NF-κB Activation in T Helper 17 Cell Differentiation

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CD28/T cell receptor ligation activates the NF-κB signaling cascade during CD4 T cell activation. NF-κB activation is required for cytokine gene expression and activated T cell survival and proliferation. Recently, many reports showed that NF-κB activation is also involved in T helper (Th) cell differentiation including Th17 cell differentiation. In this review, we discuss the current literature on NF-κB activation pathway and its effect on Th17 cell differentiation.

INTRODUCTION

NF-κB is activated during immune responses and is important for the expression of immune response related genes including cytokine, chemokine, and adhesion molecule genes (1-3). The NF-κB family is composed of RelA, RelB, c-Rel, p50 (NF-κB1), and p52 (NF-κB2) subunits. The NF-κB transcription factor binds to κB sites as dimers, either homodimers or heterodimers. The NF-κB protein contains N-terminal Rel homology domain (RHD), which makes contact with DNA and supports subunit dimerization. Of the NF-κB subunits, only RelA, RelB, and c-Rel have transactivation domain (TAD) at C-terminus and this TAD domain is important for initiation of target gene transcription (1-3). However, p50 and p52 lack TAD domain. Thus, p50 and p52 can positively regulate gene expression through heterodimerization with TAD containing NF-κB subunits or other regulators (Fig. 1).

Antigen recognition by T cell receptor (TCR) induces activation of many transcription factors including NF-κB, NF-AT, p65 (RelA), p50 (NF-κB1), p52 (NF-κB2), RelB, and c-Rel (Fig. 1). NF-κB complexes are inactive in most cells, and these complexes are located in the cytoplasm in a complex with inhibitory IκB proteins (IκBα, IκBβ, IκBε, IκBζ, p100, p105, Bcl3, and IκBns). NF-κB pathway activating signals including cytokine receptor signals and antigen receptor signals activate the IκB kinase (IKK) complex, which phosphorylates IκB. This phosphorylation induces IκB degradation, which leads to NF-κB complex translocation to the nucleus. Once in the nucleus, the NF-κB complex activates target gene transcription (1-3).

NF-κB PATHWAY IN T CELL ACTIVATION

Antigen recognition by T cell receptor (TCR) induces activation of many transcription factors including NF-κB, NF-AT, p65 (RelA), RelB, c-Rel, NF-κB2 (precursor, p100; mature form, p52), and NF-κB1 (precursor, p105; mature form, p50).

Keywords: NF-κB, Th17, T cell receptor, Autoimmune

Abbreviations: RHD, rel homology domain; TAD, transactivation domain; TCR, T cell receptor; PI3K, phosphoinositide 3-kinase; PDK1, phosphoinositide-dependent kinase 1; CBM, Carma1-Bcl10-Malt1; GLK, GCK-like kinase; Th, T helper; RA, rheumatoid arthritis; IBD, inflammatory bowel disease; SLE, systemic lupus erythematosus; PG,E2, prostaglandin E2.

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Figure 2. T cell receptor-mediated NF-κB activation. T cell receptor complex and CD28-mediated PDK1 activation are important for signaling complex formation composed of PKCθ, Carma1, Bcl10, and Malt1. This signaling complex leads to IKK complex activation and subsequently activates NF-κB during T cell activation by antigen.

CD4 T cells play an essential role in the adaptive immune response. During the adaptive immune response, activated CD4 T cells differentiate into T helper (Th) 1, Th2 or Th17 effector cells. Th1 cells are important in host defense against intracellular pathogens and Th2 cells are involved in allergic immune responses and defense against parasite infections. Th17 cells play an important role in host defense against extracellular pathogens and fungal infections. Furthermore, Th1 and Th17 cells are important in intestinal immune responses. During CD4 T cell differentiation, IL-6 and TGF-β
are important for Th17 cell differentiation. IL-23 is also involved in Th17 cell differentiation (23). In addition to the direct effect of IL-23 on Th17 cell differentiation, IL-23 stimulates intestinal TCRγδ T cells, invariant natural killer T cells (iNKT), and intestinal innate-like T cells to secrete cytokines related to Th17 differentiation (24). In addition to TGF-β and IL-23, IL-6 is also important for Th17 differentiation. However, while TGF-β negatively regulates human Th17 cell differentiation, this cytokine is important for Th17 cell differentiation in murine Th17 differentiation (25-27). During Th17 cell differentiation, the transcription factors RORγt, RORα, IRF4, and STAT3 are important for effector T cell differentiation. However, IFN-γ, IL-2, and IL-4 negatively regulate Th17 cell differentiation (28,29).

**Th17 CELLS IN AUTOIMMUNE DISEASE**

Differentiated Th17 cells produce proinflammatory cytokines such as IL-17A, IL-17F, IL-21, TNF, and GM-CSF (5,50,51). These cytokines are important in host defense against extracellular bacteria through acute immune responses (32). In addition, Th17 cells are involved in the development of autoimmune diseases including rheumatoid arthritis (RA), inflammatory bowel disease (IBD), and multiple sclerosis (26,33).

It has been suggested that unbalanced immune responses can induce inflammatory diseases such as IBD. The detailed mechanism of IBD induction, including Crohn’s disease and ulcerative colitis, has not been clarified (34-36); however, uncontrolled T cell activation and biased effector T cell (Th1, Th2, and Th17 cells) differentiation have been suggested as causative factors. Unbalanced production of Th17-related cytokines is also involved in the induction of IBD and other autoimmune disease; Th17 cells produce cytokines including IL-17A, IL-17F, IL-21, and IL-22 (37,38). IL-17 is the representative cytokine produced by Th17 cells and is involved in RA, asthma, and systemic lupus erythematosus (SLE) development. A number of studies have investigated the role of IL-17A in intestinal inflammation, and showed that IL-17A is overproduced in patients with Crohn’s disease and ulcerative colitis (39-42). In addition, IL-17 family cytokines are also increased in patients with autoimmune diseases including RA, asthma, and SLE (43-45). IL-17 and IL-23R genomic DNA sequence analysis found polymorphic regions related to IBD induction (46,47). In addition, IL-21 produced by Th17 cells was found to be involved in exacerbation of IBD (48,49). Furthermore, IL-21 gene deleted mice are resistant to Th1/Th17 cell-mediated colitis induction (50).

**EXTRINSIC EFFECT OF NF-κB ACTIVATION ON Th17 CELL DIFFERENTIATION**

The NF-κB pathway regulates antigen presenting cell functions and affects CD4 T cell differentiation into Th effector cells (51,52). Dendritic cells are the most important antigen presenting cells for Th cell differentiation. RelA deficiency reduced IL-1α, IL-1β, and IL-6 production from dendritic cells in response to LPS stimulation (53). In fact, these cytokines are involved in Th17 cell differentiation (25). In inflammatory responses, prostaglandin E2 (PGE2), an endogenous lipid mediator, enhances the production of IL-1β and TNF-α from bone marrow derived dendritic cells. In addition, PGE2 reduces the level of IL-12, but increases the level of IL-23 production. In addition to changes in cytokine production, PGE2 affects the expression of TLR-4, 2, and 9, IL-1R-associated kinase 1 (IRAK1), IKK, and p38 activator (MKK3), which are important components of the NF-κB activation pathway in dendritic cells. In addition, PGE2 reduces the level of IL-12, but increases the level of IL-23 production. In addition to changes in cytokine production, PGE2 affects the expression of TLR-4, 2, and 9, IL-1R-associated kinase 1 (IRAK1), IKK, and p38 activator (MKK3), which are important components of the NF-κB activation pathway in dendritic cells. Moreover, PGE2 treatment of bone marrow derived dendritic cells increases Th17 cell differentiation in vitro (54). Thus, it is suggested that NF-κB modulation in antigen presenting cells can also affect Th17 cell differentiation.

**INTRINSIC EFFECT OF NF-κB ACTIVATION ON Th17 CELL DIFFERENTIATION**

Binding of RORγt and RORγ to IL-17A and IL-17F promoters regulates their expression, which is important for Th17 differentiation. It has been shown that NF-κB subunits such as p65 and c-Rel are localized in the RORγt and RORγ promoters and affect RORγt and RORγ gene expression, Thus, it has been suggested that NF-κB activation is important for Th17 differentiation (55). Also, IKK β can stimulate PKCθ-mediated STAT3 promoter activation. This promoter activation is essential for Th17 cells differentiation (56). During T cell activation, MalT1 is an important component of the NF-κB activation pathway through regulation of IKK activation. In vitro conditions, naïve T cell differentiation
into Th17 cells is decreased by Mal1 deficiency (57). In addition, Carma1, which is adaptor protein for TCR-mediated NF-κB activation, is needed for expressions of IL-17A, IL-17F, IL-21, IL-22, IL-23R, and CCR6. Carma1 deficiency also blocks Th17 cell development because chromatin loci of Th17 effector molecules cannot form open conformation, but transcription factors, which are needed for Th17 cells development, were normally expressed (58). In addition, overexpression of calpastatin mimetic domain, which is a natural inhibitor of calpain, also decreased Th17 cell differentiation through stabilization of IκBα and subsequent inhibition of NF-κB activation (59). In addition, one recent report described an important role for IκBζ in Th17 differentiation, and showed that IκBζ acts with the nuclear orphan receptors RORγ and RORα to promote IL-17A gene expression (60). Thus, many data support the importance of NF-κB activation in Th17 cell differentiation.

However, recently, negative results were also reported. IL-2 is secreted from activated T cells, and acts as a negative regulator of Th17 cell differentiation (61). In the above report, c-Rel was suggested as a positive regulator of Th17 cell differentiation, c-Rel deficiency in T cells decreases IL-2 production from activated T cells. However, this condition did not affect Th17 cell differentiation. In the report, even though IL-2 was added in Th17 cell differentiation conditions, it did not affect Th17 cell differentiation, IRF-4 is a positive regulator of Th17 cell differentiation; however, it was not affected by c-Rel deficiency. Thus, the report argued that c-Rel is not involved in Th17 cell differentiation (62). It has been reported that USP18 regulates the TAK1-TAB1 complex, which is known as NF-κB pathway. USP18 deficient T cells showed NF-κB hyperactivation, and subsequently increased the level of IL-2 secretion. This dysregulation of NF-κB reduced Th17 cell differentiation (63).

CONCLUSION

NF-κB activation is important during T cell activation and for cytokine gene expression in antigen presenting cells. NF-κB activation-mediated Th17 cell cytokine gene expression is important for Th17 cell differentiation; however, different experimental systems showed different roles of antigen receptor-mediated NF-κB activation in Th17 cell differentiation (Fig. 3). Thus, deciphering the role of NF-κB in each of the Th17 cell differentiation conditions, such as different disease states, is an area of great interest.
7. Kane, I., P., J. Lin, and A. Weiss. 2002. It's all Rel-ative: NF-kappaB and CD28 costimulation of T-cell activation, Trends Immunol. 23: 413-420.
8. Farcwirth, K. A., J. I. Riley, M. H. Harris, R. V. Parry, J. C. Ruthmell, D. R. Pias, R. I. Elstrom, C. H. June, and C. B. Thompson. 2002. The CD28 signaling pathway regulates glucose metabolism, Immunity 16: 769-777.
9. Pages, F., M. Raguenieau, R. Rottapel, A. Truneh, J. Nunes, J. Imbert, and D. Olive. 1994. Binding of phosphatidylinositol-3-OH kinase to CD28 is required for T-cell signalling, Nature 369: 327-329.
10. Pagan, A. J., M. Pepper, H. H. Chu, J. M. Green, and M. K. Jenkins. 2012. CD28 promotes CD4+ T cell clonal expansion during infection independently of its YMNM and PYAP motifs, J. Immunol. 189: 2099-2107.
11. Sanchez-Lockhart, M., E. Marin, B. Graf, R. Abe, Y. Harada, C. E. Sedwick, and J. Miller. 2004. Cutting edge: CD28-mediated transcriptional and posttranscriptional regulation of IL-2 expression are controlled through different signaling pathways, J. Immunol. 173: 7120-7124.
12. Yokosuka, T., W. Kobayashi, K. Sakata-Sogawa, M. Takamatsu, A. Hashimoto-Tane, M. I. Dustin, M. Tokunaga, and T. Saito. 2008. Spatiotemporal regulation of T cell costimulation by TCR-CD28 microclusters and protein kinase C theta translocation, Immunity 29: 589-601.
13. Park, S., G., J. Schulze-Luehrman, M. S. Hayden, N. Hashimoto, W. Ogawa, M. Kasuga, and S. Ghosh. 2009. The kinase PKD1 integrates T cell antigen receptor and CD28 coreceptor signaling to induce NF-kappaB and activate T cells, Nat. Immunol. 10: 158-166.
14. Narayan, P., B. Holt, R. Tosti, and L., P. Kane. 2006. CARMA1 is required for Akt-mediated NF-kappaB activation in T cells. Mol. Cell. Biol. 26: 2327-2336.
15. Matsumoto, R., D. Wang, M. Blonska, H. Li, M. Kobayashi, B. Pappu, Y. Chen, D. Wang, and X. Lin. 2005. Phosphorylation of CARMA1 plays a critical role in T cell receptor-mediated NF-kappaB activation, Immunity 23: 575-585.
16. Garcon, F., D. T. Patton, J. L. Emery, E. Hirsch, R. Rottapel, T. Sasaki, and K. Okkenhaug. 2008. CD28 provides T-cell costimulation and enhances PTK9 activity at the immune synapse independently of its capacity to interact with the p85/p110 heterodimer, Blood 111: 1464-1471.
17. Dodson, L. F., J. S. Boomer, C. M. Deppong, D. D. Shah, J. Sim, T. L. Bricker, J. H. Russell, and J. M. Green. 2009. Targeted knock-in mice expressing mutations of CD28 reveal an essential pathway for costimulation, Mol Cell. Biol. 29: 3710-3721.
18. Villalba, M., K. Bi, J. Hu, Y. Altman, P. Bushway, E. Reits, J. Neefjes, G. Baier, R. T. Abraham, and A. Altman. 2002. Translocation of PKC-theta in T cells is mediated by a non-JNK-dependent pathway, but does not absolutely require phospholipase C, J. Cell. Biol. 157: 253-263.
19. Kang, J. A., S. P. Jeong, D. Park, M. S. Hayden, S. Ghosh, and S. G. Park. 2013. Transition from heterotypic to homotypic PDK1 homodimerization is essential for TCR-mediated NF-kappaB activation, J. Immunol. 190: 4508-4515.
20. Huang, H. C., J. I. Lan, D. Y. Chen, C. Y. Yang, Y. M. Chen, J. P., Li, C. Y. Huang, P. E. Liu, X. Wang, and T. H. Tan. 2011. The kinase GLK controls autoimmunity and NF-kappaB signaling by activating the kinase PKC-theta in T cells, Nat. Immunol. 12: 1113-1118.
21. Romagnani, S., 1994. Lymphokine production by human T cells in disease states, Ann. Rev. Immunol. 12: 227-257.
22. Korn, T., E. Bettelli, M. Oukka, and V. K. Kuchroo. 2009. IL-17 and Th17 Cells. Ann. Rev. Immunol. 27: 485-517.
23. Ahsen, P. P., A. Izucik, K. J. Maloy, and F. Powrie. 2008. The interleukin-23 axis in intestinal inflammation, Immunity 28: 147-159.
24. Gua, D. J., and C. M. Tato. 2010. Inmate IL-17-producing cells: the sentinels of the immune system, Nat. Rev. Immunol. 10: 479-489.
25. Laurence, A. and J. J. O'Shea. 2007. TH17 differentiation: of mice and men, Nat. Immunol. 8: 903-905.
26. Acosta-Rodriguez, E. V., G. Napolitani, A. Lanzavecchia, and F. Sallusto. 2007. Interleukin17-producing beta cells and 6 but not transforming growth factor-beta are essential for the differentiation of interleukin17-producing human T helper cells, Nat. Immunol. 8: 942-949.
27. Chen, Z., C. M. Tato, I. Muul, A. Laurence, and J. J. O'Shea. 2007. Distinct regulation of interleukin17 in human T helper lymphocytes, Arthritis Rheum. 56: 2936-2946.
28. Harrington, L. E., R. D. Hatton, P. R. Mangan, H. Turner, T. L. Murphy, K. M. Murphy, and C. T. Weaver. 2005. Interleukin 17-producing CD4+ effecter T cells develop via a lineage distinct from the T helper type 1 and 2 lineages, Nat. Immunol. 6: 1123-1132.
29. Park, H., Z. Li, X. O. Yang, S. H. Chang, R. Nurieva, Y. H. Wang, Y. Wang, L. Hood, Z. Zhu, Q. Tian, and C. Dong. 2005. A distinct lineage of CD4 T cells regulates tissue inflammation by producing interleukin 17, Nat. Immunol. 6: 1133-1141.
30. Littman, D. R., and A. Y. Rudensky. 2010. Th17 and regulatory T cells in mediating and restraining inflammation, Cell 140: 849-858.
31. El-Behi, M., B. Ciric, H. Dai, Y. Yan, M. Cullimore, F. Safavi, G. X. Zhang, B. N. Dittel, and A. Rostami. 2011. The encephalitogenicity of TH17 cells is dependent on IL-17 and IL-23-induced production of the cytokine GM-CSF. Nat. Immunol. 12: 508-515.
32. Cooke, A. 2006. Th17 cells in inflammatory conditions. Rev. Diabet. Stud. 5: 72-75.
33. Kraner, J. M., and S. I. Gaffen. 2007. Interleukin-17: a new paradigm in inflammation, autoimmunity, and therapy. J. Periodontol. 78: 1083-1093.
34. Kasler, A., S. Ziegler, and R. S. Blumberg. 2010. Inflammatory bowel disease, Ann. Rev. Immunol. 28: 573-621.
35. Chebotar, I. V., M. I. Zaslavskaia, T. M. Konyshkina, and A. N. Maiarzksi, 1991. IgG- and C3-dependent adhesion of neutrophils in systems with allogeneic and xenogeneic ligands, Biol. Ekol. Med. 112: 403-404.
36. Xavier, R. J., and D. K. Podolsky. 2007. Unravelling the pathogenesis of inflammatory bowel disease, Nature 448: 427-434.
37. Zhou, L., L. I. Ivanov, R. Spolski, R. Min, K. Shenderev, T. Egawa, D. E. Levy, W. J. Leonard, and D. R. Littman, 2007.
IL-6 programs TH17 cell differentiation by promoting sequential engagement of the IL-21 and IL-23 pathways, Nat. Immunol. 8: 967-974.

38. Dong, C. 2008. TH17 cells in development: an updated view of their molecular identity and genetic programming. Nat. Rev. Immunol. 8: 357-348.

39. Kobayashi, T., S. Okamoto, T. Hisamatsu, N. Kamada, H. Chinen, R. Saito, M. T. Kitazume, A. Nakazawa, A. Sugita, K. Koganei, K. Isobe, and T. Hibi. 2008. IL23 differentially regulates the Th1/Th17 balance in ulcerative colitis and Crohn's disease. Gut 57: 1682-1689.

40. Fujino, S., A. Andoh, S. Bamba, A. Ogawa, K. Hata, Y. Araki, T. Bamba, and Y. Fujiyama. 2003. Increased expression of interleukin 17 in inflammatory bowel disease. Gut 52: 382-388.

41. Zhang, Z., M. Zheng, J. Bindas, P. Schwarnberger, and J. K. Kolls. 2006. Critical role of IL-17 receptor signaling in acute TNBS-induced colitis. Inflamm. Bowel Dis. 12: 786-794.

42. Park, S. G., R. Mathur, M. Long, N. Hosh, L. Hao, M. S. Koletzko, M. Folwaczny, P. Lohse, B. Goke, T. Ochsenkuhn, K. Aoki, K. Ohya, A. M. Jetten, S. Akira, T. Muta, and H. Takayanagi. 2010. IkappaBzeta regulates T(H)17 development via the NF-kappaB pathway in lymphocyte development and function. Cold Spring Harb. Perspect. Biol. 2: a001182.

43. Kraynall, T., I. J. H. Yen, H. Jing, and D. Ganex. 2008. In vitro differentiation of dendritic cells in the presence of prostataglandin E2 alters the IL-12/IL-23 balance and promotes differentiation of Th17 cells. J. Immunol. 181: 721-735.

44. Ruan, Q., Y. Kameswaran, Y. Zhang, S. Zheng, J. Sun, J. Wang, J. DeVilglis, H. G., Liou, A. A. Beg, and Y. H. Chen. 2011. The Th17 immune response is controlled by the Rel-RORgamma-RORgamma T transcriptional axis. J. Exp. Med. 208: 2321-2333.

45. Kim, S. W., E. S. Kim, C. M. Moon, J. J. Park, T. I. Kim, W. H. Kim, and J. H. Cheon. 2011. Genetic polymorphisms of IL-18 and IL-17A and novel insights into their associations with inflammatory bowel disease. Gut 60: 1527-1536.

46. Glas, J., J. Stallhofer, S. Ripke, M. Wettke, S. Pfennig, W. Klein, J. T. Epplen, T. Griga, U. Schieman, M. Lacher, S. Koletzko, M. Foltaczky, P. Loche, B. Goke, T. Ochsenkuhn, B. Muller-Mylodos, and S. Brand. 2009. Novel genetic risk markers for ulcerative colitis in the IL2/IL21 region are in epistasis with IL23R and suggest a common genetic background for ulcerative colitis and celiac disease. Am. J. Gastroenterol. 104: 1737-1744.

47. Monteleone, G., G. I. Monteleone, D. Piran, Y. Veccchio Blanco, R. Caruso, R. Tersigni, I. Alessandroni, I. Biancone, G. C. Naccari, T. T. MacDonald, F. Pallone, 2005. Interleukin-21 enhances T-helper cell type I signaling and interferon-gamma production in Crohn's disease. Gastroenterology 128: 687-694.

48. Sarra, M. I. Monteleone, C. Stolfi, M. C. Fantini, P. Sileri, G. Sica, R. Tersigni, T. T. MacDonald, F. Pallone, and G. Monteleone. 2010. Interferon-gamma-expressing cells are a major source of interleukin-21 in inflammatory bowel disorders. Inflamm. Bowel Dis. 16: 1332-1339.

49. Stolfi, C., A. Rizzo, E. Franze, A. Rotondi, M. C. Fantini, M. Sarra, R. Caruso, I. Monteleone, P. Sileri, I. Franceschilli, F. Caprioli, S. Ferrero, T. T. MacDonald, F. Pallone, and G. Monteleone. 2011. Involvement of interleukin-21 in the regulation of colitis-associated colon cancer. J. Exp. Med. 208: 2279-2290.

50. Ouea, F., J. Arron, Y. Zheng, Y. Choi, and A. A. Beg. 2002. Dendritic cell development and survival require distinct NF-kappaB subunits. Immunity 16: 257-270.

51. O'Keefe, M. R., J. G. Grumont, H. Hochrein, M. Fuchsberger, R. Gugasyan, D. Vermec, K. Shottman, and S. Gerondakis. 2005. Distinct roles for the NF-kappaB1 and c-Rel transcription factors in the differentiation and survival of plasmacytoid and conventional dendritic cells activated by TLR9 signals. Blood 106: 3457-3464.

52. Gerondakis, S., and U. Siebenlist. 2010. Roles of the NF-kappaB pathway in lymphocyte development and function. Cold Spring Harb. Perspect. Biol. 2: a000182.

53. Molinero, L. L., A. Cubre, C. Mora-Solano, Y. Wang, and M. L. Alegrè. 2012. Protein kinase C-beta promotes Th17 differentiation via upregulation of Stat3. J. Immunol. 188: 5887-5897.

54. Brustle, A., D. Brenner, C. B. Knobbe, P. A. Lang, C. Ruan, Q., V. Kameswaran, Y. Zhang, S. Zheng, J. Sun, J. Wang, J. DeVilglis, H. Liou, A. A. Beg, and Y. H. Chen. 2011. The Th17 immune response is controlled by the Rel-RORgamma-RORgamma T transcriptional axis. J. Exp. Med. 208: 2321-2333.

55. Kwon, M. J., I. Ma, Y. Ding, R. Wang, and Z. Sun, 2012. Protein kinase C-beta promotes Th17 differentiation via upregulation of Stat3. J. Immunol. 188: 5887-5897.

56. Khayrullina, T., J. H. Yen, H. Jing, and D. Ganex. 2008. In vitro differentiation of dendritic cells in the presence of prostataglandin E2 alters the IL-12/IL-23 balance and promotes differentiation of Th17 cells. J. Immunol. 181: 721-735.

57. Ruan, Q., Y. Kameswaran, Y. Zhang, S. Zheng, J. Sun, J. Wang, J. DeVilglis, H. G., Liou, A. A. Beg, and Y. H. Chen. 2011. The Th17 immune response is controlled by the Rel-RORgamma-RORgamma T transcriptional axis. J. Exp. Med. 208: 2321-2333.

58. Molinero, L. L., A. Cubre, C. Mora-Solano, Y. Wang, and M. L. Alegrè. 2012. T cell receptor/CARMA1/NF-kappaB signaling controls T-helper (Th) 17 differentiation. Pro. Natl. Acad. Sci. USA 109: 18529-18534.

59. Igushi-Hashimoto, M., T. Usui, H. Yoshifuji, M. Shimizu, S. Kobayashi, Y. Ito, K. Murakami, A. Shiomi, N. Yukawa, D. Kawabata, T. Nojima, K. Ohmura, T. Fujii, and T. Mimori. 2011. Occlusal expression of a minimal domain of calpastatin suppresses IL-6 production and Th17 development via reduced NF-kappaB and increased STAT5 signals. Plos one 6: e27020.

60. Okamoto, K., Y. Iwai, M. Oh-Hora, M. Yamamoto, T. Morio, K. Aoki, K. Ohya, A. M. Jetten, S. Akira, T. Muta, and H. Takayanagi. 2010. IkappaBzeta regulates Th17 development by cooperating with ROR nuclear receptors. Nature 464: 1381-1385.

61. Stockinger, B. 2007. Good for Goose, but not for Gander: IL-2 interferes with Th17 differentiation, Immunity 26: 278-279.

62. Viselkova, A., M. Huber, A. Hellhund, E. Bothur, K. Reinhard, N. Bollig, N. Schmidt, T. Joeris, M. Lohoff, and U. Steinhoff. 2010. c-Rel is crucial for the induction of Fospl(+) regulatory CD(4(+)) T cells but not Th17 cells, Eur. J. Immunol.
Liu, X., H. Li, B. Zhong, M. Blonska, S. Gorjestani, M. Yan, Q. Tian, D. E. Zhang, X. Lin, and C. Dong. 2013. USP18 inhibits NF-kappaB and NFAT activation during Th17 differentiation by deubiquitinating the TAK1-TAB1 complex. *J. Exp. Med.* 210: 1575-1590.