

Review article

Interleukin-12 family members and type I interferons in Th17-mediated inflammatory disorders

Cytokines produced by antigen-presenting cells govern the fate of helper T-cell responses. Herein, we review the impact of interleukin (IL)-23 and IL-27 on the outcome of T-helper (Th) 17 cell responses and discuss their impact in the pathogenesis of T-cell-mediated inflammatory disorders of autoimmune or allergic origin. We then discuss how type I interferons might influence the course of autoimmune diseases by tipping the balance between IL-12 family members.

S. Goriely, R. Cavoy, M. Goldman

Institute for Medical Immunology, Université Libre de Bruxelles, Charleroi, Belgium

Key words: autoimmunity; interferon; interleukin-27; regulatory T cells; T-helper 17.

Michel Goldman
Institute for Medical Immunology
Université Libre de Bruxelles
8 rue Adrienne Bolland
B-6041 Charleroi
Belgium

Accepted for publication 17 October 2008

The functional subdivision of CD4 T-helper subsets in Th1 and Th2 cells has dominated T-cell biology during the last two decades. The Th2 subset, characterized by the secretion of interleukin (IL)-4, IL-5 and IL-13, mediates anti-helminth response and allergic reactions. In contrast, the Th1 subset, which produces interferon (IFN)- γ , mediates cellular response against intracellular pathogens. Until recently, Th1 effector cells were held responsible for the development of the most cell-mediated inflammatory disorders (1). This concept has largely been revisited since the discovery of the new Th17 effector subset. Indeed, several experimental studies and clinical investigations confirmed that IL-23/Th17 axis rather than IL-12/Th1 subset mediates inflammation of autoimmune or infectious origin (2). The generation of IL-23p19^{-/-} mice clearly indicated that IL-23 rather than IL-12 plays a crucial role in the development of a growing number of autoimmune and inflammatory models, including experimental allergic encephalomyelitis (EAE), collagen-induced arthritis (CIA), psoriasis and chronic intestinal inflammation (3–6). These studies have questioned the role of IL-12-mediated Th1 response in autoimmune inflammation. As extensively reviewed (7–9), our knowledge on the cytokine networks responsible for the differentiation of Th17 from naïve mouse or human precursors has rapidly evolved. In the mouse, both transforming growth factor (TGF)- β and IL-6 are critical for the commitment of the Th17 pathway (10–12). Both factors synergize for the induction of the transcription factor ROR γ t (13). In addition, other inflammatory

cytokines, such as IL-1 β and TNF- α further enhance Th17 differentiation. Autocrine production of IL-21, a cytokine that is implicated in the generation of T follicular helper cells, also plays an important role in ROR γ t and IL-17 expression (14, 15). The same cytokines contribute to the differentiation of human Th17 cells, although to different extent. IL-1 β was found to be an important inducer of Th17 cells (16, 17). The direct role of TGF- β is still controversial and may depend on the origin of T cells and culture conditions. As TGF- β strongly inhibits the development of both Th1 and Th2 cells, it might indirectly favour the expansion of Th17 cells. Interestingly, combination of IL-1 β and IL-23 promotes IL-17 production and leads to the development of both Th17 and Th1/Th17 cells. The latter cells express both ROR γ t and T-bet and are also largely found when derived from patients with Crohn's disease (18). Thus, unlike mouse cells, human Th17 cells might share some developmental features with Th1 cells. Th17 differentiation is tightly controlled; IL-12, IFN- γ and IL-4 inhibit Th17 differentiation for both mouse and human cells (16, 18, 19). Strategies that augment regulatory T cell (Treg) activity are considered for treatment of autoimmune disease. However, unlike Th1 and Th2 cells, once differentiated, recent evidence suggests that Th17 cells are poorly responsive to the suppressive action of Tregs (18, 20, 21). Thus, for the development of therapies that would target differentiated cells, it is critical to decipher how effector functions of memory Th17 cells can be modulated. In the light of these recent findings, we review

the complex role of IL-12/IFN- γ , IL-27 and type I IFN in promoting and counterbalancing autoimmune inflammation.

Th17 cells and IL-12 family members: revisiting the role of inflammatory cytokines in autoimmunity and allergy

The discovery of Th17 cells has questioned the pathogenic role of the Th1 cells in autoimmunity. It is still unclear whether the pathogenic role previously attributed to the IL-12/IFN- γ axis is solely mediated by the IL-23/IL-17 pathway or if both Th1 and Th17 effectors contribute to inflammation. Most evident findings on the exclusive pathogenic role of Th17 effectors have been obtained from animal models using immunization in complete Freund adjuvant. Adoptive transfer of Th cell lines or the use of other immunization protocols indicates that Th1 cells can also promote inflammation of Th17 effectors independently (22, 23). Furthermore, despite *in vitro* mouse data, it is also clear that at the site of inflammation, e.g. in the course of EAE or active Crohn's disease, Th cells can produce both IL-17 and IFN- γ (11, 18, 24). In keeping with this notion, in *Helicobacter hepaticus*-induced T-cell-dependent colitis, both IL-17 and IFN- γ responses synergize to drive maximal intestinal inflammation (25). Interestingly, myelin-reactive Th17 cells were unable to access the central nervous system (CNS) unless inflammation was previously established by Th1 cells (26). Thus, in various settings, Th1 and Th17 effectors seem to collaborate to the development of autoimmunity. Although the involvement of the IL-23/IL-17 axis in allergic disorders remains to be clarified, there is evidence that Th17 cells participate in the pathogenesis of bronchial asthma – especially when associated with neutrophilic inflammation – in allergic rhinitis and contact dermatitis (reviewed in 27).

It is clear that IFN- γ also displays immunomodulatory functions. Deletion of the *IL-12p35*, *IFN- γ* or *IL-12R β 2* genes or administration of anti-IFN- γ antibodies leads to increased severity of EAE and CIA, suggesting a protective rather than a causative role of the IL-12p70/IFN- γ axis in this type of inflammatory disorders (3, 28, 29). Several mechanisms have been implicated in the protective effect of IFN- γ . Th17 lineage commitment requires the presence of TGF- β , IL-6 and autocrine IL-21 production (12, 30). Interferon- γ was shown to inhibit directly Th17 differentiation (19). Along the same line, production of IFN- γ by CD8 T-cells dampens IL-17-mediated experimental autoimmune myocarditis (31). In addition, during EAE, IFN- γ was found to be required for the conversion of CD4⁺CD25⁻ T cells into CD4⁺ Tregs (29). Interferon- γ also directly acts on oligodendrocytes, leading to the induction of the endoplasmic reticular stress response pathway, and allowing the cells to maintain functional myelin sheaths (32). In the context of alloreactivity, rapid and transient production of IFN- γ by Treg themselves

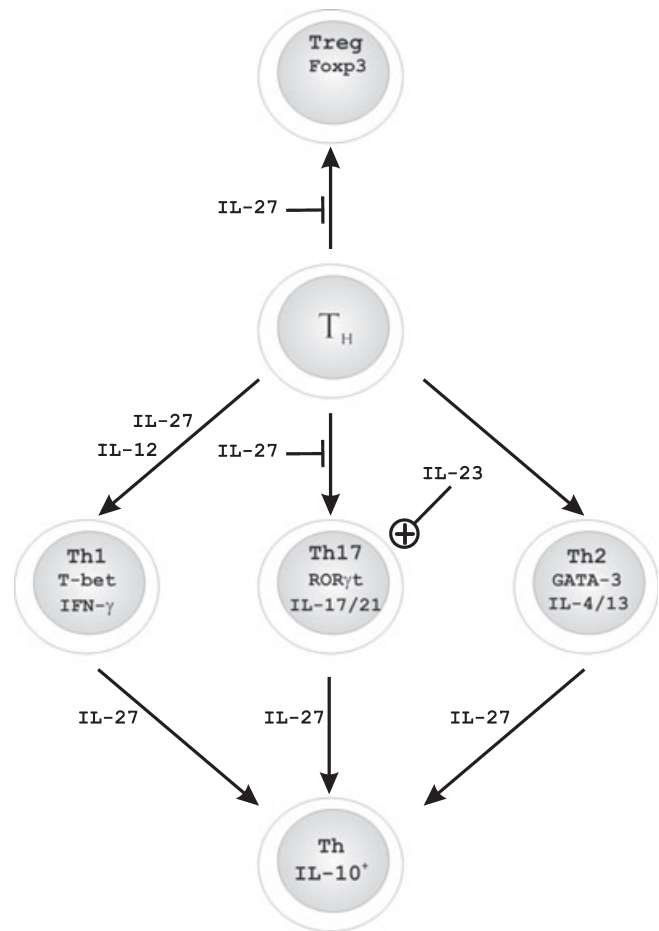


Figure 1. IL-12 family members and Th subsets. IL-12 induces secretion of IFN- γ by Th1 cells (expressing the transcription factor T-bet). IL-23 is critically involved in the inflammatory properties of the Th17 subset (expressing the orphan receptor ROR γ t). While IL-27 induces T-bet expression and initial Th1 commitment, it also inhibits Th17 differentiation. Furthermore, IL-27 promotes IL-10 production by differentiated Th cells. Finally, this cytokine also inhibits TGF- β -dependent development of induced Tregs.

contributes to their suppressive function (33, 34). The anti-inflammatory properties of IFN- γ involve induction of nitric oxide synthase and indoleamine-2,3-dioxygenase in antigen-presenting cells (34).

The divergent roles of IL-27

Cytokines produced by antigen-presenting cells, such as IL-12 or IL-23 greatly affect the outcome of autoimmune inflammation. Another related cytokine, IL-27, recently emerged as a critical player in the control of inflammation. Its role is complex as IL-27 favours initial commitment into Th1 cells but also displays immunosuppressive properties (Fig. 1). Initial works on IL-27 focused on its pro-inflammatory roles in the context of infection or

cancer. Unexpectedly, IL-27R^{-/-} mice were subsequently shown to develop severe inflammatory pathologies in the course of infection with intracellular pathogens or in allergen-induced airway hypersensitivity model (35–38). In addition, IL-27 was shown to limit IL-17-cell-driven inflammation in the CNS (39, 40), and administration of IL-27 has a strong suppressive effect during active EAE and CIA (41, 42). Interleukin-27 might also limit Th17-mediated uveitis and scleritis in humans (43). Transgenic overexpression of IL27R in T cells of lupus-prone MRL/lpr mice increases survival rate and limits the development of autoimmune glomerulonephritis (44).

In vitro, IL-27 inhibits IL-2 secretion by CD4⁺ T cells and directly antagonizes IL-6 + TGFβ-mediated differentiation into Th17 cells (39, 40, 45). Furthermore, IL-27 promotes the production of IL-10 by CD4⁺ and CD8⁺ T cells. By doing so, IL-27 promotes the emergence of Tr1 cells, which produce both IFN-γ and IL-10 and express T-bet (46–49). This effect contributes to the anti-inflammatory action of IL-27 in the course of EAE. Another function of IL-27 might be to regulate early inflammatory events during acute infections, as IL-27 neutralization protects mice against lethal septic peritonitis by enhancing the influx and oxidative burst capacity of neutrophils (50). Taken together, IL-27 seems to be able to limit overt activation of T cells irrespectively of their lineage. In the light of these observations, IL-27 appears as a good candidate for the treatment of autoimmune diseases.

Interleukin-27 itself or IL-27-inducing agents could be of interest to control allergic disorders as this cytokine promotes the differentiation of helper T-cells secreting both IL-10 and IFN-γ, a type of response which proved to be associated with protection against allergic inflammation in experimental models (51, 52), to differentiate healthy humans from allergic individuals (53) and to expand upon sublingual immunotherapy (54).

As for other cytokines, IL-27 also displays pro-inflammatory properties that should be cautiously evaluated. Indeed, IL-27R^{-/-} mice are resistant to the development of experimental colitis induced by dextran sulphate sodium (DSS) (55). Similarly, IL-27 signalling contributes to chronic intestinal inflammation in IL-10^{-/-} mice (56). Furthermore, IL-27 displays a key pathogenic role in concanavalin A-induced hepatitis (57). Interleukin-27 has also been implicated in the development of inflammation in proteoglycan-induced arthritis (58). Finally, IL-27 was also shown to inhibit peripheral conversion of T cells into inducible Treg (59).

Type I IFNs in autoimmune disorders: foes or friends?

Type I IFNs have initially been described for their antiviral activities. The best characterized type I IFNs are IFN-α subtypes and IFN-β. They are produced by most cells upon viral infection. They are also produced upon contact with viral or bacterial products by innate immune

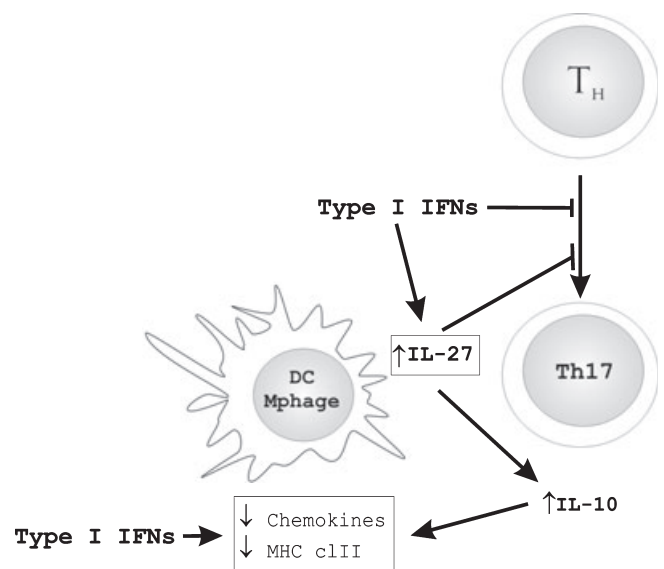


Figure 2. Impact of type I IFNs on Th17 responses: a role for IL-27. Several mechanisms may account for the anti-inflammatory properties of type I IFNs. Type I IFNs directly antagonize differentiation of naïve Th cells into Th17 effectors. Type I IFN signalling in antigen-presenting cells directly inhibits the production of inflammatory mediators and impairs antigen presentation. Furthermore, it also promotes the production of IL-27. This cytokine, in turn, negatively regulates Th17 development and promotes the expression of IL-10 by Th cells.

cells such as dendritic cells (DC) upon activation of transcription factors from the interferon regulatory factor family. They regulate multiple aspects of both innate and adaptive immune responses. As for IFN-γ, type I IFN signalling leads to the activation of immune cells (such as DC, macrophages, natural killer cells and B lymphocytes), production of pro-inflammatory chemokines and affect T-cell survival and proliferation. Hence, it is not surprising that type I IFNs have been linked to the pathogenesis of autoimmunity. Unexpectedly, several lines of evidence indicate that type I IFN also exert regulatory and beneficial effects in organ-specific autoimmune diseases.

As reviewed extensively, type I IFNs are now considered as the major players in the development of systemic lupus erythematosus (SLE) and type I diabetes (60). Disease severity of SLE patients correlates with increased blood cells and glomeruli expression of interferon-stimulated genes (61). The contribution of type I IFN signalling in SLE was further confirmed in different lupus-prone mice models. Noteworthy, in another mouse model (MRL/lpr mice), type I IFN receptor and toll-like receptor (TLR) 9 deficiencies lead to exacerbation of the disease, highlighting the contrasting effects of these cytokines and signalling pathways in lupus (62, 63).

Plasmacytoid dendritic cells (pDC) probably represent the source of this sustained IFN-α production in SLE patients (64, 65). These cells possess a unique ability to

secrete large amounts of type I IFN. In SLE patients, pDCs migrate into the skin at the site of lesions. While they represent less than 0.1% of human blood cells, pDCs are the major source of IFN- α upon exposure to TLR7 and TLR9 ligands (66, 67). Toll-like receptor 9 senses 2' deoxyribose backbone-containing natural DNA, irrespective of their unmethylated CpG content (68–70). Toll-like receptor 7 is specialized in the recognition of single-stranded viral RNA (71). The endosomal location of these TLRs limits the recognition of host-derived self nucleic acids. However, recent studies have indicated that the self-DNA containing immune complexes that are encountered in SLE could represent endogenous trigger for TLR9, through the interaction with soluble high-mobility group box 1 protein and the receptor for advanced glycation end product on pDCs (72). Furthermore, in psoriatic skin, an antimicrobial peptide, LL37, secreted by damaged epithelial cells was shown to bind extracellular self-DNA fragments to form aggregated structures (73). These particles will cause extended retention of DNA in the early endosomes and promote type I IFN synthesis. LL37 could play a similar role in SLE. The IFN- $\alpha\beta$ containing sera from SLE patients were shown to promote DC maturation from monocytes, an event that might lead to the breakdown of tolerance towards self-antigens (74).

Type I IFNs display pathogenic role in other autoimmune models or diseases. For example, induction of type I IFN by viral infection or administration of the TLR3 ligand polyI:C promotes tissue destruction in autoimmune diabetes or hepatitis (75, 76). For hepatitis, this effect was dependent on the production of CXCL9, which serves as chemoattractant for autoimmune T cells into the target organ. Local overproduction of type I IFN in transgenic systems leads to inflammation and destruction of pancreatic β cells (77). In sharp contrast, other studies have reported a protective role of IFN- α or type I IFN-inducing agents in diabetes models (78, 79).

In other clinical settings or animal models of autoimmunity, type I IFN displays anti-inflammatory properties (80). Treatment of multiple sclerosis patients with IFN- $\alpha\beta$ has proven to be beneficial in terms of prolonged remission and lower relapse rate (81). In the EAE model, IFN $\beta^{-/-}$, TRIF $^{-/-}$ and IFNAR $^{-/-}$ mice display more severe disease, and administration of polyI:C was found to be beneficial (82–84). Interestingly, while activated pDCs are associated with lupus or psoriasis, CNS pDC was recently shown to regulate negatively pathogenic CD4 $^{+}$ T-cell responses in EAE (85). In collagen-induced arthritis models, administration of type I IFN reduces inflammation and bone destruction (86). As for EAE, activation of TLR3 by systemic treatment with polyI:C suppresses the inflammatory phase of experimental arthritis in an IFN-dependent fashion (87). Along the same line, triggering of TLR9 in the course of experimental colitis dampens intestinal inflammation via the induction of type I IFNs (88). However, when adminis-

tered therapeutically, CpG ODN worsens DSS-induced colitis (89). Thus, multiple parameters including genetic background, targeted organ, stage of the disease, importance of local inflammation, dose and site of exposure might determine the balance between promoting/regulatory effects of type I IFNs on autoimmunity. Furthermore, when endogenous production of type I IFNs is triggered, the cellular source (e.g. plasmacytoid vs myeloid DC) could play an important role in dictating the local and systemic effects of these mediators.

Several cellular/molecular mechanisms have been incriminated for the anti-inflammatory action of type I IFN. As previously mentioned, type I IFN receptor is broadly expressed at the surface of immune and nonimmune cells. Type I IFN can directly affect Th cells, leading to modulation of survival, proliferation and differentiation into effector cells. Indeed, recent studies by Harrington et al. have shown that type I IFN can inhibit the differentiation of naïve Th cells into Th17 cells, and earlier works suggested that it favoured production of type 2 cytokines (19, 90). Relevant to the arthritis models, type I IFNs were also shown to inhibit the generation of osteoclasts (91, 92) and synovial cell proliferation (87). Through inhibition of matrix metalloprotease 9 synthesis, type I IFN could also affect the rate of extracellular proteolysis, thereby limiting tissue damage and leucocyte infiltration. However, in the EAE model, Prinz et al. (93) showed that the beneficial role of endogenous and locally produced type I IFN requires signalling in myeloid cells rather than in B, T or neuroectodermal CNS cells. Type I IFN signalling in macrophages and microglial cells led to a reduction in chemokine production, phagocytosis and major histocompatibility complex class II expression. Other potential mechanisms could contribute to the anti-inflammatory effects of type I IFN on myeloid cells (Fig. 2). Induction of type I IFN is required for lipopolysaccharide-induced IL-10 and IL-27 production (94–96). Two recent articles demonstrated the *in vivo* relevance of the type I IFNs–IL-27 axis. Indeed, Guo et al. (83) showed that the beneficial role of the TRIF/IFN pathway in the course of EAE was mediated by IL-27. In these experiments, type I IFN-dependent induction of IL-27 negatively regulated Th17 development and inflammation. Along this line, type I IFN signalling also regulates the expression of intracellular osteopontin, which was shown to influence the production of IL-27 by DC (97).

Concluding remark

The balance between IL-23 and IL-27 is critical for the induction of Th17-mediated inflammatory responses. Indeed, biopharmaceuticals approved or under development might act by tipping this balance. Whereas type I IFNs used in multiple sclerosis promote IL-27 synthesis, monoclonal antibodies against IL-23/IL-12p40 or

IL-23p19 are currently administered in clinical trials for multiple sclerosis, inflammatory bowel diseases or psoriasis. One might anticipate that monoclonal antibodies against IL-17 will also become part of this armamentarium. As IL-17 appears to play a role in certain allergic disorders, therapies suppressing Th17 responses might prove beneficial in such settings as well.

Acknowledgments

The Institute for Medical Immunology is supported by the government of the Walloon Region, GlaxoSmithKline Biologicals, the Fonds de la Recherche Scientifique (FRS-FNRS, Belgium) and the "Interuniversity Attraction Poles Programme- Belgian State- Belgian Science Policy". S.G. is a research associate of the FNRS. R.C. is supported by the 'Fonds Erasme pour la recherche médicale'.

References

- Gutcher I, Becher B. APC-derived cytokines and T cell polarization in autoimmune inflammation. *J Clin Invest* 2007;**117**:1119–1127.
- Weaver CT, Hatton RD, Mangan PR, Harrington LE. IL-17 family cytokines and the expanding diversity of effector T cell lineages. *Annu Rev Immunol* 2007;**25**:821–852.
- Cua DJ, Sherlock J, Chen Y, Murphy CA, Joyce B, Seymour B et al. Interleukin-23 rather than interleukin-12 is the critical cytokine for autoimmune inflammation of the brain. *Nature* 2003;**421**:744–748.
- Duerr RH, Taylor KD, Brant SR, Rioux JD, Silverberg MS, Daly MJ et al. A genome-wide association study identifies IL23R as an inflammatory bowel disease gene. *Science* 2006;**314**:1461–1463.
- Yen D, Cheung J, Scheerens H, Poulet F, McClanahan T, McKenzie B et al. IL-23 is essential for T cell-mediated colitis and promotes inflammation via IL-17 and IL-6. *J Clin Invest* 2006;**116**:1310–1316.
- Lee E, Trepicchio WL, Oestreicher JL, Pittman D, Wang F, Chamian F et al. Increased expression of interleukin 23 p19 and p40 in lesional skin of patients with psoriasis vulgaris. *J Exp Med* 2004;**199**:125–130.
- McGeachy MJ, Cua DJ. Th17 cell differentiation: the long and winding road. *Immunity* 2008;**28**:445–453.
- Dong C. TH17 cells in development: an updated view of their molecular identity and genetic programming. *Nat Rev Immunol* 2008;**8**:337–348.
- Romagnani S. Human Th17 cells. *Arthritis Res Ther* 2008;**10**:206.
- Veldhoen M, Hocking RJ, Atkins CJ, Locksley RM, Stockinger B. TGFbeta in the context of an inflammatory cytokine milieu supports de novo differentiation of IL-17-producing T cells. *Immunity* 2006;**24**:179–189.
- McGeachy MJ, Bak-Jensen KS, Chen Y, Tato CM, Blumenschein W, McClanahan T et al. TGF-beta and IL-6 drive the production of IL-17 and IL-10 by T cells and restrain T(H)-17 cell-mediated pathology. *Nat Immunol* 2007;**8**:1390–1397.
- Bettelli E, Carrier Y, Gao W, Korn T, Strom TB, Oukka M et al. Reciprocal developmental pathways for the generation of pathogenic effector TH17 and regulatory T cells. *Nature* 2006;**441**:235–238.
- Ivanov II, McKenzie BS, Zhou L, Tadokoro CE, Lepelletier A, Lafaille JJ et al. The orphan nuclear receptor RORgamma directs the differentiation program of proinflammatory IL-17(+) T helper cells. *Cell* 2006;**126**:1121–1133.
- Zhou L, Ivanov II, Spolski R, Min R, Shenderov K, Egawa T et al. IL-6 programs T(H)-17 cell differentiation by promoting sequential engagement of the IL-21 and IL-23 pathways. *Nat Immunol* 2007.
- Korn T, Bettelli E, Gao W, Awasthi A, Jager A, Strom TB et al. IL-21 initiates an alternative pathway to induce proinflammatory T(H)17 cells. *Nature* 2007;**448**:484–487.
- Acosta-Rodriguez EV, Rivino L, Geginat J, Jarrossay D, Gattorno M, Lanzavecchia A et al. Surface phenotype and antigenic specificity of human interleukin 17-producing T helper memory cells. *Nat Immunol* 2007;**8**:639–646.
- Wilson NJ, Boniface K, Chan JR, McKenzie BS, Blumenschein WM, Mattson JD et al. Development, cytokine profile and function of human interleukin 17-producing helper T cells. *Nat Immunol* 2007;**8**:950–957.
- Annunziato F, Cosmi L, Santarlasci V, Maggi E, Liotta F, Mazzinghi B et al. Phenotypic and functional features of human Th17 cells. *J Exp Med* 2007;**204**:1849–1861.
- Harrington LE, Hatton RD, Mangan PR, Turner H, Murphy TL, Murphy KM et al. Interleukin 17-producing CD4+ effector T cells develop via a lineage distinct from the T helper type 1 and 2 lineages. *Nat Immunol* 2005;**6**:1123–1132.
- Korn T, Reddy J, Gao W, Bettelli E, Awasthi A, Petersen TR et al. Myelin-specific regulatory T cells accumulate in the CNS but fail to control autoimmune inflammation. *Nat Med* 2007;**13**:423–431.
- Lohr J, Knoechel B, Wang JJ, Villarino AV, Abbas AK. Role of IL-17 and regulatory T lymphocytes in a systemic autoimmune disease. *J Exp Med* 2006;**203**:2785–2791.
- Kroenke MA, Carlson TJ, Andjelkovic AV, Segal BM. IL-12- and IL-23-modulated T cells induce distinct types of EAE based on histology, CNS chemokine profile, and response to cytokine inhibition. *J Exp Med* 2008;**205**:1535–1541.
- Luger D, Silver PB, Tang J, Cua D, Chen Z, Iwakura Y et al. Either a Th17 or a Th1 effector response can drive autoimmunity: conditions of disease induction affect dominant effector category. *J Exp Med* 2008;**205**:799–810.
- Chen Y, Langrish CL, McKenzie B, Joyce-Shaikh B, Stumhofer JS, McClanahan T et al. Anti-IL-23 therapy inhibits multiple inflammatory pathways and ameliorates autoimmune encephalomyelitis. *J Clin Invest* 2006;**116**:1317–1326.
- Kullberg MC, Jankovic D, Feng CG, Hue S, Gorelick PL, McKenzie BS et al. IL-23 plays a key role in *Helicobacter hepaticus*-induced T cell-dependent colitis. *J Exp Med* 2006;**203**:2485–2494.
- O'Connor RA, Prendergast CT, Sabatos CA, Lau CW, Leech MD, Wraith DC et al. Cutting Edge: Th1 cells facilitate the entry of Th17 cells to the central nervous system during experimental autoimmune encephalomyelitis. *J Immunol* 2008;**181**:3750–3754.

27. Oboki K, Ohno T, Saito H, Nakae S. Th17 and allergy. *Allergol Int* 2008;**57**:121–134.
28. Gran B, Zhang GX, Yu S, Li J, Chen XH, Ventura ES et al. IL-12p35-deficient mice are susceptible to experimental autoimmune encephalomyelitis: evidence for redundancy in the IL-12 system in the induction of central nervous system autoimmune demyelination. *J Immunol* 2002;**169**:7104–7110.
29. Wang Z, Hong J, Sun W, Xu G, Li N, Chen X et al. Role of IFN- γ in induction of Foxp3 and conversion of CD4⁺. *J Clin Invest* 2006;**116**:2434–2441.
30. Nurieva R, Yang XO, Martinez G, Zhang Y, Panopoulos AD, Ma L et al. Essential autocrine regulation by IL-21 in the generation of inflammatory T cells. *Nature* 2007;**448**:480–483.
31. Rangachari M, Mauermann N, Marty RR, Dirnhofer S, Kurrer MO, Komnenovic V et al. T-bet negatively regulates autoimmune myocarditis by suppressing local production of interleukin 17. *J Exp Med* 2006;**203**:2009–2019.
32. Lin W, Bailey SL, Ho H, Harding HP, Ron D, Miller SD et al. The integrated stress response prevents demyelination by protecting oligodendrocytes against immune-mediated damage. *J Clin Invest* 2007;**117**:448–456.
33. Sawitzki B, Kingsley CI, Oliveira V, Karim M, Herber M, Wood KJ. IFN- γ production by alloantigen-reactive regulatory T cells is important for their regulatory function in vivo. *J Exp Med* 2005;**201**:1925–1935.
34. Wood KJ, Sawitzki B. Interferon γ : a crucial role in the function of induced regulatory T cells in vivo. *Trends Immunol* 2006;**27**:183–187.
35. Villarino A, Hibbert L, Lieberman L, Wilson E, Mak T, Yoshida H et al. The IL-27R (WSX-1) is required to suppress T cell hyperactivity during infection. *Immunity* 2003;**19**:645–655.
36. Miyazaki Y, Inoue H, Matsumura M, Matsumoto K, Nakano T, Tsuda M et al. Exacerbation of experimental allergic asthma by augmented Th2 responses in WSX-1-deficient mice. *J Immunol* 2005;**175**:2401–2407.
37. Rosas LE, Satoskar AA, Roth KM, Keiser TL, Barbi J, Hunter C et al. Interleukin-27R (WSX-1/T-cell cytokine receptor) gene-deficient mice display enhanced resistance to *Leishmania donovani* infection but develop severe liver immunopathology. *Am J Pathol* 2006;**168**:158–169.
38. Holscher C, Holscher A, Ruckerl D, Yoshimoto T, Yoshida H, Mak T et al. The IL-27 receptor chain WSX-1 differentially regulates antibacterial immunity and survival during experimental tuberculosis. *J Immunol* 2005;**174**:3534–3544.
39. Batten M, Li J, Yi S, Kljavin NM, Danilenko DM, Lucas S et al. Interleukin 27 limits autoimmune encephalomyelitis by suppressing the development of interleukin 17-producing T cells. *Nat Immunol* 2006;**7**:929–936.
40. Stumhofer JS, Laurence A, Wilson EH, Huang E, Tato CM, Johnson LM et al. Interleukin 27 negatively regulates the development of interleukin 17-producing T helper cells during chronic inflammation of the central nervous system. *Nat Immunol* 2006;**7**:937–945.
41. Fitzgerald DC, Ciric B, Touil T, Harle H, Grammatikopoulou J, Das SJ et al. Suppressive effect of IL-27 on encephalitogenic Th17 cells and the effector phase of experimental autoimmune encephalomyelitis. *J Immunol* 2007;**179**:3268–3275.
42. Niedbala W, Cai B, Wei X, Patakas A, Leung BP, McInnes IB et al. Interleukin-27 attenuates collagen-induced arthritis. *Ann Rheum Dis* 2008;**181**:4780–4790.
43. Amadi-Obi A, Yu CR, Liu X, Mahdi RM, Clarke GL, Nussenblatt RB et al. T(H)17 cells contribute to uveitis and scleritis and are expanded by IL-2 and inhibited by IL-27/STAT1. *Nat Med* 2007;**13**:711–718.
44. Sugiyama N, Nakashima H, Yoshimura T, Sadanaga A, Shimizu S, Masutani K et al. Amelioration of human lupus-like phenotypes in MRL/lpr mice by overexpression of IL-27R α (WSX-1). *Ann Rheum Dis* 2008;**67**:1461–1467.
45. Villarino AV, Stumhofer JS, Saris CJ, Kastelein RA, de Sauvage FJ, Hunter CA. IL-27 limits IL-2 production during Th1 differentiation. *J Immunol* 2006;**176**:237–247.
46. Stumhofer JS, Silver JS, Laurence A, Porrett PM, Harris TH, Turka LA et al. Interleukins 27 and 6 induce STAT3-mediated T cell production of interleukin 10. *Nat Immunol* 2007;**8**:1363–1371.
47. Awasthi A, Carrier Y, Peron JP, Bettelli E, Kamanaka M, Flavell RA et al. A dominant function for interleukin 27 in generating interleukin 10-producing anti-inflammatory T cells. *Nat Immunol* 2007;**8**:1380–1389.
48. Fitzgerald DC, Zhang GX, El Behi M, Fonseca-Kelly Z, Li H, Yu S et al. Suppression of autoimmune inflammation of the central nervous system by interleukin 10 secreted by interleukin 27-stimulated T cells. *Nat Immunol* 2007;**8**:1372–1379.
49. Batten M, Kljavin NM, Li J, Walter MJ, De Sauvage FJ, Ghilardi N. Cutting edge: IL-27 is a potent inducer of IL-10 but not FoxP3 in murine T Cells. *J Immunol* 2008;**180**:2752–2756.
50. Wirtz S, Tubbe I, Galle PR, Schild HJ, Birkenbach M, Blumberg RS et al. Protection from lethal septic peritonitis by neutralizing the biological function of interleukin 27. *J Exp Med* 2006;**203**:1875–1881.
51. Stock P, Akbari O, Berry G, Freeman GJ, DeKruyff RH, Umetsu DT. Induction of T helper type 1-like regulatory cells that express Foxp3 and protect against airway hyper-reactivity. *Nat Immunol* 2004;**5**:1149–1156.
52. Mascarell L, Lombardi V, Louise A, Saint-Lu N, Chabre H, Moussu H et al. Oral dendritic cells mediate antigen-specific tolerance by stimulating TH1 and regulatory CD4⁺ T cells. *J Allergy Clin Immunol* 2008;**122**:603–609.
53. Van Overtvelt L, Wambre E, Maillere B, Von Hofe E, Louise A, Balazuc AM et al. Assessment of Bet v 1-specific CD4⁺ T cell responses in allergic and nonallergic individuals using MHC class II peptide tetramers. *J Immunol* 2008;**180**:4514–4522.
54. Cosmi L, Santarlasci V, Angeli R, Liotta F, Maggi L, Frosali F et al. Sublingual immunotherapy with *Dermatophagoides* monomeric allergoid down-regulates allergen-specific immunoglobulin E and increases both interferon- γ - and interleukin-10-production. *Clin Exp Allergy* 2006;**36**:261–272.
55. Honda K, Nakamura K, Matsui N, Takahashi M, Kitamura Y, Mizutani T et al. T helper 1-inducing property of IL-27/WSX-1 signaling is required for the induction of experimental colitis. *Inflamm Bowel Dis* 2005;**11**:1044–1052.
56. Villarino AV, Artis D, Bezbradica JS, Miller O, Saris CJ, Joyce S et al. IL-27R deficiency delays the onset of colitis and protects from helminth-induced pathology in a model of chronic IBD. *Int Immunol* 2008;**20**:739–752.

57. Siebler J, Wirtz S, Frenzel C, Schuchmann M, Lohse AW, Galle PR et al. Cutting edge: a key pathogenic role of IL-27 in T cell-mediated hepatitis. *J Immunol* 2008;**180**:30–33.
58. Cao Y, Doodles PD, Glant TT, Finnegan A. IL-27 induces a Th1 immune response and susceptibility to experimental arthritis. *J Immunol* 2008;**180**:922–930.
59. Neufert C, Becker C, Wirtz S, Fantini MC, Weigmann B, Galle PR et al. IL-27 controls the development of inducible regulatory T cells and Th17 cells via differential effects on STAT1. *Eur J Immunol* 2007;**37**:1809–1816.
60. Baccala R, Kono DH, Theofilopoulos AN. Interferons as pathogenic effectors in autoimmunity. *Immunol Rev* 2005;**204**:9–26.
61. Qing X, Putterman C. Gene expression profiling in the study of the pathogenesis of systemic lupus erythematosus. *Autoimmun Rev* 2004;**3**:505–509.
62. Hron JD, Peng SL. Type I IFN protects against murine lupus. *J Immunol* 2004;**173**:2134–2142.
63. Wu X, Peng SL. Toll-like receptor 9 signaling protects against murine lupus. *Arthritis Rheum* 2006;**54**:336–342.
64. Blanco P, Palucka AK, Gill M, Pascual V, Banchereau J. Induction of dendritic cell differentiation by IFN- α in systemic lupus erythematosus. *Science* 2001;**294**:1540–1543.
65. Ronnblom L, Alm GV. A pivotal role for the natural interferon α -producing cells (plasmacytoid dendritic cells) in the pathogenesis of lupus. *J Exp Med* 2001;**194**:F59–F63.
66. Colonna M, Trinchieri G, Liu YJ. Plasmacytoid dendritic cells in immunity. *Nat Immunol* 2004;**5**:1219–1226.
67. Ito T, Wang YH, Liu YJ. Plasmacytoid dendritic cell precursors/type I interferon-producing cells sense viral infection by toll-like receptor (TLR) 7 and TLR9. *Springer Semin Immunopathol* 2005;**26**:221–229.
68. Krug A, Towarowski A, Britsch S, Rothenfusser S, Hornung V, Bals R et al. Toll-like receptor expression reveals CpG DNA as a unique microbial stimulus for plasmacytoid dendritic cells which synergizes with CD40 ligand to induce high amounts of IL-12. *Eur J Immunol* 2001;**31**:3026–3037.
69. Bauer S, Kirschning CJ, Hacker H, Redecke V, Hausmann S, Akira S et al. Human TLR9 confers responsiveness to bacterial DNA via species-specific CpG motif recognition. *Proc Natl Acad Sci USA* 2001;**98**:9237–9242.
70. Haas T, Metzger J, Schmitz F, Heit A, Muller T, Latz E et al. The DNA sugar backbone 2' deoxyribose determines toll-like receptor 9 activation. *Immunity* 2008;**28**:315–323.
71. Lund JM, Alexopoulou L, Sato A, Karow M, Adams NC, Gale NW et al. Recognition of single-stranded RNA viruses by toll-like receptor 7. *Proc Natl Acad Sci USA* 2004;**101**:5598–5603.
72. Tian J, Avalos AM, Mao SY, Chen B, Senthil K, Wu H et al. Toll-like receptor 9-dependent activation by DNA-containing immune complexes is mediated by HMGB1 and RAGE. *Nat Immunol* 2007;**8**:487–496.
73. Lande R, Gregorio J, Facchinetti V, Chatterjee B, Wang YH, Homey B et al. Plasmacytoid dendritic cells sense self-DNA coupled with antimicrobial peptide. *Nature* 2007;**449**:564–569.
74. Banchereau J, Pascual V. Type I interferon in systemic lupus erythematosus and other autoimmune diseases. *Immunity* 2006;**25**:383–392.
75. Lang KS, Recher M, Junt T, Navarini AA, Harris NL, Freigang S et al. Toll-like receptor engagement converts T-cell autoreactivity into overt autoimmune disease. *Nat Med* 2005;**11**:138–145.
76. Lang KS, Georgiev P, Recher M, Navarini AA, Berghaler A, Heikenwalder M et al. Immunoprivileged status of the liver is controlled by toll-like receptor 3 signaling. *J Clin Invest* 2006;**116**:2456–2463.
77. Stewart TA, Hultgren B, Huang X, Pitts-Meek S, Hully J, MacLachlan NJ. Induction of type I diabetes by interferon- α in transgenic mice. *Science* 1993;**260**:1942–1946.
78. Sobel DO, Ahvazi B. Alpha-interferon inhibits the development of diabetes in NOD mice. *Diabetes* 1998;**47**:1867–1872.
79. Sobel DO, Goyal D, Ahvazi B, Yoon JW, Chung YH, Baggi A et al. Low dose poly I:C prevents diabetes in the diabetes prone BB rat. *J Autoimmun* 1998;**11**:343–352.
80. Billiau A. Anti-inflammatory properties of type I interferons. *Antiviral Res* 2006;**71**:108–116.
81. Buttmann M, Rieckmann P. Interferon-beta1b in multiple sclerosis. *Expert Rev Neurother* 2007;**7**:227–239.
82. Teige I, Treschow A, Teige A, Mattsson R, Navikas V, Leanderson T et al. IFN-beta gene deletion leads to augmented and chronic demyelinating experimental autoimmune encephalomyelitis. *J Immunol* 2003;**170**:4776–4784.
83. Guo B, Chang EY, Cheng G. The type I IFN induction pathway constrains Th17-mediated autoimmune inflammation in mice. *J Clin Invest* 2008;**118**:1680–1690.
84. Touil T, Fitzgerald D, Zhang GX, Rostami A, Gran B. Cutting edge: TLR3 stimulation suppresses experimental autoimmune encephalomyelitis by inducing endogenous IFN- β . *J Immunol* 2006;**177**:7505–7509.
85. Bailey-Bucktrout SL, Caulkins SC, Goings G, Fischer JA, Dzionek A, Miller SD. Cutting edge: central nervous system plasmacytoid dendritic cells regulate the severity of relapsing experimental autoimmune encephalomyelitis. *J Immunol* 2008;**180**:6457–6461.
86. Van Holten J, Reedquist K, Sattone-Roche P, Smeets TJ, Plater-Zyberk C, Vervoordeldonk MJ et al. Treatment with recombinant interferon- β reduces inflammation and slows cartilage destruction in the collagen-induced arthritis model of rheumatoid arthritis. *Arthritis Res Ther* 2004;**6**:R239–R249.
87. Yarinina A, DiCarlo E, Ivashkiv LB. Suppression of the effector phase of inflammatory arthritis by double-stranded RNA is mediated by type I IFNs. *J Immunol* 2007;**178**:2204–2211.
88. Katakura K, Lee J, Rachmilewitz D, Li G, Eckmann L, Raz E. Toll-like receptor 9-induced type I IFN protects mice from experimental colitis. *J Clin Invest* 2005;**115**:695–702.
89. Obermeier F, Dunger N, Deml L, Herfarth H, Scholmerich J, Falk W. CpG motifs of bacterial DNA exacerbate colitis of dextran sulfate sodium-treated mice. *Eur J Immunol* 2002;**32**:2084–2092.
90. Kozovska ME, Hong J, Zang YC, Li S, Rivera VM, Killian JM et al. Interferon β induces T-helper 2 immune deviation in MS. *Neurology* 1999;**53**:1692–1697.
91. Treschow AP, Teige I, Nandakumar KS, Holmdahl R, Issazadeh-Navikas S. Stromal cells and osteoclasts are responsible for exacerbated collagen-induced arthritis in interferon- β -deficient mice. *Arthritis Rheum* 2005;**52**:3739–3748.
92. Takayanagi H, Kim S, Taniguchi T. Signaling crosstalk between RANKL and interferons in osteoclast differentiation. *Arthritis Res* 2002;**4**(Suppl. 3):S227–S232.

93. Prinz M, Schmidt H, Mildner A, Knobloch KP, Hanisch UK, Raasch J et al. Distinct and nonredundant in vivo functions of IFNAR on myeloid cells limit autoimmunity in the central nervous system. *Immunity* 2008;**28**: 675–686.
94. Chang EY, Guo B, Doyle SE, Cheng G. Cutting edge: involvement of the type I IFN production and signaling pathway in lipopolysaccharide-induced IL-10 production. *J Immunol* 2007;**178**: 6705–6709.
95. Remoli ME, Gafa V, Giacomini E, Severa M, Lande R, Coccia EM. IFN-beta modulates the response to TLR stimulation in human DC: involvement of IFN regulatory factor-1 (IRF-1) in IL-27 gene expression. *Eur J Immunol* 2007;**37**:3499–3508.
96. Molle C, Nguyen M, Flamand V, Renneson J, Trottein F, De Wit D et al. IL-27 synthesis induced by TLR ligation critically depends on IFN regulatory factor 3. *J Immunol* 2007;**178**:7607–7615.
97. Shinohara ML, Kim JH, Garcia VA, Cantor H. Engagement of the type I interferon receptor on dendritic cells inhibits T helper 17 cell development: role of intracellular osteopontin. *Immunity* 2008;**29**:68–78.