Review Article

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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-κB 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 lymphoadenopathy 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-κB (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).
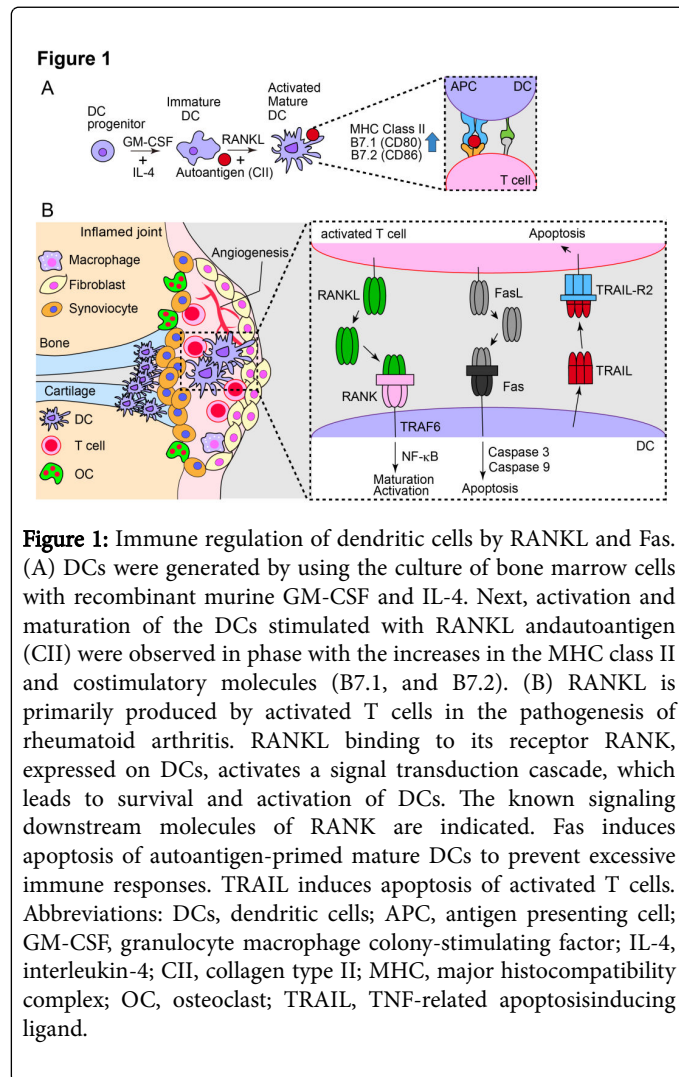
Figure 1: Immune regulation of dendritic cells by RANKL and Fas. (A) DCs were generated by using the culture of bone marrow cells with recombinant murine GM-CSF and IL-4. Next, activation and maturation of the DCs stimulated with RANKL andautoantigen (CII) were observed in phase with the increases in 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 apoptosisinducing 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-κB, 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.

Acknowledgments

References

1. Nagata S, Golstein P (1995) The FAS death factor. Science 267: 1449-1456.

2. Nagata S (1997) Apoptosis by death factor. Cell 88: 355-365.

3. Nagata S (1999) Fas ligand-induced apoptosis. Annu Rev Genet 33: 29-55.

4. Brunner T, Wasem C, Torgler R, Cima I, Jakob S, et al. (2003) Fas (CD95/Apo- ligand regulation in T cell homeostasis, cell-mediated cytotoxicity and immune pathology. Semin Immunol 15: 167-176.

5. Green DR, Ferguson TA (2001) The role of Fas ligand in immune privilege. Nat Rev Mol Cell Biol 2: 917-924.

6. Siegel RM, Chan FK, Chun HJ, Lenardo MJ (2000) The multifaceted role of Fas signaling in immune cell homeostasis and autoimmunity. Nat Immunol 1: 469-474.

7. Tibbetts MD, Zheng L, Lenardo MJ (2003) The death effector domain protein family: regulators of cellular homeostasis. Nat Immunol 4: 404-409.

8. Samali A, Zhivotovsky B, Jones D, Nagata S, Orrenius S (1999) Apoptosis: cell death defined by caspase activation. Cell Death Differ 6: 495-496.

9. Schütze S, Tchikov V, Schneider-Brachert W (2008) Regulation of TNFR1 and CD95 signalling by receptor compartmentalization. Nat Rev Mol Cell Biol 9: 655-662.

10. Steinberg AD (1994) MRL-*lpr/lpr* disease: theories meet Fas. Semin Immunol 6: 55-69.

11. Singer GG, Carrera AC, Marshak-Rothstein A, Martínez C, Abbas AK (1994) Apoptosis, Fas and systemic autoimmunity: the MRL-*lpr/lpr* model. Curr Opin Immunol 6: 913-920.

12. Nagata S (1998) Human autoimmune lymphoproliferative syndrome, a defect in the apoptosis-inducing Fas receptor: a lesson from the mouse model. J Hum Genet 43: 2-8.

13. Rieux-Laucat F, Le Deist F, Fischer A (2003) Autoimmune lymphoproliferative syndromes: genetic defects of apoptosis pathways. Cell Death Differ 10: 124-133.

14. Edwards CK, Zhou T, Zhang J, Baker TJ, De M, et al. (1996) Inhibition of superantigen-induced proinflammatory cytokine production and inflammatory arthritis in MRL-*lpr/lpr* mice by a transcriptional inhibitor of TNF-alpha. J Immunol 157: 1758-1772.

15. Watanabe-Fukunaga R, Brannan CI, Copeland NG, Jenkins NA, Nagata S (1992) Lymphoproliferation disorder in mice explained by defects in Fas antigen that mediates apoptosis. Nature 356: 314-317.

16. Morse HC, Roths JB, Davidson WF, Langdon WY, Fredrickson TN, et al. (1985) Abnormalities induced by the mutant gene, *lpr*. Patterns of disease and expression of murine leukemia viruses in SJL/J mice homozygous and heterozygous for *lpr*. J Exp Med 161: 602-616.

17. Creagh EM (2014) Caspase crosstalk: integration of apoptotic and innate immune signalling pathways. Trends Immunol 35: 631-640.

18. Perl A, Gergely P Jr, Nagy G, Koncz A, Banki K (2004) Mitochondrial hyperpolarization: a checkpoint of T-cell life, death and autoimmunity. Trends Immunol 25: 360-367.

19. Mundle SD, Raza A (2002) Defining the dynamics of self-assembled Fas-receptor activation. Trends Immunol 23: 187-194.

20. Gross A, McDonnell JM, Korsmeyer SJ (1999) BCL-2 family members and the mitochondria in apoptosis. Genes Dev 13: 1899-1911.

21. Krammer PH, Arnold R, Lavrik IN (2007) Life and death in peripheral T cells. Nat Rev Immunol 7: 532-542.

22. Roberts AI, Devadas S, Zhang X, Zhang L, Keegan A, et al. (2003) The role of activation-induced cell death in the differentiation of T-helper-cell subsets. Immunol Res 28: 285-293.

23. Chen Y, Inobe J, Marks R, Gonnella P, Kuchroo VK, et al. (1995) Peripheral deletion of antigen-reactive T cells in oral tolerance. Nature 376: 177-180.

24. Ishimaru N, Yanagi K, Ogawa K, Suda T, Saito I, et al. (2001) Possible role of organ-specific autoantigen for Fas ligand-mediated activation-induced cell death in murine Sjogren's syndrome. J Immunol 167: 6031-6037.

25. Mountz JD, Zhou T, Long RE, Bluethmann H, Koopman WJ, et al. (1994) T cell influence on superantigen-induced arthritis in MRL-*lpr/lpr* mice. Arthritis Rheum 37: 113-124.

26. Merad M, Manz MG (2009) Dendritic cell homeostasis. Blood 113: 3418-3427.

27. Anderson DM, Maraskovsky E, Billingsley WL, Dougall WC, Tometsko ME, et al. (1997) A homologue of the TNF receptor and its ligand enhance T-cell growth and dendritic-cell function. Nature 390: 175-179.

28. Caux C, Massacrier C, Vanbervliet B, Dubois B, Van Kooten C, et al. (1994) Activation of human dendritic cells through CD40 cross-linking. J Exp Med 180: 1263-1272.

29. van Kooten C, Banchereau J (1997) Functions of CD40 on B cells, dendritic cells and other cells. Curr Opin Immunol 9: 330-337.

30. Rescigno M, Martino M, Sutherland CL, Gold MR, Ricciardi-Castagnoli P (1998) Dendritic cell survival and maturation are regulated by different signaling pathways. J Exp Med 188: 2175-2180.

31. Yamamoto M, Sato S, Hemmi H, Sanjo H, Uematsu S, et al. (2002) Essential role for TIRAP in activation of the signalling cascade shared by TLR2 and TLR4. Nature 420: 324-329.

32. Van Gool SW, Vandenberghe P, de Boer M, Ceuppens JL (1996) CD80, CD86 and CD40 provide accessory signals in a multiple-step T-cell activation model. Immunol Rev 153: 47-83.

33. Banchereau J, Steinman RM (1998) Dendritic cells and the control of immunity. Nature 392: 245-252.

34. Ashany D, Savir A, Bhardwaj N, Elkon KB (1999) Dendritic cells are resistant to apoptosis through the Fas (CD95/APO-1) pathway. J Immunol 163: 5303-5311.

35. Willems F, Amraoui Z, Vanderheyde N, Verhasselt V, Aksoy E, et al. (2000) Expression of c-FLIP(L) and resistant to CD95-mediated apoptosis to monocyte- derived dendritic cells: inhibition by bisindolylmaleimide. Blood 95: 3478-3482.

36. Rescigno M, Piguet V, Valzasina B, Lens S, Zubler R, et al. (2000) FAS engagement induces the maturation of dendritic cells (DCs), the release of interleukin (IL)-1 beta, and the production of interferon gamma in the

absence of IL-12 during DC- T cell cognate interaction: a new role for Fas ligand in inflammatory responses. J Exp Med 192: 1661-1668.

37. van Duivenvoorde LM, van Mierlo GJ, Boonman ZF, Toes RE (2006) Dendritic cells: vehicles for tolerance induction and prevention of autoimmune diseases. Immunobiology 211: 627-632.

38. Wenink MH1, Han W, Toes RE, Radstake TR (2009) Dendritic cells and their potential implication in pathology and treatment of rheumatoid arthritis. Handb Exp Pharmacol : 81-98.

39. Thomas R, Davis LS, Lipsky PE (1994) Rheumatoid synovium is enriched in mature antigen-presenting dendritic cells. J Immunol 152: 2613-2623.

40. Liu Z, Xu X, Hsu HC, Tousson A, Yang PA et al. (2003) CII-DC-AdTRAIL cell gene therapy inhibits infiltration of CII-reactive T cells and CII-induced arthritis. J Clin Invest 112: 1332-1341.

41. Menges M, Rössner S, Voigtländer C, Schindler H, Kukutsch NA, et al. (2002) Repetitive injections of dendritic cells matured with tumor necrosis factor alpha induce antigen-specific protection of mice from autoimmunity. J Exp Med 195: 15-21.

42. Arakaki R, Nagaoka A, Ishimaru N, Yamada A, Yoshida S, et al. (2009) Role of plasmacytoid dendritic cells for aberrant class II expression in exocrine glands from estrogen-deficient mice of healthy background. Am J Pathol 174: 1715-1724.

43. Tsokos GC, Lo MS, Costa Reis P, Sullivan KE (2016) New insights into the immunopathogenesis of systemic lupus erythematosus. Nat Rev Rheumatol 12: 716-730.

44. Wong BR, Josien R, Choi Y (1999) TRANCE is a TNF family member that regulates dendritic cell and osteoclast function. J Leukoc Biol 65: 715-724.

45. Yasuda H, Shima N, Nakagawa N, Yamaguchi K, Kinosaki M, et al. (1998) Osteoclast differentiation factor is a ligand for osteoprotegerin/osteoclastogenesis-inhibitory factor and is identical to TRANCE/RANKL. Proc Natl Acad Sci U S A 95: 3597-3602.

46. Lacey DL, Timms E, Tan HL, Kelley MJ, Dunstan CR, et al. (1998) Osteoprotegerin ligand is a cytokine that regulates osteoclast differentiation and activation. Cell 93: 165-176.

47. Simonet WS, Lacey DL, Dunstan CR, Kelley M, Chang MS, et al. (1997) Osteoprotegerin: a novel secreted protein involved in the regulation of bone density. Cell 89: 309-319.

48. Shalhoub V, Elliott G, Chiu L, Manoukian R, Kelley M, et al. (2000) Characterization of osteoclast precursors in human blood. Br J Haematol 111: 501-512.

49. Kong YY, Yoshida H, Sarosi I, Tan HL, Timms E, et al. (1999) OPGL is a key regulator of osteoclastogenesis, lymphocyte development and lymph-node organogenesis. Nature 397: 315-323.

50. Fata JE, Kong YY, Li J, Sasaki T, Irie-Sasaki J, et al. (2000) The osteoclast differentiation factor osteoprotegerin-ligand is essential for mammary gland development. Cell 103: 41-50.

51. Choi Y, Woo KM, Ko SH, Lee YJ, Park SJ, et al. (2001) Osteoclastogenesis is enhanced by activated B cells but suppressed by activated CD8(+) T cells. Eur J Immunol 31: 2179-2188.

52. Yoneda T, Ishimaru N, Arakaki R, Kobayashi M, Izawa T, et al. (2004) Estrogen deficiency accelerates murine autoimmune arthritis associated with receptor activator of nuclear factor-kappa B ligand-mediated osteoclastogenesis. Endocrinology 145: 2384-2391.

53. Izawa T, Ishimaru N, Moriyama K, Kohashi M, Arakaki R, et al. (2007) Crosstalk between RANKL and Fas signaling in dendritic cells controls immune tolerance. Blood 110: 242-250.

54. Firestein GS (2003) Evolving concepts of rheumatoid arthritis. Nature 423: 356-361.

55. McInnes IB, Schett G (2007) Cytokines in the pathogenesis of rheumatoid arthritis. Nat Rev Immunol 7: 429-442.

56. Takayanagi H (2007) Osteoimmunology: shared mechanisms and crosstalk between the immune and bone systems. Nat Rev Immunol 7: 292-304.

57. Pan G, Ni J, Wei YF, Yu G, Gentz R, et al. (1997) An antagonist decoy receptor and a death domain-containing receptor for TRAIL. Science 277: 815-818.

58. Schneider P, Bodmer JL, Thome M, Hofmann K, Holler N, et al. (1997) Characterization of two receptors for TRAIL. FEBS Lett 416: 329-334.

59. Sheikh MS, Huang Y, Fernandez-Salas EA, El-Deiry WS, Friess H, et al. (1999) The antiapoptotic decoy receptor TRID/TRAIL-R3 is a p53-regulated DNA damage-inducible gene that is overexpressed in primary tumors of the gastrointestinal tract. Oncogene 18: 4153-4159.

60. Song K, Chen Y, Goke R, Wilmen A, Seidel C, et al. (2000) Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is an inhibitor of autoimmune inflammation and cell cycle progression. J Exp Med 191: 1095-1104.

61. Sheridan JP, Marsters SA, Pitti RM, Gurney A, Skubatch M, et al. (1997) Control of TRAIL-induced apoptosis by a family of signaling and decoy receptors. Science 277: 818-821.

62. Lamhamedi-Cherradi SE, Zheng SJ, Maguschak KA, Peschon J, Chen YH (2003) Defective thymocyte apoptosis and accelerated autoimmune diseases in TRAIL-/- mice. Nat Immunol 4: 255-260.

63. Zhang XR, Zhang LY, Devadas S, Li L, Keegan AD, et al. (2003) Reciprocal expression of TRAIL and CD95L in Th1 and Th2 cells: role of apoptosis in T helper subset differentiation. Cell Death Differ 10: 203-210.

64. Liu Z, Xu X, Hsu HC, Tousson A, Yang PA, et al. (2003) CII-DC-AdTRAIL cell gene therapy inhibits infiltration of CII-reactive T cells and CII-induced arthritis. J Clin Invest 112: 1332-1341.

65. Fanger NA, Maliszewski CR, Schooley K, Griffith TS (1999) Human dendritic cells mediate cellular apoptosis via tumor necrosis factor-related apoptosis- inducing ligand (TRAIL). J Exp Med 190: 1155-1164.

66. Izawa T, Kondo T, Kurosawa M, Oura R, Matsumoto K, et al. (2012) Fas-independent T-cell apoptosis by dendritic cells controls autoimmune arthritis in MRL/*lpr* mice. PLoS One 7: e48798.

67. Ichikawa K, Liu W, Fleck M, Zhang H, Zhao L, et al. (2003) TRAIL-R2 (DR5) mediates apoptosis of synovial fibroblasts in rheumatoid arthritis. J Immunol 171: 1061-1069.

68. Leung BP, Conacher M, Hunter D, Mclnnes IB, Liew FY, et al. (2002) A novel dendritic cell-induced model of erosive inflammatory arthritis: distinct roles for dendritic cells in T cell activation and induction of local inflammation. J Immunol 169: 7071-7077.

69. Ma L, Qian S, Liang X, Wang L, Woodward JE, et al. (2003) Prevention of diabetes in NOD mice by administration of dendritic cells deficient in nuclear transcription factor-kappaB activity. Diabetes 52: 1976-1985.