

Role of Fas and RANKL Signaling in Peripheral Immune Tolerance

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Abstract

The death receptor, Fas, has been well-characterized and is a critical factor in apoptosis in immune cells. Fas also has an important role in maintaining immune tolerance as demonstrated in the autoimmune-prone MRL/lpr mouse strain which carries a defect in Fas-mediated apoptosis of T cells. However, the role of Fas-independent apoptosis remains to be characterized in autoimmune diseases. In dendritic cells (DCs), binding of receptor activator of nuclear factor- κ B ligand (RANKL) to RANK perpetuates the survival of mature DCs. However, cross-talk between the RANK/RANKL pathway and Fas-mediated signaling during the function or activation of DCs has not been well-studied. This short communication review describes a mechanism involving interactions between activated DCs and T cells in the autoimmune response of MRL/lpr mice and a novel Fas-independent apoptosis pathway in T cells that maintains peripheral tolerance, and controls autoimmunity in MRL/lpr mice.

Keywords: Fas; T cell; Apoptosis; DC; RANKL; Autoimmunity

The FasL/Fas System in Autoimmunity

The death receptor, Fas, also known as CD95 or tumor necrosis factor receptor superfamily member 6, is expressed extracellularly on various cells and it triggers a signal transduction pathway leading to apoptosis [1,2]. Interaction of Fas with its ligand, FasL (FasL/CD95L), has been shown to regulate numerous physiological and pathological processes *via* programmed cell death [3]. Both beneficial and harmful effects of Fas-mediated apoptosis on the immune system have been characterized [4-6]. Signaling downstream of Fas has also been found to be intricately regulated [7-9].

Studies of autoimmune diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), autoimmune lymphoproliferation syndrome (ALPS), and Sjögrens syndrome (SS) [10,11] have widely used the MRL/lpr mouse strain. This murine model carries a defect in Fas-mediated apoptosis of its T cells which results from a spontaneous mutation in the gene encoding Fas. As a result, onset of autoimmunity in this model is a consistent phenotype [10]. In humans, mutations in the gene encoding Fas occur in patients with ALPS [12,13].

T Cell Apoptosis and Activation-Induced Cell Death (AICD)

Splenomegaly and systemic lymphadenopathy characterize MRL/lpr mice [14-16]. In addition, Fas-mediated apoptosis of peripheral T cells has been shown to be impaired in MRL/lpr mice [10,11]. Fas-FasL interaction results in formation of the death-inducing signaling complex (DISC), comprising an adaptor protein called Fas-associating DD (FADD) and a proenzyme form of caspase-8. Activated initiator caspase-8 and caspase-9 then process and activate the downstream effector caspase-3, -6, and -7, which are responsible for the classical phenotypic changes associated with

apoptosis [17-19]. Proteins of the Bcl-2 family are localized to membranes of distinct organelles including mitochondria. Both the pro-apoptotic (Bax, Bad) and anti-apoptotic (Bcl-2, Bcl-X_L) members of the family can form ion-conducting channels in lipid membranes [20]. The death of peripheral T cells is one of the systems used to maintain immunological tolerance [21]. The mechanism responsible for this process is referred to as AICD, and it mediates the deletion of overactivated or autoreactive T cells in the periphery [22-24]. Since the deletion of peripheral T cells by AICD is impaired in MRL/lpr mice, increased numbers of autoreactive T cells are present and they trigger the induction of autoimmune lesions in multiple organs [10,25].

Dendritic Cells (DCs) and Their Role in Tolerance

In their immature state, DCs are able to take up and present antigen. These cells are referred to as antigen-presenting cells and low numbers of these cells are distributed throughout the tissues of the human body [26]. Following the activation of immature DCs by receptor activator of nuclear factor- κ B (RANK)/RANK ligand (RANKL) [27], CD40/CD40L [28,29], or Toll-like receptor signaling [30,31], DCs achieve a mature state in which they are no longer capable of antigen uptake. However, mature DCs are able to initiate antigen-specific T-cell responses. During the latter process, both major histocompatibility complex (MHC) molecules and costimulatory molecules (e.g., CD80 and CD86) are also up-regulated [32]. It is hypothesized that immature DCs induce antigen-specific tolerance by deleting antigen-specific T cells or inducing regulatory T cells [33]. Thus, DCs have a critical role in coordinating the immune response against non-self and self-antigens. It has been reported that FLIP_L is constitutively expressed in DCs to play an inhibitory role for Fas-mediated apoptosis of DCs [34-36]. Correspondingly, DCs have been found to prime autoreactive T cells and induce the local inflammation of the synovial membrane in RA [37-40]. In addition, antigen-pulsed DCs have been shown to induce disease in experimental autoimmune encephalomyelitis (EAE), a murine model of multiple sclerosis [41]. It has also been shown that

plasmacytoid DCs play a pivotal role in Sjögrens syndrome [42], and that conventional DCs have been demonstrated to be critical for the development of systemic lupus erythematosus in a murine model [43]. However, the capacity for DCs to regulate autoreactive T cells in the periphery remains largely uncharacterized (Figure 1A and B).

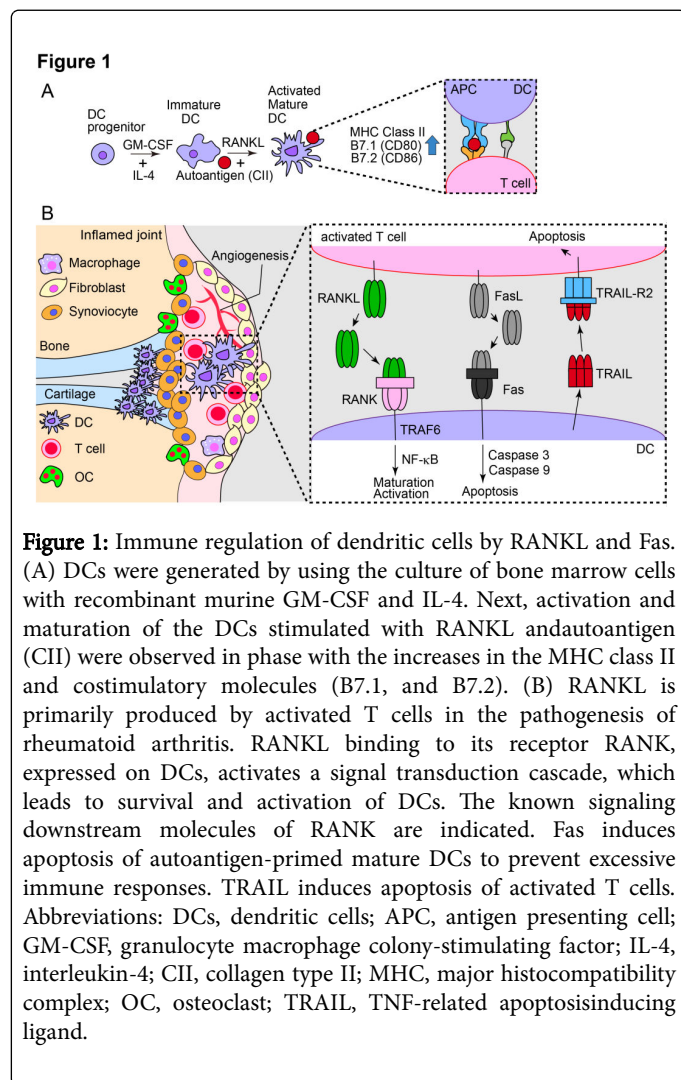


Figure 1: Immune regulation of dendritic cells by RANKL and Fas. (A) DCs were generated by using the culture of bone marrow cells with recombinant murine GM-CSF and IL-4. Next, activation and maturation of the DCs stimulated with RANKL and autoantigen (CII) were observed in phase with the increases in the MHC class II and costimulatory molecules (B7.1, and B7.2). (B) RANKL is primarily produced by activated T cells in the pathogenesis of rheumatoid arthritis. RANKL binding to its receptor RANK, expressed on DCs, activates a signal transduction cascade, which leads to survival and activation of DCs. The known signaling downstream molecules of RANK are indicated. Fas induces apoptosis of autoantigen-primed mature DCs to prevent excessive immune responses. TRAIL induces apoptosis of activated T cells. Abbreviations: DCs, dendritic cells; APC, antigen presenting cell; GM-CSF, granulocyte macrophage colony-stimulating factor; IL-4, interleukin-4; CII, collagen type II; MHC, major histocompatibility complex; OC, osteoclast; TRAIL, TNF-related apoptosis-inducing ligand.

AICD of DCs Mediated by RANK and Fas Signaling

RANKL is a member of the tumor necrosis factor (TNF) protein family and is expressed on osteoblasts, stromal cells, and activated T cells. This type II membrane protein is able to bind the signaling receptor, RANK, as well as osteoprotegerin, a decoy receptor [27,44-47]. RANK is expressed by myelomonocytic cells ranging from osteoclast precursors to mature DCs [44,48]. Mice that do not express RANKL or RANK do not develop mammary glands, they lack lymph nodes, and they exhibit severely reduced osteoclastogenesis and defects in the early differentiation of T and B cells [49,50]. The activated B and CD4+ cells, but not CD8+ T cells, induced osteoclast differentiation in the presence of M-CSF alone, while CD8+ T cells profoundly suppressed osteoclastogenesis [51]. We previously demonstrated that estrogen deficiency induces RANKL expression by CD4+ T cells, and activation of these cells may help accelerate autoimmune arthritis. Estrogenic action also appeared to affect RANKL-mediated

osteoclastogenesis and joint destruction in a mouse model of RA [52]. Furthermore, we recently reported that expression levels of MHC class II B7.1 and B7.2 were higher on bone marrow-derived DCs (BMDCs) obtained from MRL/lpr mice following stimulation by RANKL than on a parallel population of cells obtained from MRL+/+mice [53]. These results, in combination with the observation that the growth, activation, and apoptosis of DCs in the periphery is regulated by crosstalk between Fas and RANKL signaling, support a model in which RANKL/Fas signaling is critical for maintaining immune tolerance by DCs. Thus, AICD of DCs that is associated with RA may be mediated by Fas and RANK signaling pathways (Figure 1B) [53].

Autoimmune Arthritis and DCs

Rheumatoid arthritis (RA) is an autoimmune disease that is characterized by a synovial infiltration of immune cells and chronic inflammation [54]. Correspondingly, many types of immune cells have been implicated in the pathogenesis of RA in both murine models and human patients [45,55]. In particular, interactions between immune cells and osteoclasts (e.g., T-cell priming by activated DCs) may contribute to the pathogenesis of RA [56]. In MRL/lpr mice, receptor RANKL-activated DCs is critical in the pathogenesis of RA [53].

Autoimmunity, TNF-Related Apoptosis Inducing Ligand (TRAIL), and DC Therapy

To date, it has been reported that TRAIL interacts with at least two death receptors, death receptor 4 (DR4, TRAIL-R1) and death receptor 5 (DR5, TRAIL-R2), and also with two decoy receptors, decoy receptor 1 [DcR1, TRAIL-R3, TRID] and decoy receptor 2 [DcR2, TRAIL-R4, TRUNDD] [57-59]. TRAIL, like FasL, induces apoptosis by cross-linking and oligomerizing its receptors and forming a death-inducing signaling complex through recruitment of an adaptor molecule and the initiator caspase-8 and subsequent mitochondria-dependent or independent activation of the downstream effector caspase-3 [60]. In several tumor cell lines, apoptosis *via* TRAIL/TRAIL-R has been reported, particularly involving DR4 and DR5 which possess intracellular death domains that are similar to those of Fas and TNF receptor I [57,61]. Mice deficient in TRAIL exhibit a severe defect in thymocyte apoptosis [62], although the relationship between peripheral T cells undergoing apoptosis and TRAIL/TRAIL-R2 remains unclear. TRAIL-R plays a [63], while DCs overexpressing TRAIL may inhibit the development of CII-induced arthritis [64]. Similarly, while interferon- γ stimulation has been shown to up-regulate TRAIL expression on DCs [65], it remains unclear whether the expression of TRAIL by DCs is regulated by RANK/RANKL signaling. In our previous study, BMDCs that were obtained from MRL/lpr mice had levels of TRAIL expression that were significantly enhanced by RANKL stimulation [66]. Synovial cells from patients with osteoarthritis express undetectable levels of TRAIL-R2, on the other hand synovial cells from patients with RA express abundant levels of TRAIL-R2 [67].

DCs could be localized in lymph nodes 48 hours after transfer, could induce a specific CD4 T cell response, and that T cell expressed peripheral cell autoantigen when DCs were injected into the footpad [68]. On the other hand, intraperitoneal administration of the CII-pulsed DCs led predominantly to migration into the spleen, and TRAIL is expressed on the transfected DCs and induces apoptosis of T cells in the spleen [64]. These observations provide additional support for the use of DC therapies to mediate a therapeutic effect. Recently,

DCs have been used extensively in the treatment of autoimmune diseases with the hope of reversing established pathologic process. For example, repeated injections of DCs induced to maturation by TNF- α have been shown to induce antigen-specific protection against experimental autoimmune encephalomyelitis [41]. Conversely, inflammatory arthritis has been induced in congenic DBA/1 mice following the transfer of collagen-pulsed BMDCs [69]. DCs deficient of NF- κ B, following treatment with oligonucleotides, have been shown to prevent diabetes in NOD mice [69]. Finally, it is likely that more than one autoantigen is involved in human RA, and therefore the choice of the appropriate antigens with which to pulse DCs may present additional challenges.

In conclusion, the repeated transfer of activated Fas-deficient DCs to MRL/*lpr* mice might provide the opportunity for Fas-independent apoptosis of CD4⁺ T cells *via* TRAIL/TRAIL-R2 to provide a therapeutic effect on lymphoproliferation and autoimmune arthritis. Consequently, targeting of this alternative apoptosis pathway may represent a powerful preventive and therapeutic strategy for immune disorders.

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