

The Fas - Fas Ligand apoptotic pathway

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Background on apoptosis

Cell death can be achieved by two fundamentally different mechanisms, apoptosis and necrosis. Apoptosis is characterized by several morphological features that include condensation of nuclei and internucleosomal degradation of DNA, cell membrane blebbing, and formation of apoptotic bodies. By contrast, necrosis is recognized by swelling of the cell and organelles, followed by disintegration of the cell and the release of cytoplasmic material. Although the necrotic signalling pathway remains largely uncharacterized at the molecular level, apoptosis is known to be dependent on a family of intracellular cysteine proteases, called **CASPASES** (Cysteine Aspartate Specific ProteASEs). Caspases ([Nicholson DW, 1999](#)) are initially synthesized as inactive cytosolic proteases (proenzymes) which have a p20 and a p10 domain that, in response to apoptotic stimulation, are cleaved to form the active enzyme. Active caspases then cleave other caspases, Bcl-2 family members, or act on various nuclear substrates, such as lamins and caspase-activated DNase (CAD), finally leading to apoptosis. Caspases contain a cysteine residue within the active site, and which cleave their substrate exclusively after an aspartic acid residue, a sequence of 3 amino acids before aspartate determines substrate specificity. Caspases can be divided into inflammatory caspases (-1, -4, -5, -11, -12, -13 and -14), which cleave and activate proinflammatory cytokines, and proapoptotic caspases, which cleave and activate proapoptotic substrates. Proapoptotic caspases comprise initiator caspases (-2, -8, -9 and -10), which, in turn, cleave and activate effector or executioner caspases (-3, -6 and -7).

Apoptosis can be induced either from the cell surface, by ligand-dependent triggering of death receptors (e.g. CD95/Fas; TNF-R1; TNF related apoptosis-inducing ligand receptor 1, TRAIL-R1/DR4 and TRAIL-R2/DR5), or by the stimulation of intracellular receptor proteins, such as apoptotic protease-activating factor 1 (Apaf-1), which is activated by its ligand cytochrome c once it is released from damaged mitochondria ([Ranger AM et al., 2001](#)). Both systems transmit apoptotic signals through protein-protein interactions that are mediated by motifs called the death domain (DD), the death effector domain (DED) and the caspase recruitment domain (CARD).

Death domains (DD) are 80-100 residue long motifs found both in cytoplasmic proteins (FADD: Fas-associated protein with Death Domain; TRADD: TNF Receptor-associated protein with Death Domain; and RIP: Receptor Interacting Protein) and in transmembrane proteins including members of the TNF-receptor superfamily, like Fas, TNF-R1, TRAIL-R1/DR4 and TRAIL-R2/DR5. DD serve as recruiting modules

through their ability to heterodimerize with the DD of distinct proteins, including adaptor proteins such as FADD, TRADD and RIP. Death-effector domain (DED) is a protein interaction domain found in inactive procaspases (-8 and -10) and proteins that regulate caspase activation in the apoptosis cascade. The DED recruits procaspases into complexes with members of the TNF-receptor superfamily. This recruitment is mediated by a homotypic interaction between the procaspase DED and a second DED in a FADD adaptor molecule that is directly associated with activated members of the TNF-receptor superfamily. Complex formation allows transprocessing of procaspase to the active form. This, in turn, activates downstream caspases and initiates apoptosis.

Caspases-8 (FLICE)- and -10 (FLICE 2)-inhibitory proteins were identified in virus and human and designated v-FLIP and c-FLIP, respectively ([Thome M et al., 1997](#); [Irmeler M et al., 1997](#)). The human FLIP was also cloned by several labs independently and termed Casper, I-FLICE, FLAME-1, CASH and CLARP. FLIP contains two death DEDs and a caspase-like domain. FLIP interacts with adapter protein FADD and caspase-8 and -10, and potently inhibits apoptosis induced by all known death receptors. Several splicing isoforms of c-FLIP occur, two of which are expressed as proteins *in vivo*: short FLIP (c-FLIP_s) of 26 kDa and long FLIP (c-FLIP_L) of 55 kDa. c-FLIP_s consist essentially of two repeats of a DED and c-FLIP_L contains a carboxy terminal inactive caspase-like domain which confers on the molecule an overall structural homology with caspase-8 and caspase-10 (Thome M and Tschopp J, Nature Reviews Immunology, 2001).

Caspase recruitment domains (CARD) are 90-100 amino acids long motifs. CARD mediates the association of adaptor proteins (RAIDD, Apaf-1) and procaspases (-2 and -9), through heterodimerization of the respective CARD, recruiting procaspases to upstream signaling complexes and allowing autoactivation.

The Fas- Fas Ligand pathway

Although Fas - Fas Ligand (FasL) interactions are not limited to the immune system, it is where most of their functional studies have originated. Apoptosis in the immune system is a fundamental process regulating lymphocyte maturation, receptor repertoire selection and homeostasis. In the immune system, apoptosis occurs during T and B lymphocyte repertoire selection and cytolytic T-cell-mediated killing (Fig.1).

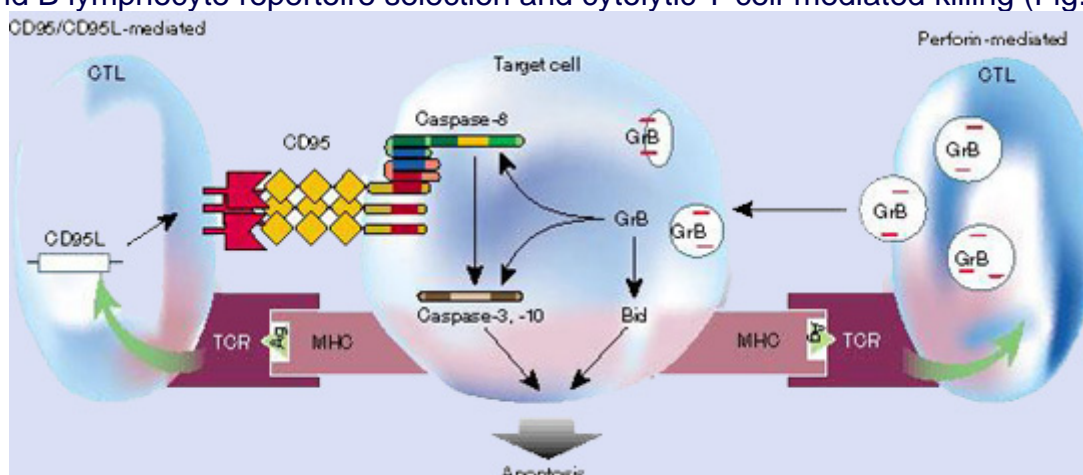


Figure 1

Apoptosis also plays an essential role in the removal of excess T- and B-cells as part of the mechanisms maintaining cellular homeostasis during immune responses. Defects in this process lead to the accumulation of potentially autoreactive T- and B-cells. A subset of members of the TNF-R superfamily is involved in death transducing

signals in cells of the immune system. This family is constantly expanding and includes receptors for TNF- α , lymphotoxin- α , TNF related apoptosis-inducing ligand (TRAIL) and FasL. Members of this TNF-R1 family contain one to five extracellular cysteine-rich domains, and in their cytoplasmic tail a death domain (DD) essential for transduction of the apoptotic signal. Fas (CD95 or Apo-1) is one such family member ([Itoh et al., 1991](#)) and has a major role in the immune system. The Fas protein is a type 1 transmembrane glycoprotein with three extra-cellular cysteine-rich domains (CRD). Fas is ubiquitously expressed on a variety of normal cells, including lymphocytes and hepatocytes. Its expression can be increased by the activation of lymphocytes but also by cytokines such as interferon- γ and TNF. It is a type I transmembrane glycoprotein of relative molecular mass ~ 45,000 (molecule with 320 amino-acid residues, 157 amino acid extracellular domain), but alternative splicing can result in a soluble form termed decoy receptor 3 (DcR3), that binds FasL and inhibits FasL-induced apoptosis. Fas-mediated apoptosis is triggered by its ligand, FasL ([Suda T et al., 1993](#)), which is expressed in a far more restricted way than the receptor, including activated T-cells, NK (natural killer) cells. On the other hand, it has long been known that certain sites in the body, for example, the eye, the testes and the brain are "privileged". They are protected from attack by the immune system. Many factors are involved in immune privilege, such as tight junctions between the cells of the tissue, little expression of class I histocompatibility molecules, and expression of FasL. For instance, the corneal epithelium and the retina of the eye, Sertoli cells of the testis and the trophoblast of the placenta express FasL. Indeed, the placenta also enjoys immune privilege. It is almost as foreign to the mother as a kidney transplant from her husband would be, but unlike the kidney, she will not reject it. When threatened by a cytotoxic T cell, cells from "privileged" sites avoid being killed by forcing the T lymphocyte to commit suicide by apoptosis ([Green DR and Ferguson TA](#)). Some tumors also express FasL, which has been suggested as a mechanism to escape immune surveillance. FasL is a TNF-related type II transmembrane molecule of ~ 40 kDa but can also be cleaved from the membrane by a metalloprotease, while soluble human FasL can induce apoptosis, soluble mouse FasL cannot.

Both Fas and FasL are predicted to form trimers, with extra-cellular cysteine-rich domain (CRD) 2 and CRD3 forming the major contact surfaces for FasL. Recently, it has been found that Fas and TNF-R share a self-association domain in CRD1, termed the "pre-ligand assembly domain" (PLAD) and formation of preassociated receptor complexes is necessary for TNF-R and Fas signaling ([Siegel RM et al., 2000](#)). Following Fas - FasL ligation a complex of proteins associates with activated Fas (Fig.2).

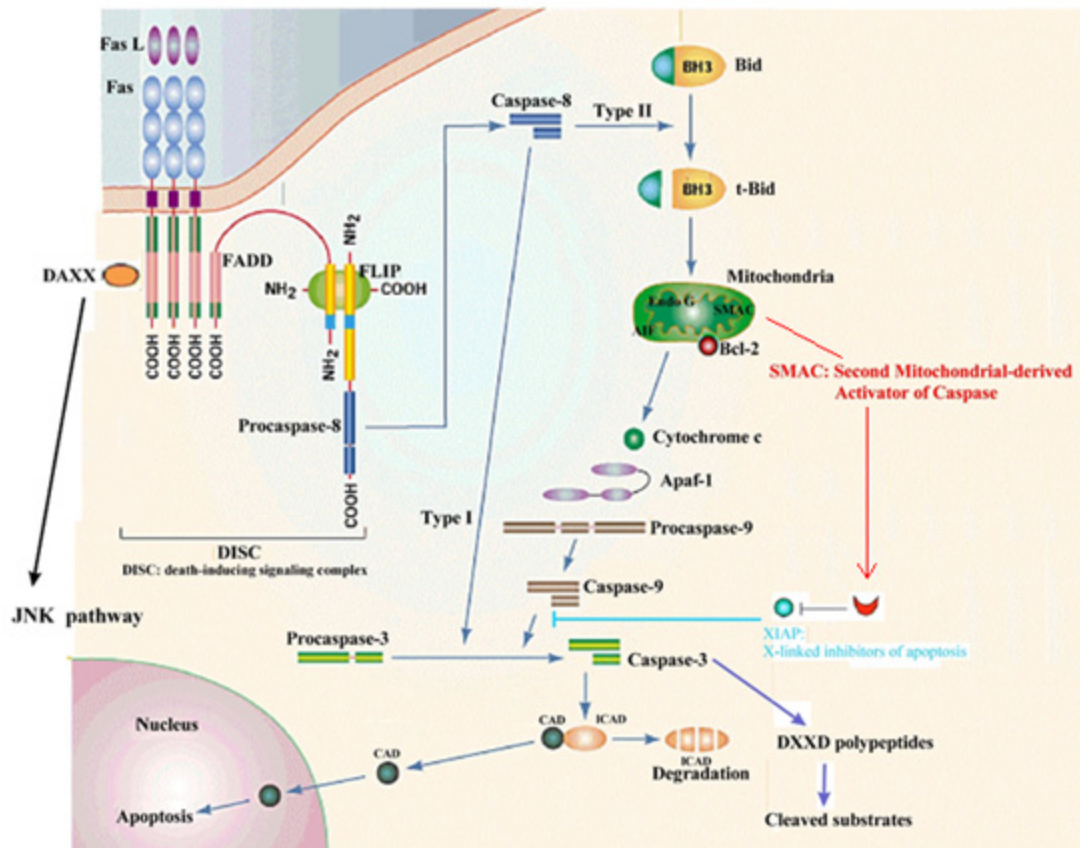


Figure 2

This death-inducing signalling complex (DISC) forms within seconds of receptor engagement. First, the adaptor FADD binds via its own DD to the DD in Fas. FADD also carries a DED, and, again by homologous interaction, recruits the DED-containing procaspase-8 into the DISC. Next, procaspase-8 is activated proteolytically and active caspase-8 is released from the DISC into the cytoplasm in the form of a heterotetramer of two small subunits (~ p10) and two large subunits (~ p20). Recently two different pathways of Fas-mediated apoptosis have been identified. Fas-mediated apoptosis in type I cells (lymphoid cells) is initiated by large amounts of active caspase-8 formed at the DISC followed by direct cleavage of procaspase-3. Activated caspase-3 cleaves a variety of substrates, including DNA repair enzymes, such as poly-ADP ribose polymerase and DNA protein kinase; cellular and nuclear structural proteins, including nuclear mitotic apparatus, lamins, and actin; and endonucleases ([Sakahira H et al., 1998](#)), such as caspase-activated deoxyribonuclease (CAD) inhibitor (ICAD) and many other cellular constituents. Moreover, caspase-3 has the ability to activate other caspases, such as procaspase-6 and -7, resulting in an amplification of cellular destruction. In contrast, in type II cells (hepatocytes) very little DISC and small amounts of active caspase-8 are formed, so the caspase cascade has to be amplified by activating the apoptosome, the second initiator complex of apoptosis. Then, Caspase-8 cuts the Bcl-2 family member Bid; truncated Bid induced insertion of BAX into mitochondrial membrane and mitochondria release pro-apoptotic molecules such as cytochrome c and smac/diablo. Together with the apoptosis protease-activating factor Apaf-1, procaspase-9 in the cytoplasm, these molecules form the apoptosome. Caspase-9 activates further downstream procaspases-3 (Fig. 2). Bid-deficient mice are resistant to Fas-induced hepatocellular apoptosis ([Yin XM et al., 1999](#)).

Fas-mediated apoptosis may also be activated by the recruitment of molecules other than FADD. The DD in Fas undergo homotypic interaction with the DD of receptor interacting protein (RIP) kinase ([Kelliher MA et al., 1998](#)). RIP, in turn, binds the adapter molecule RAIDD (RIP-associated ICH-1/CED-3-homologous protein with a death domain) to recruit and activate procaspase-2 via homotypic interaction of their CARD. Moreover, ligation of Fas leads to activation of the c-Jun N-terminal kinase (JNK) pathway in many cell types. Fas was reported to engage the JNK pathway via Death Domain associated protein (Daxx)-mediated activation of Ask1/MKK5. Overexpressed Daxx was shown to potentiate anti-Fas Ab-induced apoptosis and JNK activation.

Diseases involving the Fas - Fas Ligand pathway:

In tumors

CD8⁺ cytotoxic T lymphocytes (CTL) and CD4⁺ T cells play crucial roles in host defense against malignancies. However, it is also becoming clearer that neoplastic cells may evade cell-mediated immunity at multiple levels of the effector/target interaction which, consequently, may impact the metastatic process. Malignant melanoma accounts for most of the increasing mortality from skin cancer. Melanoma cells were found to express FasL. In metastatic lesions, Fas expressing T-cell infiltrates were proximal to FasL expressing tumor-cells. Binding of tumor-associated FasL to its cognate receptor Fas on tumor infiltrating T-cells, produces apoptosis, in the susceptible target T-cells ([Hahne M et al., 1996](#)). *In vitro*, apoptosis of Fas-sensitive target cells occurred on incubation with melanoma tumor cells; and *in vivo*, injection of FasL expressing mouse melanoma cells in mice led to rapid tumor formation. In contrast, tumorigenesis was delayed in Fas deficient mice in which immune effector cells cannot be killed by FasL. Thus FasL may contribute to the immune privilege of tumors ([Ferguson TA and Griffith TS, 1997](#)).

Genetic defects in the Fas - Fas Ligand pathway: *lpr* mice

Dysregulation of apoptosis, particularly in the Fas - FasL pathway, is considered to be involved in the pathogenesis of autoimmune diseases such as systemic lupus erythematosus (SLE). [Watanabe-Fukunaga et al., \(1992\)](#) demonstrated that MRL/*lpr* mice carrying the lymphoproliferation (*lpr*) mutation have defects in the Fas gene. The autosomal recessive *lpr* mutation of the murine MRL strain is associated with the development of massive lymphadenopathy and an autoimmune syndrome resembling human SLE and rheumatoid arthritis (RA). This mutation corresponds to a marked decrease of the expression of the Fas receptor, as a consequence of an *ETn* retrotransposon insertion into the second intron of the gene ([Wu J et al., 1993](#); [Kobayashi S et al., 1993](#); [Chu J et al., 1993](#)), and results in the accumulation of a large number of non-malignant CD4-CD8- T lymphocytes in lymph nodes and spleen ([Morse HC et al., 1982](#); [Budd R et al., 1985](#)). The *lpr* autoimmune syndrome of glomerulonephritis, vasculitis, and arthritis is regularly manifested at an early age in the MRL mouse background, but by contrast, the same mutation causes essentially no autoimmune disease when bred onto the C57BL/6 background. On other backgrounds, such as C3H, the onset is delayed and the autoimmune manifestations are milder than in MRL mice suggesting that modifier genes make a major contribution to the disease phenotype ([Izui S et al., 1984](#); [Davidson WF et al., 1984](#); [Morse HC 3rd et al., 1985](#)).

Peripheral activated T cells from *lpr/lpr* mutant mice that express a reduced number of Fas receptors have a defect in T-cell receptor (TCR)-induced apoptosis. [Dhein et al.](#), propose that TCR-induced apoptosis in activated T cells occurs through a FasL-mediated autocrine suicide ([Dhein et al. in 1995](#)). Their results suggested a

mechanism for suppression of the immune response and for peripheral tolerance by T-cell deletion. [Brunner et al. in 1995](#) provided supporting evidence by showing that the interaction between Fas and FasL inhibits activation-induced apoptosis (AICD). Because T-cell receptor ligation can induce apoptosis in a single T hybridoma cell, [they](#) suggested that the Fas - FasL interaction could induce cell death in a cell-autonomous manner. Likewise, [Ju et al in 1995](#) showed that the interaction between Fas and FasL accounts for activation-induced T-cell death. In the autoimmune-prone MRL/*lpr* mice, as a consequence of the defect in the AICD, CD4-CD8- double-negative (DN) T lymphocytes accumulating in this strain overexpress the FasL. Owing to the massive overexpression of the FasL, the DN T lymphocytes exhibited cytotoxic activity against tumor cells bearing spontaneously, or after transfection, the Fas molecule ([Chu JL et al., 1995](#); [Watanabe D et al., 1995](#)) or against H-2 compatible or incompatible Fas expressing thymocytes or lipopolysaccharide-induced blasts ([Benihoud K et al., 1997](#)). Therefore, the overexpression of FasL by activated MRL/*lpr* lymphocytes could be responsible for a chronic, non-antigen-specific autoimmune attack on organs expressing low levels of the Fas receptor. Indeed, the *lpr* mutation is leaky, and low, but non-negligible, levels of transcription ([Wu J et al., 1993](#); [Kobayashi S et al., 1993](#)) and translation ([Mariani SM et al., 1994](#)) of the wild-type Fas molecule have been reported in this strain, as illustrated by the observation of the existence of non-negligible amounts of Fas on MRL/*lpr* hepatocytes, in contrast to hepatocytes from mice rendered completely Fas-deficient by gene targeting ([Adachi M et al., 1995](#)).

Genetic defects in the Fas - Fas Ligand pathway: in humans

[Rieux-Laucat et al](#) in 1995 analyzed expression of the FAS receptor and its function in 3 children including 2 siblings, with a lymphoproliferative syndrome, 2 of whom also had autoimmune disorders. A large deletion in the FAS gene and no detectable cell surface expression characterized the most affected patient. Clinical manifestations in the 2 sibs were less severe. A deletion within the intracytoplasmic domain of FAS was detected and FAS-mediated apoptosis was impaired. On other hand, 5 unrelated children were described ([Fisher et al. 1995](#)) with a rare autoimmune lymphoproliferative syndrome (ALPS) characterized by autoimmune phenomena, massive nonmalignant lymphadenopathy and expanded populations of CD4⁻CD8⁻ T lymphocytes which evoke a genetic defect in the AICD mechanisms. Each child had defective FAS-mediated T lymphocyte apoptosis associated with a unique, deleterious FAS gene mutation. One mutation appeared to cause a simple loss of function; however, 4 others had a dominant-negative phenotype when coexpressed with normal FAS. Thus, FAS is the cause of this disorder of lymphocyte homeostasis and peripheral self-tolerance. ALPS resemble to *lpr/gld* disease in the mouse (*gld* mice bear mutated genes for FasL). In both the mouse and the human, hypergammaglobulinemia is a prominent feature of the disease. In the mouse, autoantibodies, especially antinuclear antibodies, form immune complexes that are deposited in the kidney to cause glomerulonephritis. Autoantibodies were seen ([Fisher et al., 1995](#)) in only 2 of the ALPS patients, and antinuclear antibodies were not observed. However, one patient developed glomerulonephritis, and all 5 children had autoimmune cytopenias and rashes. In contrast to the mouse *lpr* mutation, which is recessive, simple recessive inheritance was ruled out in all 5 ALPS patients studied because all showed 1 mutated FAS allele and 1 normal allele. In each case, the novel FAS mutation in the affected child was inherited from a carrier parent. Parental genetic mosaicism was observed in the mother of one patient in whom a normal and a mutant FAS allele were observed and whose apoptosis defect was less

marked than that of her affected son. Fisher, suggested that modifier genes make a major contribution to the disease phenotype and account for the fact that the heterozygous parent was unaffected. In the *lpr* mouse, the typical autoimmune syndrome is regularly manifested at an early age in the MRL mouse background, but by contrast, the same mutation causes essentially no autoimmune disease when bred onto the C57BL/6 and C3H background. Thus, it is not surprising that in an outbred human population, individuals bearing the same FAS gene mutation may have dramatically different phenotypes. Defining the additional segregating gene(s) that causes expression of the full manifestations of ALPS in the presence of FAS dysfunction will be important for understanding how FAS participates in immune regulation.

Fas-mediated liver diseases

In normal mice, hepatocytes, which are Fas-expressing cells, are highly sensitive to Fas-mediated apoptosis initiated *in vitro* by an anti-Fas monoclonal antibody. *In vivo* injection of this antibody leads to massive apoptosis in the liver with death of the animal within a few hours ([Ogasawara J et al., 1993](#)). These findings suggest that the Fas antigen is important in programmed cell death in the liver, and may be involved in fulminant hepatitis in some cases. The role of T lymphocytes in hepatocyte destruction during the course of acute viral hepatitis has been suggested based on animal models expressing human hepatitis B virus transgenes ([Ando K et al., 1993](#), [Takahashi H et al., 1995](#)). In patients with acute hepatitis B, a polyclonal and multispecific CTL response to viral polymerase was observed ([Rehermann B et al., 1995](#)). These CTL activities could be mediated, at least in part, by Fas-induced apoptosis. Indeed, a significant increase in Fas mRNA has been detected in the liver during the course of acute liver failure in hepatitis B ([Galle PR et al., 1995](#)) and chronic hepatitis C ([Hiramatsu N et al., 1994](#)) with strong FasL expression on infiltrating lymphocytes ([Galle PR et al., 1995](#)).

[Bobé et al. \(1997\)](#) investigated the consequences of the *in vivo* interaction of lymphocytes overexpressing the FasL with hepatocytes expressing normal amounts of Fas. These experimental conditions were met by creating hematopoietic chimeras by grafting wild-type MRL+/+ with MRL/*lpr* lymphoid cells which overexpress FasL (MRL/*lpr* -> +/+ chimeras). In parallel with elevated serum transaminase levels, histological examination of MRL/*lpr* -> +/+ chimeras livers showed infiltrations of activated lymphocytes (polyclonal population of FasL-expressing T lymphocytes) in periportal areas and intralobular foci, with hepatocytes undergoing apoptosis in their vicinity.

Fas-mediated rheumatoid diseases

Synoviocytes are Fas-expressing cells, particularly in arthritic mice ([Ito MR et al., 1997](#)) and RA patients ([Nakajima T et al., 1995](#)). Indeed, these cells are sensitive *in vitro* to anti-Fas monoclonal antibody-induced apoptosis ([Hasunuma T et al., 1996](#); [Sakai K et al., 1998](#)) particularly in RA synovium ([Asahara H et al., 1996](#)). The Fas receptor has also been detected on human chondrocytes ([Kim HA et al., 1999](#)) and osteoblasts ([Nakashima T et al., 1998](#)). Furthermore, T cells infiltrating the RA affected joints express FasL ([Hoa TT et al., 1996](#); [Sumida T et al., 1997](#)). Soluble Fas receptor, which may inhibit the regulation of these activated T lymphocytes by AICD, has also been observed in the synovial fluid of the inflamed joints of RA patients ([Hasunuma T et al., 1997](#)). These observations suggest that at least two mechanisms may be implicated in RA damage: first, impaired clearance of activated T cells due to a defective step in the Fas-mediated apoptotic pathway; second, overexpression of FasL on synovium-infiltrating lymphocytes. To test this latter

hypothesis, [Bonardelle et al. \(2001\)](#) evaluated the consequences of an *in vivo* interaction between long-lived MRL/*lpr* lymphocytes overexpressing FasL and Fas-expressing synoviocytes of the wild-type MRL strain. These experimental conditions were met in hematopoietic chimeras created by grafting lethally irradiated wild-type MRL+/+ with MRL/*lpr* lymphoid cells (MRL/*lpr* -> +/+ chimeras). MRL/*lpr* -> +/+ chimeras developed severe rheumatoid disease, with synovitis, pannus, bone erosion and periostitis within a few weeks post grafting. In conclusion, there is increasing evidence that derangement of the usually highly controlled apoptotic program is the underlying cause of various diseases.

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