7 Induction of Immunity and Inflammation by Interleukin-12 Family Members

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Abstract. The interleukin (IL)-12 family is composed of three heterodimeric cytokines, IL-12 (p40p35), IL-23 (p40p19), and IL-27 (EBI3p28), and of monomeric and homodimeric p40. This review focuses on the three heterodimeric members of the IL-12 family. The p40 and p40-like (EBI3) subunits have homology to the IL-6R, the other subunits (p35, p19, and p28) are homologous to each other and to members of the IL-6 superfamily. On the basis of their structural

similarity, it was expected that the members of the IL-12 family have overlapping pro-inflammatory and immunoregulatory functions. However, it was surprising that they also show very distinct activities. IL-12 has a central role as a Th1-inducing and -maintaining cytokine, which is essential in cell-mediated immunity in nonviral infections and in tumor control. IL-23 recently emerged as an end-stage effector cytokine responsible for autoimmune chronic inflammation through induction of IL-17 and direct activation of macrophages. Very recently, IL-27 was found to exert not only a pro-inflammatory Th1-enhancing but also a significant anti-inflammatory function.

7.1 Structure of IL-12 Family Members

Interleukin (IL)-12 was discovered as "natural killer cell stimulatory factor (NKSF)" in 1989 (Kobayashi et al. 1989) and by another group as "cytotoxic lymphocyte maturation factor (CLMF)" in 1990 (Stern et al. 1990). It was the first cytokine to be found with a heterodimeric structure (Gately et al. 1998; Trinchieri 1998). IL-12 is composed of a p35 and a p40 subunit. Both subunits are covalently linked. Each subunit is expressed by its own gene, whereby the *p*35and *p*40 genes are located on different chromosomes. The sequence of p35 shows homology with that of IL-6 and G-CSF (Merberg et al. 1992) and encodes a p35 subunit that shows a four-α-helix bundle structure typical of cytokines. The sequence of the p40 subunit is homologous to the extracellular portion of members of the hemopoietin receptor family, in particular to the IL-6 receptor α-chain (IL-6Rα) and the ciliary neurotrophic factor receptor (CNTFR) (Gearing and Cosman 1991). Therefore, IL-12 represents a heterodimeric cytokine with one chain (p35) having the actual cytokine structure and the other chain (p40) showing the structure of a cytokine receptor. While IL-12 might have evolved from the IL-6/IL-6R family, it has meanwhile established its own family (Fig. 1). In 2000, a novel p40p19 heterodimeric molecule was found and designated IL-23 (Oppmann et al. 2000). Only 2 years later, another IL-12 family member termed IL-27 was described, which consists of the p40-like subunit EBI3 noncovalently linked to a p28 subunit (Pflanz et al. 2002). Thus, the novel IL-12 family consists of cytokines with a p40 or a p40-like (EBI3) receptor component together with members of the long-chain four-α-helix bundle cytokine family (p35, p19, and p28) (Fig. 1). This

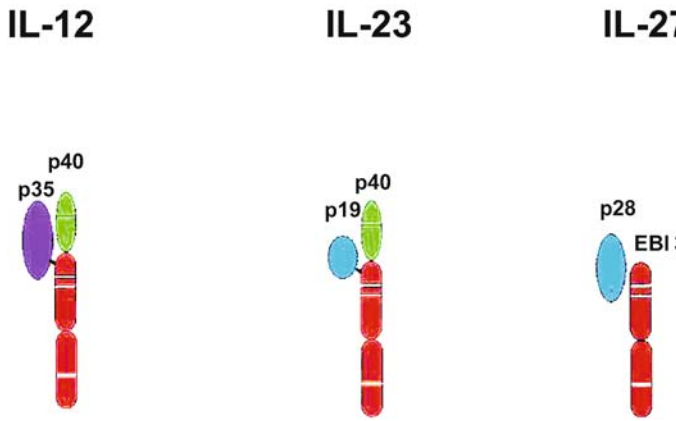

Fig. 1. Members of the heterodimeric IL-12 family. This figure focuses on the three heterodimeric IL-12 family members and does not show monomeric and homodimeric IL-12p40, which can be secreted in molar excess relative to the secretion of IL-12 and IL-23. The four-α-helix bundle cytokine p35 is shown in *purple*, p19 and p28 are shown in *blue*. For p40 and EBI3, an Ig-like domain (*green*) and cytokine receptor homology domains (*red*) are shown. Parts of Figs. 1–3 have kindly been provided by Rob Kastelein (DNAX Research Institute)

review focuses on the three heterodimeric IL-12 family members and does not elaborate on monomeric and homodimeric IL-12p40 with their antagonistic and agonistic properties.

7.2 Expression of IL-12 Family Members and Their Receptors

All IL-12 family members are produced by activated dendritic cells (DCs) and macrophages, which function as antigen-presenting cells. Expression of p35, p19, and p28 is found in many different cell types. However, p40 transcription appears to be restricted to antigen-presenting cells. Coexpression of both chains of IL-12, IL-23, and IL-27 in one cell is required to generate the bioactive form of either member of the IL-12 family (Gubler et al. 1991; Oppmann et al. 2000; Pflanz et al.

2002). Free subunits of p35, p19, and p28 chains are not or only inefficiently secreted in humans or mice. In contrast, p40 can be secreted as monomer, homodimer, or polymer in a 10- to 1,000-fold excess relative to heterodimeric IL-12 (D'Andrea et al. 1992). Stimuli for expression of IL-12 family members include pathogen-associated molecular patterns (PAMPs), which are ligands for toll-like receptors (TLRs) on phagocytes and DCs. In addition, optimal production of IL-12 (and probably also of IL-23 and IL-27) requires cytokines (IFN-γ, IL-4, IL-13) (Trinchieri 2003). Activated T cells can enhance IL-12 production not only by cytokine secretion but also by direct cell-to-cell contact via CD40L/CD40 interaction (Schulz et al. 2000).

Target cells for all IL-12 family members are natural killer (NK) and T cells. In addition, macrophages and DCs appear to express functional receptors for IL-12 and IL-23 (Belladonna et al. 2002; Grohmann et al. 1998, 2001). For IL-27, a receptor has also been described on monocytes, Langerhans' cells, activated DCs, and endothelial cells (Pflanz et al. 2004; Villarino et al. 2004). The activities of IL-12 are mediated by a high-affinity (50-pM) receptor composed of two subunits, designated IL-12Rβ1 and IL-12Rβ2 (Gately et al. 1998) (Fig. 2). Both receptor chains are members of the class I cytokine receptor family and are most closely related to glycoprotein gp130, the common receptor β-chain of the IL-6-like cytokine superfamily. IL-23 was found to bind to IL-12Rβ1 but not IL-12Rβ2 (Oppmann et al. 2000). Instead, a novel gp130-like subunit designated IL-23R was identified, which together with IL-12Rβ1 allows for high-affinity binding of IL-23 (Parham et al. 2002). One chain of the IL-27 receptor complex is the WSX-1/TCCR chain (Pflanz et al. 2002). In 2004, the second chain of the IL-27 receptor complex was found to be gp130 (Pflanz et al. 2004).

The individual members of the IL-12 family have overlapping, but also distinct, activities. This may partially be based on different receptor components expressed on different target cells or during different developmental stages of the target cells (naïve vs. memory Th cells).

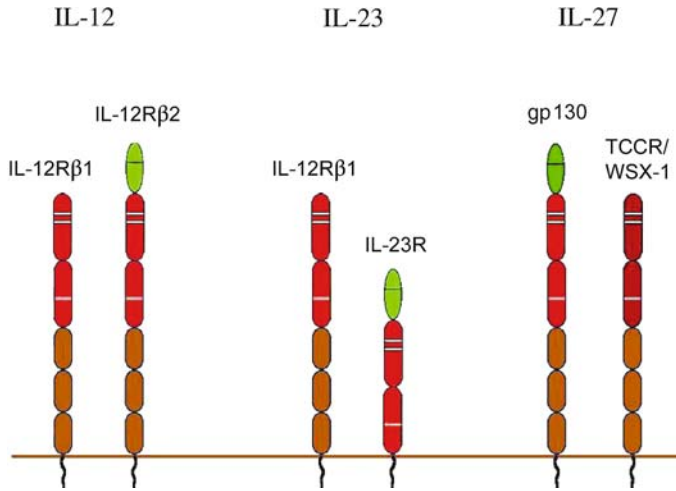

Fig. 2. Receptors for the members of the IL-12 family. The receptor subunits can carry an Ig-like domain (*green*), cytokine receptor homology domains (*red*) and fibronectin-like domains (*brown*)

7.3 Signal Transduction

IL-12 induces via its IL-12Rβ1/β2 receptor complex tyrosine phosphorylation of the Janus-family kinases Jak2 and Tyk 2, which in turn activate signal transducer and activator of transcription (STAT) 1, STAT3, STAT4, and STAT5 (Presky et al. 1996) (Fig. 3). Activation of STAT4 is essential for the specific cellular effects of IL-12. STAT4$^{-/-}$ mice show a phenotype that is identical to the phenotype of IL-12p35$^{-/-}$ mice (Kaplan et al. 1996).

Binding of IL-23 to its receptor complex IL-12Rβ1/IL-23R results in tyrosine phosphorylation of Jak2 and Tyk2, leading to activation of STAT1, STAT3, and STAT4. In contrast to the IL-12-induced predominant formation of STAT4 homodimers, IL-23 rather induces STAT3/STAT4 heterodimers (Fig. 3) (Parham et al. 2002). Formation of different DNA-binding STAT dimers by IL-12 and IL-23 appears to contribute to their distinct functional properties.

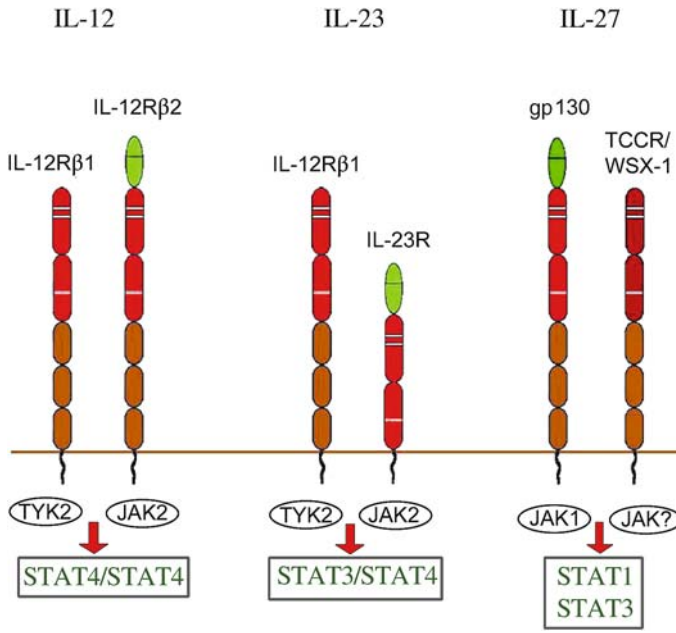

Fig. 3. Signal transduction components activated by IL-12 family members. Differential formation of STAT dimers might be essential for the distinct activities of the individual members of the IL-12 family

Upon binding of IL-27 to its receptor complex WSX-1/gp130, Jak1, STAT1 and STAT3 are activated (Pflanz et al. 2004). Activation of STAT1 and STAT3 by IL-27 might be the basis for its capability of downregulating T cell hyperactivity and IFN-γ production (Villarino et al. 2003; Hamano et al. 2003). In addition, it is of particular interest that IL-27-induced activation of STAT1 can directly induce expression of the transcription factor T-bet, which can regulate IL-12 responsiveness of T cells by upregulating IL-12Rβ2 (Takeda et al. 2003). Current and future research will help to further clarify the pleiotropic effects of IL-27-dependent signaling and link it to biological functions.

7.4 Biology of IL-12 Family Members

The biological functions of the individual members of the IL-12 family are surprisingly distinct and overlap only partially. Initially after the discovery of the latest members of this family, very similar immunological functions were expected of the individual family members based on their structural resemblance. However, more recent studies indicate distinct activities. The three heterodimeric members of the IL-12 family are pro-inflammatory cytokines. IL-12 represents the prototypic molecule for induction and maintenance of T helper 1 (Th1) cells secreting IFN-γ. On the basis of the expression of the individual receptor complexes for IL-12, IL-23, and IL-27, it appears that the three family members act on Th cells *at different stages of the Th1 differentiation pathway*. Naïve Th cells express the receptors for IL-27 and IL-12, but not for IL-23 (Brombacher et al. 2003). On the other hand, memory Th cells express the receptor for IL-23, but have only low or no expression of the receptors for IL-27 or IL-12 (Oppmann et al. 2000; Chen et al. 2000). Mullen et al. showed that T-bet expression in committed Th1 cells precedes exposure to IL-12 (Mullen et al. 2001). This argues for a role of IL-27 for the induction and IL-12 for the maintenance of a Th1 response. Indeed, two studies looking at murine models of *Leishmania major* and *Toxoplasma gondii* infection also demonstrate that IL-12 is required for the expansion and the fixation of Th1 cells (Park et al. 2000; Yap et al. 2000).

Distinct functions of the individual members of the IL-12 family not only apply to distinct time points of Th1 cell differentiation or activation. They also apply to *distinct effector mechanisms* initiated by IL-12, IL-23, and IL-27. There is ample evidence for an IL-12/IFN-γ axis (Gately et al. 1998; Trinchieri 1998) (Fig. 4). However, it is clear that murine IL-23 does not regulate IFN-γ production (Cua et al. 2003). Also, human IL-23 induces only modest amounts of IFN-γ in naïve and memory T cells compared to IL-12 (Oppmann et al. 2000). Moreover, IL-23 but not IL-12 can activate murine memory T cells for production of the pro-inflammatory cytokine IL-17 (Aggarwal et al. 2003) (Fig. 4). The activation of IL-17 production by IL-23 appears to be the key mechanism for the emerging role of IL-23 in chronic inflammation (see Sect. 7.7). IL-17 plays an important role in tissue destruction during autoimmune diseases such as multiple sclerosis, rheumatoid arthritis, and psoriasis

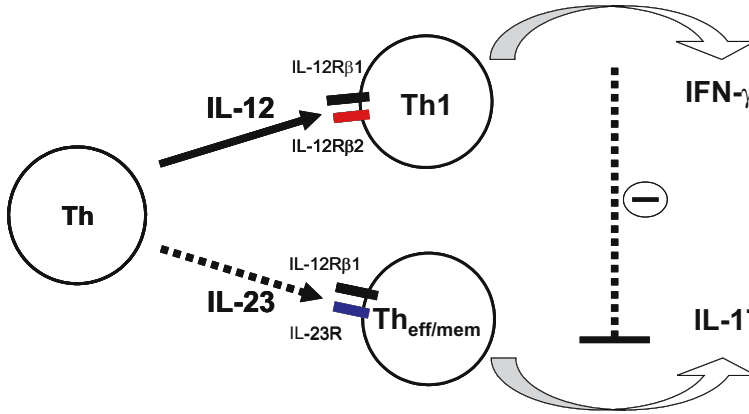

Fig. 4. Th cell differentiation pathways initiated by IL-12 or IL-23. Shown are the IL-12/IFN-γ axis and the IL-23/IL-17 pathway. There is evidence for cross-regulation of these two pro-inflammatory responses (Murphy et al. 2003). The *dashed arrow* indicates that it is presently unclear whether IL-23 drives naïve precursor Th cells or already differentiated Th cells

(Kolls and Linden 2004; Matusevicius et al. 1999; Ziolkowska et al. 2000; Teunissen et al. 1998).

Further evidence for distinct actions of the three IL-12 family members was recently provided by studies shedding light on an unexpected anti-inflammatory potential of IL-27 (Villarino et al. 2003; Hamano et al. 2003). It was found that activation of WSX-1 exerts a powerful negative feedback mechanism that limits T cell hyperactivity and IFN-γ production. The molecular basis for this protective immunoregulatory role of IL-27 might be its ability to activate preferentially STAT1 and STAT3 (Villarino et al. 2004) (Fig. 3).

7.5 Role of IL-12 Family Members in Host Defense

While the role of IL-12 in host defense has been characterized extensively (Gately et al. 1998; Trinchieri 1998; Brombacher et al. 2003), the analysis of the function of IL-23 and IL-27 in resistance and immunity to pathogens is still in the initial phase.

The property of IL-12 to stimulate IFN-γ production during innate and adaptive immune responses is the basis for its essential role in resistance to different types of pathogens. IL-12 has a key role in protection against intracellular protozoan, fungal, and bacterial infections (Brombacher et al. 2003). The role of IL-12 in protection during viral infections appears to be minor (Schijns et al. 1998; Oxenius et al. 1999). For viral infections, type I IFN (IFN-α/β) is of great importance (Guidotti and Chisari 2001). Thus, IL-12 has a pathogen-dependent role in host defense. The data from murine experimental infections were confirmed by the analysis of patients with mutations in the IL-12p40 or the IL-12Rβ1 gene (Ottenhoff et al. 1998). These patients responded normally to standard viral immunizations but developed chronic courses of salmonellosis or mycobacteriosis (Ottenhoff et al. 1998). It is intriguing that IFN-γ deficiency of humans predisposes them primarily against mycobacterial infection (Maclennan et al. 2004). In contrast, patients with IL-12/IL-12Rβ1 deficiency developed salmonellosis (Maclennan et al. 2004). This strongly suggests that IL-12/IL-23 mediate their actions in salmonellosis partly through IFN-γ-independent pathways.

In some murine models of intracellular infection, IL-12p35$^{-/-}$ mice (deficient in IL-12) showed higher resistance than IL-12p35/40$^{-/-}$ mice (deficient in IL-12 *and* IL-23) (Brombacher et al. 2003). This pointed to a role of IL-23 in host responses against these intracellular pathogens. To address this question more directly, very recently infection experiments using IL-23p19$^{-/-}$ have been started. Initial results looking at *T. gondii* infection show a limited role of IL-23 in protection (Lieberman et al. 2004). A significant role of IL-23 (or other p40-dependent proteins such as monomeric or homodimeric p40) in intracellular infection is more evident in the absence of IL-12 (Decken et al. 1998; Lehmann et al. 2001; Lieberman et al. 2004). Presently it is too early to draw final conclusions for the role of IL-23 in innate and adaptive immunity during infection.

First studies looking at the role of IL-27 in host defense were conducted with WSX1/TCCR$^{-/-}$ mice. In *Listeria monocytogenes*, *Leishmania major*, or mycobacterial BCG infection, a role of WSX-1/TCCR signaling in IFN-γ production as well as in granuloma formation was proposed (Chen et al. 2000; Yoshida et al. 2001). However, more recent studies in *Trypanosoma cruzi* or *Toxoplasma gondii* infection show

that WSX-1/TCCR is not required for Th1/IFN-γ-mediated immunity to these parasitic infections, but rather for the suppression of excessive production of IFN-γ and T cell hyperactivity (Villarino et al. 2003; Hamano et al. 2003). On the other hand, EBI3$^{-/-}$ mice have a defect in a Th2-mediated colitis model but show an unaltered phenotype in a Th1-mediated colitis model (Nieuwenhuis et al. 2002). This extends the action of IL-27 to Th2 induction (unless EBI-3 could associate with a different subunit than p28, forming a cytokine different from IL-27). Presently it is not clear how these pleotropic effects by IL-27/WSX-1 signaling can be reconciled. It was suggested that the outcome of IL-27/WSX-1 signaling depends on the intensity of Th1 polarization. In a weakly Th1-biased situation such as leishmaniasis, enhancement of early IFN-γ production (Yoshida et al. 2001; Artis et al. 2004) occurs by the IL-27/WSX-1 interaction. However, in extremely polarized Th1 situations such as trypanosomiasis or toxoplasmosis WSX-1 appears to mediate a protective immunosuppressive effect (Villarino et al. 2004).

7.6 Antitumor Activity of IL-12 Family Members

Both endogenous IL-12 and treatment with exogenous IL-12 have been shown to exert profound antitumor and antimetastatic activity in murine models of transplantable and chemically induced tumors (Colombo and Trinchieri 2002). These antitumor activities include innate and adaptive immune mechanisms. In all tumor studies, the antitumor effect of IL-12 was at least partially dependent on IFN-γ (Brunda et al. 1995). IFN-γ and a number of cytokines and chemokines induced by IFN-γ (e.g., IFN-inducible protein 10) have a direct toxic effect on the tumor cells and/or can induce anti-angiogenic mechanisms. Both Th1 cells and cytotoxic T cells contribute to the tumor antigen-specific responses initiated by IL-12. This results in protective immunity to challenge with the same type of tumor (Brunda et al. 1993) and might provide the basis for potential tumor-specific vaccination using IL-12 as an adjuvant. The induction of Th1 cells by IL-12 not only results in elevated IFN-γ production, but also in higher levels of opsonizing and complement-fixing IgG antibody isotypes that have been demonstrated to contribute to antitumor responses (Quaglino et al. 2002). Unfortunately, the induction of

efficient in vivo antitumor responses requires high doses of recombinant IL-12. Since IL-12 is a pro-inflammatory cytokine, high-dose treatment led to considerable toxicity in mice and humans (Trinchieri 1998). It remains a challenge to translate the promising preclinical data obtained with IL-12 immunotherapy to human cancer patients and at the same time minimize the toxicity by IL-12 treatment.

The antitumor potential of IL-23 was recently started to be studied in models of colon carcinoma cells and melanoma cells (Lo et al. 2003; Wang et al. 2003). Potent activities were found in these initial studies. $CD8^+$ T cells but not $CD4^+$ T cells or NK cells were found to be required for the IL-23-induced antitumor effects and the induction of systemic immunity. Interestingly, compared with IL-12-expressing tumor cells, IL-23-transduced tumor cells lacked an early host response but achieved comparable antitumor and antimetastatic activity (Lo et al. 2003). This indicates that IL-23 displays some antitumor mechanisms that are distinct from the actions of IL-12.

Very recently, a first study described the antitumor activity of IL-27 in a murine tumor model of colon carcinoma. Potent protective immunity induced by IL-27 was found (Hisada et al. 2004). The antitumor response depended on $CD8^+$ T cells, IFN-γ, T-bet but not on STAT4.

Taken together, all members of the IL-12 family appear to have profound effects in tumor control. For the future, clinical trials will have to reveal how the members of the IL-12 family can be used for treatment of cancer patients without inducing major toxicities.

7.7 Role of IL-12 Family Members in Organ-Specific Autoimmunity

Historically, IFN-γ producing Th1 cells induced by IL-12 were considered to be mediators of autoimmunity. These studies aiming to look at the role of IL-12 in autoimmunity were in many cases done using neutralizing anti-p40 antibodies, $p40^{-/-}$ or IL-12R$\beta1^{-/-}$ mice. With today's knowledge on p40 being shared between IL-12 and IL-23 and that on IL-12Rβ1 being used by both IL-12 and IL-23, it has become clear that any conclusions from these studies leave open whether IL-12 and/or IL-23 were responsible for the observed effects. More specific

information on the role of IL-12 can be derived from the analysis of mice deficient in IL-12p35 or IL-12Rβ2. On the other hand, the recent generation of IL-23p19$^{-/-}$ mice has allowed for definitive analysis of the role of IL-23 in autoimmunity (Cua et al. 2003; Murphy et al. 2003).

7.7.1 Experimental Autoimmune Encephalomyelitis

Experimental autoimmune encephalomyelitis (EAE), a murine model of multiple sclerosis, is considered to be a Th1-mediated autoimmune disease. EAE could not be induced in IL-12p40$^{-/-}$ mice, but was even more severe in IL-12p35$^{-/-}$ and IL-12Rβ2$^{-/-}$ mice than in wild-type mice (Gran et al. 2002; Zhang et al. 2003). These data exclude an essential role of IL-12 in EAE and instead point to IL-23. Indeed, IL-23p19$^{-/-}$ mice were found to be completely resistant to EAE induction (Cua et al. 2003). IL-23p19$^{-/-}$ mice showed no symptoms of EAE but normal induction of Th1 cells. It is noteworthy that the generation of a Th1 response to myelin oligodendrocyte glycoprotein in this model required IL-12 and not IL-23. Intracerebral expression of IL-23 in IL-23p19$^{-/-}$ or IL-12p40$^{-/-}$ mice reconstituted EAE. However, IL-23 treatment of IL-12p40$^{-/-}$ mice led to delayed disease and reduced disease severity as compared to IL-23 treatment of IL-23p19$^{-/-}$ mice (Cua et al. 2003). In IL-12p40$^{-/-}$ mice, prior intraperitoneal administration of IL-12 and subsequent intracerebral expression of IL-23 by gene transfer resulted in disease severity similar to wild-type mice. This suggests that IL-23 is essential for EAE by local inflammatory effector mechanisms and IL-12 contributes to disease expression by promoting Th1 development. Since the IL-23R components were expressed only on recruited inflammatory macrophages, direct activation of macrophages by IL-23 appears to be responsible for the CNS inflammation during EAE. In addition, more recent data shows that IL-23p19$^{-/-}$ mice are severely impaired in their capacity to develop IL-17 producing Th effector/memory cells (Murphy et al. 2003; Ghilardi et al. 2004). IL-17 production by memory Th cells has been found earlier to be induced by IL-23 (Aggarwal et al. 2003) (Fig. 4). Upon transfer of IL-17 producing wild-type Th cells from mice with EAE to naïve recipient mice, the pathogenic IL-23-driven IL-17-producing Th cells can invade the CNS and promote EAE (Langrish et al. 2005).

7.7.2 Rheumatoid Arthritis

In collagen-induced arthritis (CIA), a murine model of rheumatoid arthritis (RA), IL-23p19$^{-/-}$ mice displayed resistance, whereas IL-12p35$^{-/-}$ mice were highly susceptible (i.e., more susceptible than wild-type mice), suggesting an unexpected suppressive action of IL-12 on chronic joint inflammation (Murphy et al. 2003). Again, in addition to the function of IL-23 vs IL-12 in chronic inflammation of the CNS, IL-23 but not IL-12 is essential for development of joint autoimmune inflammation. Moreover, IL-23p19$^{-/-}$ mice were resistant in CIA despite developing collagen-specific, IFN-γ-producing Th1 cells (Murphy et al. 2003). Murphy et al. reported that lymph node cells from antigen-primed wild-type and IL-12p35$^{-/-}$ mice have an increased frequency of IL-17-producing CD4^{+} T cells as compared with IL-23p19$^{-/-}$ mice (Murphy et al. 2003). Therefore, IL-17 production depends on IL-23 in CIA as described above for EAE. The more severe course of CIA in IL-12p35$^{-/-}$ mice than in wild-type mice was associated with elevated IL-17 production in IL-12p35$^{-/-}$ mice vs wild-type mice. These data for the first time suggest that the IL-23/IL-17 pathway is negatively regulated by the IL-12/IFN-γ axis (Fig. 4). Recently in IL-17$^{-/-}$ mice suppression of CIA was described confirming the central role of IL-17 in RA (Nakae et al. 2003). A role for IL-17 in human autoimmune tissue destruction has been suggested before by others who found IL-17 expression in several human autoimmune diseases, including multiple sclerosis (Matusevicius et al. 1999), RA (Ziolkowska et al. 2000), and psoriasis (Teunissen et al. 1998).

7.7.3 Psoriasis Vulgaris

Psoriasis vulgaris is a T cell-driven disease with Th1 cells predominating in lesional skin (Austin et al. 1999). Keratinocytes with transgenic expression of p40 show production of IL-23, but not IL-12, in the skin leading to an inflammatory cutaneous response with elevated numbers of Langerhans' cells (Kopp et al. 2003). Moreover, in lesional skin of patients with psoriasis vulgaris, an increase of p40 and p19 but not of p35 mRNA compared with nonlesional skin was detected (Lee et al. 2004). This emphasizes a major role of IL-23 in cutaneous chronic inflammatory responses.

7.7.4 Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) encompasses two disease entitities, Crohn's disease and ulcerative colitis. Crohn's disease most commonly affects the terminal ileum and ascending colon. An immunopathological function of IL-12 in IBD was assumed for Crohn's disease, since patients with Crohn's disease were found to express IL-12 in the gut (Parronchi et al. 1997). In addition, in mouse models of IBD, treatment with anti-IL-12p40 antibodies prevented or terminated disease (Neurath et al. 1995; Davidson et al. 1998). Interestingly, treatment with anti-IFN-γ could suppress induction of IBD but was unable to reverse ongoing IBD (Davidson et al. 1998). Based on these outcomes, it was concluded that IL-12 might play a role in colitis independent of its ability to generate IFN-γ-producing T cells. With the discovery of IL-23, the role of IL-12 in IBD needed to be readdressed, since anti-p40 antibodies used before neutralized both IL-12 and IL-23. Indeed, very recent studies in IL-23p19$^{-/-}$ mice revealed an essential role of IL-23 in development of IBD (Yen et al., unpublished). Also, IL-23 expression was found in patients with active Crohn's disease (Stallmach et al. 2004). Moreover, murine lamina propria dendritic cells were found to express constitutively IL-23 in the terminal ileum driven by the intestinal flora (Becker et al. 2003). Interestingly, IL-23 expression in this part of the small intestine was accompanied by expression of IL-17 (Becker et al. 2003). This suggests that IL-23 might predispose the terminal ileum to initiate chronic inflammatory responses mediated by IL-17. These data place the IL-23/IL-17 pathway in the center of the manifestation of chronic intestinal inflammation. The IL-12/IFN-γ axis might contribute to the induction and progression of IBD but is not essential.

Presently only few data are available on the potential role of IL-27 in IBD. Expression of EBI3, one of the subunits of IL-27, was found in patients with ulcerative colitis and in a subgroup of patients with Crohn's disease (Omata et al. 2001). Since a major anti-inflammatory function of IL-27 has been described (Villarino et al. 2004), it will be exciting to define a potential role of IL-27 in IBD and other autoimmune diseases.

7.7.5 Insulin-Dependent Diabetes Mellitus

For insulin-dependent diabetes mellitus (IDDM), some evidence was provided for an involvement of IL-12. A role of IL-12 in IDDM is based on the pancreatic expression of IL-12p40 found in several studies (Rothe et al. 1996; Zipris et al. 1996). In NOD (nonobese diabetes) mice, which are genetically predisposed to the development of IDDM, IL-12 treatment accelerated the onset of disease (Trembleau et al. 1995). However, using a different protocol of IL-12 administration, suppression of IDDM development in NOD mice was found (O'Hara et al. 1996). Also, IL-12p40$^{-/-}$ mice backcrossed to the NOD background showed a reduced incidence of IDDM (Adorini et al. 1997). However, these mice are also unable to produce IL-23. Therefore, studies with IL-12p35$^{-/-}$ (lacking only IL-12) and IL-23p19$^{-/-}$ (lacking only IL-23) should allow for clarification of the individual roles of IL-12 vs IL-23 in the pathogenesis of IDDM.

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