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**REVIEW ARTICLE** **OPEN ACCESS**

# Role of FAS in Apoptosis

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**ABSTRACT**
*Fas ligand (FasL or CD95L) is a type-II transmembrane protein that belongs to the tumor necrosis factor (TNF) family. The Fas receptor is a death receptor on the surface of cells that leads to programmed cell death (apoptosis) and play an important role in the regulation of the immune system and the progression of cancer. This review article focused on FAS receptor and Fas ligand (FasL or CD95L) up-to-date information.*
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## INTRODUCTION

The FAS receptor (FasR), also known as apoptosis antigen 1 (APO-1 or APT), cluster of differentiation 95 (CD95) or tumor necrosis factor receptor superfamily member 6 (TNFRSF6) is a protein that in humans is encoded by the*TNFRSF6* gene [1]. The Fas receptor is a death receptor on the surface of cells that leads to programmed cell death (apoptosis). It is one of two apoptosis pathways, the other being the mitochondrial pathway [2]. FasR is located on chromosome 10 in humans and 19 in mice. The mature Fas protein has 319 amino acids, has a predicted molecular weight of 48 kiloDaltons and is divided into 3 domains: an extracellular domain, a transmembrane domain, and a cytoplasmic domain. The extracellular domain has 157 amino acids and is rich in cysteine residues. The transmembrane and cytoplasmic domains have 17 and 145 amino acids respectively. Exons 1 through 5 encode the extracelluar region. Exon 6 encodes the transmembrane region. Exons 7-9 encode the intracellular region.

Fas forms the death-inducing signaling complex (DISC) upon ligand binding. Membrane-anchored Fas ligand trimer on the surface of an adjacent cell causes oligomerization of Fas. Recent studies which suggested the trimerization of Fas could not be validated [3]. FADD also contains a death effector domain (DED) near its amino terminus [5] which facilitates binding to the DED of FADD-like interleukin-1 beta-converting enzyme (FLICE), more commonly referred to as caspase-8. FLICE can then self-activate through proteolytic cleavage into p10 and p18 subunits, two each of which form the active heterotetramer enzyme. Active caspase-8 is then released from the DISC into the cytosol, where it cleaves other effector caspases, eventually leading to DNA degradation, membrane blebbing, and other hallmarks of apoptosis.

Recently, Fas has also been shown to promote tumor growth, since during tumor progression, it is frequently down regulated or cells are rendered apoptosis resistant. Cancer cells in general, regardless of their Fas apoptosis sensitivity, depend on constitutive activity of Fas. This is stimulated by cancer-produced Fas ligand for optimal growth [4].

Fas ligand (FasL or CD95L) is a type-II transmembrane protein that belongs to the tumor necrosis factor (TNF) family. Its binding with its receptor induces apoptosis. Fas ligand/receptor interactions play an important role in the regulation of the immune system and the progression of cancer.

## FAS RECEPTORS

**FasR:** The Fas receptor (FasR), or CD95, is the most intensely studied member of the death receptor family. The gene is situated on chromosome 10 in humans and 19 in mice. Previous reports have identified as many as eight splice variants, which are translated into seven isoforms of the protein. Many

of these isoforms are rare haplotypes that are usually associated with a state of disease. Apoptosis-inducing Fas receptor is dubbed isoform 1 and is a type 1transmembrane protein. It consists of three cysteine-rich pseudorepeats, a transmembrane domain, and an intracellular death domain.

**DcR3:** Decoy receptor 3 (DcR3) is a recently discovered decoy receptor of the tumor necrosis factor super-family that binds to FasL, LIGHT, and TLA1. DcR3 is a soluble receptor that has no signal transduction capabilities (hence a "decoy") and functions to prevent FasR-FasL interactions by competitively binding to membrane-bound Fas ligand and rendering them inactive [6].

**FUNCTIONS IN APOPTOSIS**

Apoptosis triggered by Fas-Fas ligand binding plays a fundamental role in the regulation of the immune system. Its functions include:

**T-cell homeostasis:** the activation of T-cells leads to their expression of the Fas ligand. T cells are initially resistant to Fas-mediated apoptosis during clonal expansion, but become progressively more sensitive the longer they are activated, ultimately resulting in activation-induced cell death (AICD). This process is needed to prevent an excessive immune response and eliminate autoreactive T-cells. Humans and mice with deleterious mutations of Fas or Fas ligand develop an accumulation of aberrant T-cells, leading to lymphadenopathy, splenomegaly, and lupus erythematosus.

**Cytotoxic T-cell activity:** Fas-induced apoptosis and the perforin pathway are the two main mechanisms by which cytotoxic T lymphocytes induce cell death in cells expressing foreign antigens [7].

**Immune privilege:** Cells in immune privileged areas such as the cornea or testes express Fas ligand and induce the apoptosis of infiltrating lymphocytes. It is one of many mechanisms the body employs in the establishment and maintenance of immune privilege.

**Maternal tolerance:** Fas ligand may be instrumental in the prevention of leukocyte trafficking between the mother and the fetus, although no pregnancy defects have yet been attributed to a faulty Fas-Fas ligand system.

**Tumor counterattack:** Tumors may over-express Fas ligand and induce the apoptosis of infiltrating lymphocytes, allowing the tumor to escape the effects of an immune response (Krammer, 2005). The up-regulation of Fas ligand often occurs following chemotherapy, from which the tumor cells have attained apoptosis resistance.

Defective Fas-mediated apoptosis may lead to oncogenesis as well as drug resistance in existing tumors. Germline mutation of Fas is associated with autoimmune lympho proliferative syndrome (ALPS), a childhood disorder of apoptosis. FasL is synthesized as a transmembrane molecule and soluble FasLtrimers can be generated through processing by a metalloprotease [8]. Fas signaling play a critical role in lymphocyte homeostasis. Repeated activation of antigen receptors on T cells induces FasLexpression, leading to Fas-transduced apoptosis. Failure of this process, caused by mutations in Fas (lpr or Fas gene deletion) or FasL, evokes lymphadenopathy and autoimmunity [9]. This receptor also plays a role in regulating physiological death of hepatocytes.

Apoptotic cell death induced by the engagement of Fas by FasL plays a major role in modulation of immune function, particularly in activation-induced cell death (AICD) [10]. Activation-induced cell death serves two functions: (i) to limit the expansion of T cell clones after the elimination of antigen; and (ii) to inactivate autoreactive peripheral T cells that may have evaded screening for self-reactivity in the thymus by negative selection [11]. Numerous disease states have been associated with aberrant activity of the Fas/FasL pathway of cell death. It has also been suggested that the observed depletion of $CD4^+$cells during HIV infection involves AICD, following cross-linking of CD4 by gp120/anti-gp120 immune complexes and consequent cell death by a Fas-dependent pathway (Levels of both Fas and FasL have been shown to be increased in renal tissue undergoing acute rejection [12]. Evidence has been presented for increased Fas expression in sudden infant death syndrome,Sjogren's syndrome, myositis, Down syndrome and in human ageing [13].

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