The Role of FasL and Fas in Health and Disease

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Abstract

The FS7-associated cell surface antigen (Fas, also named CD95, APO-1 or TNFRSF6) attracted considerable interest in the field of apoptosis research since its discovery in 1989. The groups of Shin Yonehara and Peter Krammer were the first reporting extensive apoptotic cell death induction upon treating cells with Fas-specific monoclonal antibodies. Cloning of Fas and its ligand, (also known as CD178, CD95L or TNFSF6), laid the cornerstone in establishing this receptor-ligand system as a central regulator of apoptosis in mammals. Therapeutic exploitation of FasL-Fas-mediated cytotoxicity was soon an ambitious goal and during the last decade numerous strategies have been developed for its realization. In this chapter, we will briefly introduce essential general aspects of the FasL-Fas system before reviewing its physiological and pathophysiological relevance. Finally, FasL-Fas-related therapeutic tools and concepts will be addressed.

The FasL-Fas System

Structure of Fas

Fas is the prototypic representative of the death receptor subgroup of the tumor necrosis factor receptor family. In the human genome, the Fas gene is located on chromosome 10q24.1, containing 9 exons and spanning about 26 kb of DNA. Consensus sequences for "TATA" and "CAAT" boxes are missing in the 5' upstream sequence resulting in multiple transcription initiation sites. Due to alternative splicing seven variants of mRNA transcripts have to date been observed encoding several soluble forms of Fas with negative regulatory effects in vitro, e.g., a Fas molecule lacking the transmembrane domain. Mature Fas is a type I transmembrane protein of 319 aa, divided into a 157 aa extracellular and a 145 aa intracellular domain (Fig. 1).

The extracellular domain of Fas contains three cysteine rich domains (CRDs), the structural hallmark of the TNF receptor family. Functionally all three CRDs of Fas are required for ligand binding, but sites for direct contact are exclusively provided by CRD2 and CRD3. Although CRD1 has no ligand specificity, it is a prerequisite for efficient receptor-ligand interaction and Fas signaling. As a major part of the so called preligand binding assembly domain (PLAD) it mediates formation of signaling incompetent Fas complexes which in contrast to Fas monomers have high affinity for FasL.

The C-terminal half of the intracellular domain of Fas comprises the death domain (DD) (Fig. 1), which is essential for apoptosis induction and characteristic for the subgroup of death receptors. The death domain is not limited to death receptors, but can also be found in cytoplasmic...
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Adaptor proteins and kinases. Serving as a homophilic interaction domain, the death domain mediates homo- or heteromerization of DD proteins, presumably facilitated through charged residues on the DD surface. Expression of Fas has been reported for many types of cells, including fibroblasts, epithelial cells and cells of the hematopoetic system. In the latter, a correlation between Fas expression and maturation status has been observed.

Structure of Fasl

The gene of human Fasl is located on chromosome 1q23, spanning about 8 kb of DNA and consisting of 4 exons. Like the majority of ligands of the TNF family, mature Fasl is a 40 kDa type II transmembrane glyco-protein.

The extracellular portion (179 aa) of Fasl has three potential N-glycosylation sites and contains two antiparallel β-sheets forming a “jelly roll” known as the TNF homology domain (THD), the characteristic structural feature of the TNF ligand family (Fig. 1). Although sequence homology between THDs from different TNF family ligands does not exceed 35% the tertiary structure is essentially similar and mediates ligand homotrimerization and receptor binding.