts a salient loop structure penetrating into the receptor-binding site, which is the cleft between neighboring subunits as in other TNF family members. The structure and a model building of the TRAIL/receptor complex demonstrate that the loop alters drastically the common receptor-binding surface most likely for the specific recognition of cognate partners that also belong to a huge receptor superfamily. The structure provides a framework for mutagenesis studies to elucidate the virtually unknown biological functions of TRAIL ligation and for the design of TRAIL mutants with therapeutic potential.