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IL-23 in Infections, Inflammation, Autoimmunity and Cancer: Possible Role in HIV-1 and AIDS

Govardhana Rao Yannam,
Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE, USA

Tanuja Gutti, and
Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE, USA

Larisa Y. Poluektova
Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE, USA. 985880 Nebraska Medical Center, Omaha, NE, USA

Larisa Y. Poluektova: lpoluekt@unmc.edu

Abstract

The growing family of interleukin (IL)-12-like cytokines produced by activated macrophages and dendritic cells became the important players in the control of infections, development of inflammation, autoimmunity and cancer. However, the role of one of them—heterodimer IL-23, which consists of IL12p40 and the unique p19 subunit in HIV-1 infection pathogenesis and progression to AIDS, represent special interest. We overviewed findings of IL-23 involvement in control of peripheral bacterial pathogens and opportunistic infection, central nervous system (CNS) viral infections and autoimmune disorders, and tumorogenesis, which potentially could be applicable to HIV-1 and AIDS.

Keywords

IL-23; Central nervous system; Bacterial infection; Interleukin-17; Autoimmune disorders; HIV-1

Introduction

Effective immune response towards a pathogen is invaluable in maintaining the integrity of the host. Initiation of an effective immune response requires close interactions between antigen-presenting cells of innate (macrophages and dendritic cells) and adaptive immunity (T and B cells). Cytokines produced by macrophages and dendritic cells (DC) are essential during host defense mechanisms in response to pathogens. In HIV-1 infection, the heterodimer of Interleukin (IL)-12 family—IL-23, represents special interest due to its possible involvement in the control of opportunistic infections, inflammation and tumorogenesis associated with AIDS.

Since its initial description (Oppmann et al. 2000), IL-23 has gained attention because of its unique heterodimer structure and similarity to key immune response cytokines IL-6/IL-12.

Correspondence to: Larisa Y. Poluektova, lpoluekt@unmc.edu.

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IL-23 discovery had a significant impact on our understanding of myeloid cell derived cytokines and T-cell pathways that govern chronic inflammation (Langrish et al. 2004). IL-23 receptor (IL23R) represents one of the most significant human genetic polymorphisms in autoimmunity including ankylosing spondylitis, psoriasis, multiple sclerosis (MS), sarcoidosis and inflammatory bowel diseases (Duerr et al. 2006; Huber et al. 2008; Illes et al. 2008; Liu et al. 2008; Agarwal et al. 2009; Ban et al. 2009; Takaku et al. 2009; De Nitto et al. 2010). Unfortunately, in HIV-1 and other lentiviral infections, the role of IL-23 and its receptor-expressing cells remain indefinite. The first discussion of the possible involvement of IL-23 as a new player in cytokine control in HIV-1 pathogenesis was published by Alfano and co-authors (Alfano et al. 2008). It was observed that strong and sustained production of IL-23 by peripheral blood mononuclear cells in response to bacterial lipopolysaccharides (LPS) is associated with high viral load during primary infection (Louis et al. 2010). The reduced expression of IL-23 mRNA in immune-reconstituted by antiretroviral therapy patients (Lee et al. 2004b) with opportunistic infections brought our attention to the possible involvement of IL-23 in AIDS pathogenesis. Recently the discovery of the IL-23 receptor expression on cells that are involved in the development of the microbiota-induced tertiary lymphoid tissue (Aloisi and Pujol-Borrell 2006) during chronic inflammatory responses generates a suggestion that in the case of HIV-1-infection dysfunction or progressive loss of these cells may be the cause of the systemic opportunistic pathogens invasion.

In this article, we focus on the role of IL-23 in several inflammatory pathologies, antibacterial/antiviral protection from opportunistic infections associated with HIV-1, and with special emphasis on neurological disorders.

The infections associated with AIDS tend to fall into well-recognized patterns: the most common pathogens include *Candida albicans, Pneumocystis carinii, Mycobacterium tuberculosis, Toxoplasma gondii, Cryptococcus neoformans, Mycobacterium avium intracellulare* and cytomegalovirus (Lloyd 1996; Mamidi et al. 2002).

Malignant disease in patients with HIV infection also occurs as two prevalent tumors: Kaposi's sarcoma of skin and mucosal surfaces; and non-Hodgkin's lymphoma, which often arises within the central nervous system (Stanley et al. 1991; Cianfrocca and Roenn 1998; Hannon et al. 1998; Bohlius et al. 2009).

Autoimmune-like disorders often associated or exacerbated by HIV-1 infection are atopic dermatitis, psoriasis (Namazi 2004; Morar et al. 2010), inflammatory bowel syndrome (Kotler et al. 1993; Mohan et al. 2007; Cecchinato et al. 2008) and pneumonitis (Griffiths et al. 1995; Ingiliz et al. 2006; Segal et al. 2011).

Overall, autoimmunity in HIV-1-infected patients is associated with the detection of the antibodies to the variety of autoantigens: organ-specific autoantibodies such as antiplatelet antibodies, anti-cardiac myosin antibodies, anti-smooth muscle-specific antibodies, and anti-erythroid cell-specific antibodies; nonorgan-specific antibodies such as antinuclear antibodies, antihistone antibodies, anti-double-stranded DNA antibodies, and antiphospholipid antibodies; autoantibodies against cell surface molecules such as CD4, MHC class I and II. Some of these autoantibodies have been thought to contribute to systemic autoimmune disease [reviewed in (Onlamoon et al. 2005)].

Structure of IL-23 cytokine and regulation of secretion

IL-23 comprises of a 19-kD 4-fold helical core α subunit (IL-23p19), linked to an additional 40-kD distinct β subunit (IL-12p40) by disulfide bonding. IL-23 shares its p40 subunit with IL-12 but has a unique p19 subunit. IL-12 is composed of two covalently linked subunits, IL-12p35 and IL-12p40. The expression of the p35 and p40 genes is independently

regulated. Production of p35 is rate limiting and the formation of biologically active IL-23 requires the synthesis of subunits, p40 and p19 within the same cell. Expression of the two subunits is tightly regulated and IL-23p19 is poorly secreted in the absence of IL-12p40. In vitro, p19 is secreted as a complex with the p40 subunit of IL-12. This association is necessary for its biological function, because purified p19 is biologically inert in vitro. IL-23 is produced by activated dendritic cells (DC) (Oppmann et al. 2000), macrophages (Pirhonen et al. 2002), monocytes (Lee et al. 2004b; Tchatalbachev et al. 2010). IL-23 rather than IL-12 is the primary type 1 cytokine produced by activated human pro-inflammatory macrophages (M1) (Verreck et al. 2004). Production of IL-23 is stimulated through activation of toll-like receptors (TLRs) by their ligands (including LPS, peptidoglycan, CpG DNA and poly I:C). Such interactions result in increased expression of p40 and p19, consequently enhancing the release of IL-23 (Langrish et al. 2004). However, generation pathway (blood-born or specific tissue residents), location in epithelial/endothelial barriers, program phenotype and ability to produce IL-23 in response to different pathogenic and non-pathogenic triggers for monocytes, macrophages and DC remains underinvestigated. Another aspect of IL-23 biology is the ability of non-hematopoietic epithelial/endothelial cells to directly produce or upregulate it production by resident macrophages/DC. Unfortunately, as of today, the only ability of human keratinocytes to express IL-23 mRNA and produce functional protein has been observed (Lee et al. 2004a; Piskin et al. 2006). The production of IL-23 p19 subunit by activated mouse astrocytes in response to LPS > LPS +IFNγ > IL-1β> IL-1β/IFNγ > IFNγ was also detected by PCR and confirmed by sequencing (Constantinescu et al. 2005; Xu and Drew 2007a).

Several factors are known to regulate the overall production of IL-23:

a. *PRRs*: The immune system is equipped with a variety of cell surface and cytoplasmic pattern recognition receptors (PRRs) that recognize conserved structures termed microbe-associated molecular patterns (MAMPs), which are expressed by a wide variety of organisms. A number of PRR families have been described, such as toll-like receptors (TLRs) and nucleotide-binding and oligomerization domain (NOD)-like receptors (NLRs) (Kawai and Akira 2009; Wang et al. 2011). Certain microbes possess a MAMP signature that specifically activates the IL-23 axis (Siegemund et al. 2007). This leads to preferential production of IL-23 at mucosal surfaces such as gut, as described in mucosal immunity section below. The preferential production of IL-23 in the gut may be a function of the pattern of PRR expression on intestinal immune cells as well as the nature of the PRR stimuli present in the intestinal lumen. Myeloid cells are differentially regulated in response to TLR signaling. IL-12 is strongly induced following TLR4, TLR8 stimulation. TLR2 agonists such as peptidoglycan (a cell wall component found in all bacteria, but particularly abundant in Gram-positive strains) are much more powerful inducers of IL-23 than TLR4 ligands such as LPS (a cell wall component of Gram-negative bacteria) (Re and Strominger 2001; Smits et al. 2004). There has been some evidence that activation of DC through TLR2 preferentially induces production of IL-23 over IL-12 (Langrish et al. 2004). TLR2 stimulation in combination with nucleotide oligomerization domain-containing protein 2 (NOD2) stimulation also induces expression of IL-23 (van Beelen et al. 2007). Stimulation of TLR3 and TLR7 also augments the expression of IL-23p19 by macrophages (Pirhonen et al. 2002; Al-Salleeh and Petro 2007). In addition, in mice with defective TLR4 signaling ($TLR4^{lps\text{-}d}$), mice deficient in TLR9 ($TLR9^{-/-}$) and double mutant mice ($TLR4^{lps\text{-}d}/TLR9^{-/-}$), the maximal classical activation of lung macrophages and expression of IL-23, required cooperative interactions between TLR4 and TLR9 (Bhan et al. 2010). Only synthetic TLR7/8 ligand, a mimic of viral ssRNA (such as HIV-1), induced IL-23 production by

lamina propria (LP) intestinal $CD1c^+$ DCs, and this proinflammatory cytokine response was synergistically enhanced following combined TLR7/8 and TLR4 stimulation (Dillon et al. 2010).

b. *LPS:* As the powerful inducer of IL-23 in human monocytes/macrophages/DC the regulation of LPS-induced expression of IL-23 is of special interest. LPS-induced expression of IL-23 could be down-regulated by interferon-stimulated response element (ISRE) in the *Il23a* promoter in macrophages (Sheikh et al. 2010, 2011). Global gene expression analysis of purified human monocytes showed that LPS-induced expression of IL-23 can be also regulated via triggering receptor expressed on myeloid cells-1 (TREM-1), which is an orphan immunoreceptor expressed on monocytes, macrophages, and neutrophils (Dower et al. 2008).

c. β-*glucans* in fungal cell walls and Dectin-1 receptor agonists such as curdlan triggers striking production of IL-23 by DC (LeibundGut-Landmann et al. 2007; Agrawal et al. 2010) and convert development of regulatory T cells in IL-17 producers (Osorio et al. 2008).

d. *Granulocyte macrophage colony-stimulating factor (GM-MCSF)*: In a mouse model, the study of the relative ability of bone-marrow-derived dendritic cells (BMDCs) versus bone-marrow-derived macrophages (BMDMs) to produce IL-23 in response to *S. pneumoniae* infection were compared (Wang et al. 2011). BMDCs and BMDMs constitutively released IL-23 at very low levels. Following infection with *S. pneumoniae* or stimulation with single cognate TLR2 or −4 agonist (lipoteichoic acid or pneumolysin), the levels of IL-23 in the culture supernatants of BMDCs and BMDMs were significantly increased. Interestingly, treatment with cognate TLR9 or NOD2 agonist (CpG or MDP) did not result in a significant induction in IL-23 production in BMDCs and BMDMs. The levels of IL-23 were ~5-fold higher in culture supernatants of BMDCs compared with those of BMDMs in response to *S. pneumoniae* infection. This indicates that in vitro generated with GM-MCSF DCs are more potent producers of IL-23 in response to *S. pneumoniae* infection than macrophage expanded from bone marrow precursors with macrophage colony-stimulating factor (M-CSF) (Wang et al. 2011). GM-CSF-mediated polarization to M1 monocytes/macrophages was associated with increased expression of interferon-regulatory factor 5 (IRF5) (Krausgruber et al. 2011).

e. *IFNγ→IL-23:* IFNγ has a variety of effects on IL-23 production. Production of IL-12 from macrophages and DCs is dependent on IFNγ. Contrary, the expression of IL-23 in response to microbial stimulation seems to be less dependent on IFNγ. The addition of IFNγ has enhanced IL-23 expression slightly by type 1 macrophages (M1, GM-CSF-mediated), and has no effect on IL-23 production by monocyte-derived DCs in response to microbial stimulation (Ghilardi et al. 2004). Type 2 macrophages (M2, polarized in M-CSF) were unable to produce IL-23 in response to microbial stimulation (Ghilardi et al. 2004). However, pretreatment of macrophages with IFNγ enhanced p19 expression induced by viral stimulation (Pirhonen et al. 2002). These results were confirmed in relation to the intracellular pathogens (van de Wetering et al. 2009). GM-CSF and IFN-γ primed human monocytes enhanced IL-23 production (not only IL-12p40 but also IL-23p19 subunit) and M1 generated by culturing $CD14^+$ monocytes for 6 days in the presence of GM-CSF were stronger producers of IL-23 compared with freshly isolated $CD14^+$ monocytes. GM-CSF or IFN-γ (known to enhance the expression of the IL-23 subunit IL-12p40 could prime monocytes directly for enhanced IL-23 production in response to stimulation with heat killed *Salmonella* (van de Wetering

et al. 2009). Thus, it appears that IFNγ controls IL-23 expression in some circumstances but plays a less stringent role than in IL-12 responses.

f. *IL-23→IFN*γ: The reverse situation was observed in regulation of IFNγ production by IL-23 in murine lymphocytes (Sieve et al. 2010). IL-23 antagonizes IL-12-induced secretion of IFNγ. When splenocytes or purified populations of T cells were cultured with IL-23, IFNγ secretion in response to IL-12 was dramatically reduced. According to this report, IL-23 receptor was not required and IL-23 inhibited signaling through the IL-12 receptor by reducing IL-12-induced signal transducer and activator of transcription 4 (STAT4) phosphorylation. These observations suggest that IL-23 may be an important factor in determining the responsiveness of lymphocytes to IL-12 and their subsequent secretion of IFNγ (Sieve et al. 2010).

g. *CD40:* IL-23 production can be enhanced *via CD40-CD40L interaction*, resulting in increased production of IL-23, and creating a potent positive feedback for augmenting IL-23 production by APC (Uhlig et al. 2006; Sender et al. 2010).

h. *IL-10* is an important factor that downregulates the production of IL-23 by macrophages. IL-23 p19 expression was significantly enhanced in IL-$10^{-/-}$ mice compared with WT mice. Pretreatment with IL-10 inhibited IL-23 p19 expression in mouse peritoneal macrophages (Liu et al. 2009). Addition of neutralizing antibodies to IL-10R during IFNγ-stimulation of mouse monocytes/macrophages significantly upregulates expression of IL-23R (Parham et al. 2002).

IL-23 receptor (IL-23R)

IL-23 exerts its biological activities through the interaction with IL-23 receptors. The receptor complex is a heterodimer made up of IL-23R (unique for IL-23) and IL-12Rβ1 (shared with IL-12) subunits (Parham et al. 2002). The IL-23R, consisting of an extracellular N-terminal immunoglobulin-like domain and two cytokine receptor domains, binds to the IL-23p19, while the IL-12Rβ1 subunit contains three membrane-proximal fibronectin type III and two cytokine receptor domains that interact with IL-12/23p40 (Langrish et al. 2004). Human (h)IL-23R is a 629 amino acid type I transmembrane protein, with sequence homology with IL-12Rβ2 and gp130. The gene for hIL-23R is located on chromosome 1p31.2–32.1, which is very close to IL-12Rβ2, suggesting that a gene duplication occurred sometime during evolution (Lankford and Frucht 2003). The murine counterpart of hIL-23R is 644 amino acids in length and has 84% sequence homology with the protein-coding regions of the hIL-23R gene (Parham et al. 2002). The important difference was noted for the expression of human and mouse IL-23R. If murine IL-23R was detected on 1 week polarized Th1 and Th2 clones, hIL-23R was present only on Th1 clones. Mice with large B-cells Ig +, but not LPS-activated splenic B-cells had mIL-23R. In human, it was found on resting EBV-transformed B cells. The most dramatic differences were noted for DCs and monocyte/macrophages. Neither human LPS-activated nor monocyte/CD34+ cell-derived DCs stimulated with GM-CSF/TNF-α were strong IL-23R expressing cells. In contrast, murine BMDCs and LPS-stimulated BMDM showed significant levels of expression, which allows us suggest the possibility of autocrine regulation. It was also shown that among humans, natural killer cell populations with the highest levels of IL-23R expression were found on non-cytolitic clones (Parham et al. 2002).

The expression of IL-23R on non-lymphoid and lymphoid immune cells is tightly regulated by retinoid-related orphan nuclear receptors (ROR)α and (ROR) γt [reviewed in (Jetten 2009)]. RORγt is exclusively expressed in a few distinct cell types of the immune system. Overexpression of both greatly increased expression of IL-23R without cytokine stimulation. Deficiency of either reduced IL-23R expression (Yang et al. 2008). The balance

of forkhead/winged-helix transcription factor (Foxp3) specific for natural and adaptive regulatory Tαβ cells (Treg) and RORγt expressing IL-17-producing Tαβ cells is an important factor of antibacterial and inflammatory responses (Lochner et al. 2008). Foxp3 was shown to bind to RORγt, suggesting that it directly regulates RORγt activity (Ichiyama et al. 2008). Moreover, the differentiation of human Th17 cells preferentially occurs from Foxp3 natural naive Treg in the presence of IL-2 and IL-1β and is increased by IL-23 and TGF-β (Valmori et al. 2010).

Expression of IL-23R was found on γδT cells. They show a rapid and robust response before the development of the adaptive immunity mediated by conventional T cells in tissues: in human intestine, in mice skin, in the uterine and vaginal epithelial, and they occur in tongue, lung, and mammary tissue (Moens et al. 2011).

In mice, *Il23r* is a candidate gene positively regulated by c-Maf [basic region/leucine zipper factors and binds to a consensus site [MARE (Maf recognition element)] during Th17 cell development. Authors suggested that c-Maf does not play an essential role in the early differentiation of Th17 cells but rather in the development and/or maintenance of memory Th17 cells (Sato et al. 2011).

Recently the expression of IL-23R was identified on a novel innate lymphoid cell population that accumulates in the inflamed tissues. These cells characterized by the expression of $Thy1^{high}SCA\text{-}1^{+}ROR\gamma t$, production of IL-17 and IFN-γ and is activated in response to microbes (Buonocore et al. 2010). Moreover, cells comparable in phenotype and location to the lymphoid tissue inducer (LTi) cells were identified in human lymphoid tissue, however they do have significant differences with mouse LTi (Spits and Di Santo 2011). LTi cells originate from hematopoietic precursor cells in the fetal liver characterized as $CD45^{int}CD4^{+}CD3^{-}CD127\ (IL\text{-}7R\alpha)^{+}Lin^{-}$ cells in mice and in humans as lineage-negative $CD45^{int}CD4^{-}CD3^{-}CD127^{hi}Lin^{-}$ cells. These cells did not show expression of IFNγ, but express high levels of IL-22 upon IL-23 stimulation (Kim et al. 2011; Sonnenberg et al. 2011).

The IL-23 receptor functional complex was also found on human plasma cells. In the presence of IL-2+IL-23 in culture medium, stimulation of IgM production was observed. Moreover, the bone marrow plasma cells also expressed IL-23R, but the functional relevance of these findings remains unknown (Cocco et al. 2010).

Likewise, polymorphisms in the gene encoding the IL-23 receptor are found to be important susceptibility factors for some disorders such as inflammatory bowel disease and psoriasis (Duerr et al. 2006; McGovern and Powrie 2007; Smith et al. 2008).

The signaling pathways

The signaling pathway of IL-23R is well investigated. It involves the Janus associated kinase 2 (Jak2), tyrosine kinase 2 (Tyk2) and several members of the signal transducer activator of transcription (STAT) family, including STAT1, STAT3, STAT4 and STAT5 (Parham et al. 2002). Stimulation of the receptor complex activates Jak2 and Tyk2, resulting in phosphorylation of the receptor complex, and formation of docking sites for STATs (1, 3, 4 and 5), same spectrum of Janus kinase (Jak)/signal transducers and activators of transcription (STAT) signaling molecules as IL-12 (Parham et al. 2002; Cua et al. 2003). The STATs are subsequently dimerized, phosphorylated, and translocated into the nucleus and activate target genes (Lankford and Frucht 2003). In lymphocytes, IL-23 induces a strong phosphorylation of STAT3 and a relative weak activation of STAT4, whereas the reverse is true for IL-12-induced phosphorylation of STAT4 and STAT3 (Cua et al. 2003; Smith et al. 2008). The phosphorylation of STAT3 is essential for development of IL-17-

producing T helper (Th17) cells (Kikly et al. 2006) whereas, STAT4 is important for increasing IFNγ production and subsequent differentiation of Th1 cells (Ghilardi et al. 2004). Overall, this process orchestrates the cytokine cascade, activating the necessary immune cells involved in the eradication of any pathogenic/antigenic challenge.

IL-23 transgenic and knockout mice

The importance of IL-23 in the development and maintenance of host immunity and prevention of undesirable inflammatory responses were best exemplified in animal models of IL-23 manipulation. IL-23 transgenic (over expressing p19 subunit) mice displayed impaired growth accompanied by systemic inflammation, cytokine dysregulation, elevated neutrophil, lymphocyte and macrophage infiltration, and multi-organ dysfunction leading to premature death. Tissue-specific expression of p19 yielded two outcomes. Animals expressing p19 in bone marrow-derived cells had a similar phenotype of systemic inflammation as seen in animals with the ubiquitous p19 expression. In contrast, animals expressing p19 in liver were fertile, had a normal life span, and did not show signs of systemic or localized inflammation. These results indicate that hemo-poietic expression of p19 is necessary and sufficient to induce systemic inflammation, impaired growth and premature death (Wiekowski et al. 2001).

IL-23 knockout (KO) mice demonstrated impaired bacterial/parasitic clearance, reduced NK cell number, and reduced delayed type hypersensitivity response and a deficiency in T helper (Th) cell development (Ghilardi et al. 2004; Happel et al. 2005; Schulz et al. 2008a; Meeks et al. 2009; Riol-Blanco et al. 2010).

IL-23 and $CD4^+$ cell subsets as a target for HIV-1

It is well established that HIV-1 destroys the immune system, which employs an array of specialized cells and effector mechanisms to control opportunistic infection. These include $CD4^+$ T helper 1 (Th1) cells that produce IFN-γ, IL-2, and lymphotoxin and are involved in cellular immunity, $CD4^+$ Th2 cells that produce IL-4, IL-5, IL-10, and IL-13 and provide help for B cells in their activation and differentiation leading to immunoglobulin production and humoral immune responses. Th1 cells provide help to cytotoxic CD8-positive T cells and macrophages to kill virus-infected cells and cells infected with intracellular pathogens. The production of immunoglobulin under the control of Th2 cells is one of the mechanisms that leads to elimination of extracellular bacteria, and, through the IgE mediated activation of mast cells, to protection against parasites. Another subset of $CD4^+$ lymphocytes sensitive to HIV-1 is regulatory T cells (Tregs, $CD3^+CD4^+CD25^+FoxP3^+$ cells), which also gradually decline from peripheral blood of HIV-1-infected patients (Prendergast et al. 2010). At the same time Tregs accumulates in lymph nodes (Andersson et al. 2005; Nilsson et al. 2006; Kinter et al. 2007) and mucosal sites (Epple et al. 2006). Overall, the stage of disease is associated with different proportions of $CD4^+$ cells of different phenotype and stage of development in peripheral blood, lymphoid and mucosal tissues (Dunham et al. 2008).

These concepts have been refined in recent years with the recognition of additional $CD4^+$ T cell subsets producing IL-17 (Th17) cells in control of pathogenic and opportunistic infections (OI). Introduction of highly active anti-retroviral therapy (ART) in infected patients significantly slowed progression of disease to AIDS and the development of the most common and recurrent opportunistic infections—*Pneumocystis carinii* pneumonia (PCP), candidiasis, disseminated *Mycobacterium avium* complex (MAC) disease, toxoplasmosis, activation of cytomegalo-viral infection and other infections (Heaton et al. 2010; Li et al. 2010).

It was suggested that potential trigger for AIDS development in humans (HIV-1) and macaques (SIV) is the loss of $CD4^+$ Th17, which is key for antibacterial defense in the gut. This process leads to microbial translocation, elevation of LPS and LPS control mechanisms in circulation, immune activation, possible conversion of Treg in Th17 (Osorio et al. 2008) and ongoing systemic loss of $CD4^+$ cells (Schnittman and Fox 1997; Douek 2007; Ancuta et al. 2010; Klatt and Brenchley 2010; Prendergast et al. 2010).

Recent studies on SIV infected Rhesus macaques (Macaca mulatta) infected with 100 animal-infectious doses of uncloned pathogenic SIVmac251 intravenously showed that there was a ~10–25 fold increase in the expression of IL-23 (also IL-21, and TGFβ) genes in total jejunal cells in earlier stages of infection before the CD4 cell loss (7–17 days) (Kader et al. 2009). However, the same authors found a ~2–4 fold down regulation of IL-23 mRNA in peripheral blood mononuclear cells (as well as IL-21, TGFβ) compared to uninfected animals at 13 weeks post infection. The treatment with antiretroviral drugs did not restore the expression of IL-23 (Kader et al. 2009).

We reviewed IL-23-related effects below in regard of pathogenic and protective functions of IL-17-producing cells. IL-17 cytokine family has at least six (A-F) members and IL-17A/F were associated with IL-23-mediated induction (Kastelein et al. 2007). Virtually all human/mouse cells do have the receptor to IL-17A/F and engagement of these receptors on external (gut, skin, lung, mucosal and corneal epithelium), internal epithelial barrier (synovial epithelial cells, renal epithelium, choroid plexus) and endothelial cells (Pedroso et al. 2011) leads to the production of innate protective antibacterial/antiviral peptides, as well as wound healing (Li et al. 2011).

IL-23/IL-17 axis and autoimmunity

Upon activation, naive $CD4^+$ T cells differentiate into different lineages of effector Th subsets. Each subset is characterized by its unique cytokine profile and biological functions. Th17, a newly described Th subset that produces IL-17, IL-17F and IL-22 in preference to other cytokines, has been shown to play an important role in clearing specific pathogens and in inducing autoimmune tissue inflammations. IL-23 support survival of highly pathogenic Th17 cells. Th17 cells produce IL-17 (IL-17A), IL-17F, IL-6, IL-22 and TNF-α but not IFNγ or IL-4 and, therefore, this subset is different from the classical Th1 or Th2 subset (Cua et al. 2003; McGovern and Powrie 2007). IL-17 enhances T cell priming and induces inflammation by stimulating fibroblasts, endothelial cells, macrophages and epithelial cells to produce multiple proinflammatory mediators, including IL-1, IL-6, TNF-α, NOS-2, metalloproteases and chemokines (Nakae et al. 2003; Kolls and Linden 2004). Th17 cell was a main pathogenic cell type in models of autoimmunity such as experimental autoimmune encephalomyelitis (EAE) and collagen-induced arthritis (CIA), animal models of multiple sclerosis (MS) and rheumatoid arthritis (RA), respectively, as well as in the pathogenesis of allergic responses such as contact hypersensitivity and delayed type hypersensitivity in IL-17-deficient mice (Nakae et al. 2002).

Role of IL-23 has been identified in patients with a variety of allergic and autoimmune diseases such as rheumatoid arthritis (Murphy et al. 2003), multiple sclerosis, inflammatory bowel disease (IBD) (Hue et al. 2006; Uhlig et al. 2006) and psoriasis suggesting the contribution of IL-17 to the induction and/or development of such diseases. Thus, the IL-23/Th17/IL-17 axis is likely to be associated with T cell-mediated autoimmune diseases.

IL-23/IL-17 axis and bacterial infections

Several researchers addressed the role of IL-23 in differentiation of naïve T cells to Th17 cells and their subsequent function. It was initially believed that IL-23 induces the

differentiation of Th17 cells. Subsequent studies showed that was not true because naïve T cells do not express IL-23R. Later studies revealed that TGF-β, IL-6 and autocrine IL-21 direct the de novo generation of Th17 cells (Mangan et al. 2006; Veldhoen et al. 2006). TGFβ induces the generation of Foxp3 expressing regulatory Treg, but the presence of IL-6 deviates TGFβ driven Treg toward Th17 polarization. Combination of TGF-β and IL-6 also induces the expression of ROR-γt, a critical factor for Th17 lineage determination (Ivanov et al. 2006). More recently, other transcription factors including an additional member of ROR family, RORa, IRF4 (Dong 2008) and aryl hydrocarbon receptor (Quintana et al. 2008) have also been implicated in this pathway. Additionally, TGFβ and IL-6 up-regulate IL-23R expression on naive T cells (conferring responsiveness to IL-23), thus aiding IL-23 in terminal differentiation of Th17 cells. In the absence of IL-23, Th17 cells stalled at the early activation phase resulting in less proliferation and failed to maintain IL-17 production (McGeachy et al. 2009). IL-23 is also essential for Th17 proliferation and for full effector function (Parham et al. 2002; Duerr et al. 2006). IL-23 is required for survival of already differentiated Th17 cells, during restimulation of Th17 cells and essential for IL-17 production by Th17 cells. IL-23 stabilizes the phenotype of Th17 cells through transcription factor STAT3 pathway (Zhou et al. 2007; Yang et al. 2008). It is important to point out that virtually all cells in human/mice do have receptors for IL-17. It is not completely clear who is playing the leading role in control of bacterial infection of external epithelial barriers.

As mentioned before, IL-22 is also coordinately expressed in Th17 cells along with other cytokines and the expansion and maintenance of IL-22-secreting $CD4^+$ T cells is dependent on IL-23 (Liang et al. 2006; Ness-Schwickerath et al. 2010). IL-23-dependent IL-22 secretion resulted in increased production of antimicrobial peptides by keratinocytes, offering an important mechanism by which IL-23 may perform a protective role during infection (Liang et al. 2006).

Recently it was shown that mouse $CD4^+$ lymphoid tissue-inducer cells promote innate immunity in the gut to enteric rodent pathogen *C. rodentium*. Adult $CD4^+$ LTi cells proliferate and upregulate IL-22 production within the first 6 days postinfection. $CD4^+$ LTi cells were found to be the dominant source of IL-22, and infection-induced $CD4^+$ LTi cell responses were predominantly IL-23 dependent (Sonnenberg et al. 2011). It was also shown for $Rag2^{-/-}$ immunodeficient mice that non-T, non-B LTi-like cells can rapidly produce IL-17 in vivo when challenged with the product of fungal pathogens. Moreover, consistent with their rapid responsiveness to IL-23, LTi-like cells constitutively expressed IL-23R mRNA at levels significantly greater than T cells, but expression levels of IL-12Rβ2 mRNA in $CD4^+$ LTi-like cells were low compared with those in memory $CD4^+$ T cells (Takatori et al. 2009).

IL-23-dependent IL-17 responses are important for protective immunity against *extracellular bacterial infections* for optimal induction of chemokines, recruitment of neutrophils, and bacterial killing. On exposure to bacterial pathogens, innate immune cells release cytokines such as TNFα to initiate the inflammatory response. Happel et al., showed that common p40 subunit of IL-12/23, IFNγ and IL-17 are critical for host defense against *Klebsiella pneumonia* (Happel et al. 2005). On intrapulmonary *K. pneumoniae* inoculation IL-12/23 p40–deficient mice are exquisitely sensitive and IL-23 $p19^{-/-}$, $IL\text{-}17R^{-/-}$, and IL-12 $p35^{-/-}$ mice also show increased susceptibility to infection. IL-$12p35^{-/-}$ mice show normal IL-17 and IL-17F but reduced IFNγ induction whereas IL-$12/23p40^{-/-}$ mice fail to generate pulmonary IFNγ, IL-17, or IL-17F responses to infection. In IL-$23p19^{-/-}$ mice pulmonary IL-17 and IL-17F production was severely impaired (despite normal IFNγ induction) and animals had substantial mortality from a sublethal dose of bacteria. In addition, administration of recombinant IL-17 restored bacterial control in IL-23p19-deficient mice, suggesting that IL-17 induced by IL-23 plays a significant role in the early

host defense against *K. pneumonia* (Happel et al. 2005). The IL-23/IL-17 axis is also necessary for host protection against *Citrobacter rodentium* (Simmons et al. 2002). In another animal model of *S. aureus* cutaneous infection, it was found that mice deficient in γδ but not αβ T cells had substantially larger skin lesions with higher bacterial counts and impaired neutrophils recruitment compared with wild type (WT) mice. This neutrophil recruitment was dependent upon epidermal Vγ5+ γδ T cell production of IL-17, which requires IL-23. This was critical for host defense, since IL-17R deficient mice had a phenotype similar to that of γδ T cell–deficient mice. Importantly, γδ T cell–deficient mice inoculated with *S. aureus* and treated with a single dose of recombinant IL-17 had lesion sizes and bacterial counts resembling those of WT mice, demonstrating that IL-17 could restore the impaired immunity in these mice (Cho et al. 2010). In a well-established opiate abuse and *S. pneumoniae* lung infection mouse model it was demonstrated that *Streptococcus pneumoniae* induces IL-23 and IL-17 expression in the lungs as early as 2 h following infection. Morphine treatment causes a decrease in both IL-23 and IL-17 synthesis during the early stages of infection, leading to delayed neutrophil recruitment (Wang et al. 2011). This results in an increased bacterial burden within the lungs and the initiation of systemic disease. This study further established the critical role of IL-23→IL-17 cytokine pathway for protective immunity against extracellular bacterial infections (Ye et al. 2001; Happel et al. 2005).

In mouse models, Th17 cells provide protection against *Klebsiella pneumoniae, Citrobacter rodentium, Staphylococcus aureus, Pseudomonas aeroginosa, and Candida albicans* infections—all extracellular bacteria and fungi.

The importance of Th1 cell immunity in host resistance to the *intracellular bacterium* is well established (Cooper et al. 2002). However, the relative roles of interleukin IL-12-Th1 and IL-23/Th17 cell responses in immunity to intracellular pathogens have only recently been characterized (Lin et al. 2009). This was studied in an animal model of *Francisella tularensis* (*F. tularensis*). For *F. tularensis* infection, IL-17A, but not IL-17F or IL-22, induced IL-12 production in DCs, mediated Th1 responses and induced IL-12 and IFNγ production in macrophages mediated bacterial killing. Similar to other pulmonary infection models (Happel et al. 2005), early induction of IL-23p19 and the more sustained production of IL-12p35 in the *F. tularensis* live vaccine strain (LVS)-infected lungs suggests important IL-23 function during the early immune response. In vitro experimental exposure of human monocytes to *L. monocytogenes*, as well as *S. aureus, S. pneumoniae* upregulated the IL23A mRNA levels were 48 -, 30- and 6-fold, respectively. Despite donor specific gene variations and despite the different invasion strategies of the bacteria studied, the common program of gene expression induced by all three bacterial pathogens and a key cytokine—IL-23 was identified (Tchatalbachev et al. 2010).

Similarly, in a *Bordetella pertussis* model, it was shown that IL-17A treatment of macrophages enhanced bacterial clearance (Higgins et al. 2006) and was thought to be mediated by direct macrophage activation. This suggests that IL-17A can modulate the innate responses and contribute to immunity and clearance of some intracellular bacteria until the arrival of adaptive immune cells to the site of infection.

As mentioned earlier, it was earlier believed that for intracellular bacteria, such as *Mycobacterium tuberculosis*, IL-23 had no role in protection from infection (Khader et al. 2005; Wozniak et al. 2006). But recently, there is accumulating evidence for the role of IL-17 during mycobacterial infections. Pulmonary infection with *Mycobacterium bovis* bacille Calmette-Guerin (BCG) (Umemura et al. 2007) or *M. tuberculosis* (Khader et al. 2007) stimulated the early secretion of IL-17, within 1 and 14 days respectively, and this preceded the development of IFN-γ-secreting T cells. It is possible that the subsequent

production of IFN-γ during mycobacterial infections down-regulates the IL-17-secreting T cell response (Khader et al. 2007), and therefore difficult to identify an independent protective effect of Th17 T cells early in the course of *M. tuberculosis* infection. During pulmonary BCG infection, IL-17 deficient mice showed reduced IFN-γ T cell and delayed type hypersensitivity responses to mycobacterial antigens and impaired granuloma formation in the lungs, suggesting IL-17 was required for the development of optimal Th1 T cell responses (Umemura et al. 2007). Infection of IL-17$^{-/-}$ mice with *M. tuberculosis* revealed that IL-17 was not essential to control the growth of *M. tuberculosis* during acute infection (Khader et al. 2007), and it was assumed that the emerging IFN-γ-secreting CD4^{+} and effector CD8^{+} T cells were sufficient to inhibit mycobacterial replication in absence of IL-17. More recently however, it has been suggested that IL-17 is necessary for the maintenance of Th1 T cell immunity during chronic *M. tuberculosis* infection, as infected IL-17$^{-/-}$ mice showing reduced survival late in the course of infection, as compared to wild type mice (Wozniak et al. 2010). Catabolism of tryptophan by IFNγ-inducible indoleamine-2,3-dioxygenase (Ido1) was important to control the balance between adaptive (Cooper and Khader 2008) and innate (Happel et al. 2005) control in murine model of *M. tuberculosis* infection (Desvignes and Ernst 2009). In IFNγ receptor knockout mice significant increase in IL-23p19 expression in chronic phase of disease with neutrophils recruitment to the lungs in large numbers due IL-17 overproduction was observed. Low concentrations of kynurenines were capable of controlling the development of Th17 cells in vitro, in an IL-23-dependent fashion (Desvignes and Ernst 2009).

The unique requirement for the IL-23-Th17 cell pathway in induction of Th1 cell responses during *F. tularensis* LVS (Butchar et al. 2007; Lin et al. 2009; Markel et al. 2010), *M. tuberculosis* (Khader et al. 2005; Desvignes and Ernst 2009), but not other intracellular infections is intriguing. This suggests that different intracellular bacteria may stimulate differential TLRs on APCs and produce distinct polarizing cytokines that impact host immune response to infection. It is likely that some intracellular bacterial infections can effectively induce IL-12-IFNγ responses in the host, whereas other pathogens require the IL-23-IL-17A pathway for effective induction of host IL-12-IFNγ responses for pathogen control. Induction of IL-12 by *F. tularensis* LVS infection is dependent on TLR-2 signaling (Hong et al. 2007), whereas induction of IL-12p40 by a heat-shock protein of *Francisella* is dependent on TLR-4 (Ashtekar et al. 2008). BCG lipomannans induce IL-12p40 through TLR-2 (Quesniaux et al. 2004). In contrast, long-term up-regulation of the IL-23p19 message by BCG in human monocytes was observed (Begum et al. 2004).

Toxoplasma gondii is an opportunistic pathogen in AIDS patients. Neutralization of IL-12 enhanced mortality in mice infected with *T. gondi* (Hunter et al. 1994). IL-12p40 and p35 KO mice were infected with *T. gondii* and their response to infection was compared with wild type (WT) animals. In this study, none of WT mice succumbed after infection. In contrast, in p40 $^{-/-}$ mice, 100% of the mice had succumbed by 20 days post infection. The p35$^{-/-}$ mice exhibited intermediate sensitivity to *T. gondii* compared to WT and p40$^{-/-}$ mice (Lieberman et al. 2004). The p35$^{-/-}$ p40$^{-/-}$ mice exhibited higher parasite burden than WT mice, however, IL-23p19$^{-/-}$ mice were as resistant to *T. gondii* as WT (Vossenkamper et al. 2004). Thus, IL-12 plays a primary role in resistance to *T. gondii*, but IL-23 can also contribute to resistance in the absence of IL-12. A similar role was reported in the pathogenesis of *Leishmania*, another major intracellular protozoan parasite (Murray 1997; Engwerda et al. 1998). A recent study showed that IL-23 regulates the *T. gondii* mediated small bowel inflammation via IL-22 but is independent of IL-17 (Munoz et al. 2009).

Candida albicans—the ubiquitious yeast (fungus) living in warm, moist areas of the body becomes a generalized infection for HIV-1 immunosuppressed patients. For a long time the Th1 and IFNγ were believed to be critical in host defense against *C. albicans*. In a murine

model of cutaneous candidiasis the dependence upon IL-23, for an effective immune response against *C. albicans* within skin as well as epidermal hyperplasia was shown (Kagami et al. 2010). However, the evaluation of the contribution of the IL-23/IL-17 pathway to *C. albicans* infection in mice with gastrointestinal infection led to the different conclusion (Zelante et al. 2007). Comparatively assessed $p19^{-/-}$, $p35^{-/-}$, $p40^{-/-}$ and C57BL/6 mice for survival, fungal growth, tissue pathology and parameters of inflammatory and adaptive Th1/Th17 immunity showed that IL-23/IL-17 pathway impaired anti-fungal immune resistance (Zelante et al. 2007). IL-23 acted as a molecular connection between uncontrolled fungal growth and inflammation, being produced by dendritic cells in response to a high fungal burden and counter-regulating IL-12p70 production. Both IL-23 and IL-17 subverted the inflammatory program of neutrophils, which resulted in severe tissue inflammatory pathology associated with infection. The role of IL-23 in candidiasis was recently reviewed by (Wei et al. 2011).

In relation to protection against bacteria we have to point out that IL-23 also regulates granulopoiesis in a neutrostat regulatory feedback loop through IL-17A-producing neutrophil regulatory (Tn) cells, most of which express γδ TCR. Both normal and neutrophilic (*Itgb2*$^{-/-}$) mice showed reduced circulating neutrophil counts when deficient in IL-12 p40. Injection of rmIL-23, but not rmIL-12 into p40-deficient mice restored circulating neutrophil numbers (Smith et al. 2007).

IL-23 and mucosal immunity

For an effective mucosal homeostasis, immune responses are tightly regulated to ensure protective immunity to the host, and it is of utmost importance that the adaptive and innate immune systems are able to recognize pathogenic organisms while ignoring the commensal flora. IL-23 has recently been shown to be a key player in influencing the balance between tolerance and immunity at mucosal surfaces such as in the gut, the lung, and the skin. IL-23 orchestrates T- cell-dependent and T-cell-independent pathways through effects on Th1 and T17- associated cytokines (Ahern et al. 2008). Of various immune regulators, Treg cells, by secreting TGF-β and IL-10, prevent unwanted immune responses and maintain a ‘high threshold’ for immune activation. Treg cells express high levels of the transcription factor foxp3 and play a non-redundant role in immune homeostasis. IL-23, by acting as a switch factor, allows induction of cellular immunity during an infection by overcoming the suppressive effects of Treg cells in the intestine. This is evident by a dramatic increase in the Tregs in the intestine when IL-23 is absent (Izcue et al. 2008), and the inability to elicit an immune response against gut pathogens in IL-$23p19^{-/-}$ mice (Mangan et al. 2006). From these observations, it has become clear that aberrant expression of IL-23 in the gut certainly can be a major driver of chronic inflammation leading to autoimmune colitis. There is ever-growing evidence that IL-23 seems to play a more dominant role in mucosal tissues. Many gut pathogens evoke a strong IL-23 response, which is essential for host defense. IL-23 activates the adoptive and innate immune systems to produce IL-17A, IL-17F, IL-22, and TNF, all of which help to stimulate epithelial cells to produce antimicrobial factors. These properties are important in host defense against a number of infections as mentioned earlier, such as *Klebsiella pneumonia, Candida albicans and Toxoplasma gondii*. IL-23 thus provides a robust innate immune response for first-line defense against environmental assaults, such as in the gut, the lung, and the skin. It is when this response goes unchecked that its pro-inflammatory actions overcome the beneficial role of IL-23 (Tato and Cua 2008). The source of intestinal IL-23 could be the unique subset of $CD14^{+}$ population of macrophages that not only produce IL-23 in response to commensal flora, but increased production of IFNγ by lamina propria infiltrating lymphocytes, which in turn trigger further abnormal macrophage differentiation with an IL-23-hyperproducing phenotype (Kamada et al. 2008). An important subset of $CD4^{+}$ Th17 and their gut-homing precursors

$CD4^+CD161^+$ appears to be preferentially infected and depleted during acute HIV/SIV infection (Macal et al. 2008; Ancuta et al. 2010; Prendergast et al. 2010). Th17 cells secrete both IL-17 and IL-22, which in turn induce the production of other cytokines, β-defensins, and other antimicrobial peptides important for host defense (Schulz et al. 2008b). These cells are considered particularly important for mucosal defense against opportunistic pathogens, including fungi such as *Candida albicans*, and for maintaining epithelial integrity. Relative to controls, SIV-infected macaques coinfected with *Salmonella typhimurium* showed increased dissemination of *Salmonella*, which was associated with depletion of mucosal Th17 cells (Raffatellu et al. 2008). This finding suggested that IL-17 deficiency contributes to defective intestinal barrier function and host protection. However, the association of IL-23-producing activated dendritic cells/macrophages and development and survival of IL-17-producing cells in gut-associated immune compartment was not rigorously investigated.

In summary, IL-23 mediates both protective and pathological functions. Under homeostatic conditions, low levels of IL-23 may contribute to mucosal barrier function and microbicidal activity through IL-17 and IL-22. In the presence of a strong inflammatory stimulus, there is increased production of IL-23 and other inflammatory mediators that inhibit Treg responses leading chronic inflammatory pathways at mucosal barrier as seen in inflammatory bowel disease (Ahern et al. 2008).

IL 23 and neurological disorders

Experimental autoimmune encephalitis and multiple sclerosis (EAE and MS)

Historically, the most well-established murine model of brain inflammation is EAE. It was previously believed that IL-12 induced Th1 cells triggered autoimmune diseases such as EAE (Gately et al. 1998; El-Behi et al. 2011). However subsequent studies have demonstrated that the similar structure, IL-23, not IL-12, is essential for the development of these autoimmune diseases (Cua et al. 2003; Ciric et al. 2009;). Mice deficient in IFN-γ, IFN-γR, IL-12βR2 and STAT1, which are critical molecules in IL-12/IFN-γ mediated responses, were not resistant but, were more susceptible to EAE (Engwerda et al. 1998; Chen et al. 2006). Subsequently targeting IL-12 subunits further questioned IL-12 association with chronic inflammatory conditions. Mice deficient in either the IL-23p19 subunit or the IL-12/23p40 subunit are resistant to EAE, whereas IL-12p35-deficient mice remain susceptible to these diseases (Cua et al. 2003; Murphy et al. 2003).

Targeting of p19 and p35 subunits revealed that IL-23, rather than IL-12, is crucial during the pathogenesis of these autoimmune diseases. Genetic deficiency or in vivo neutralization of IL-23p19 chain confers resistance against EAE (Cua et al. 2003; Chen et al. 2006; Thakker et al. 2007). IL-23 p19 deficient mice were still able to mount Th1 response but were resistant to EAE (Cua et al. 2003). Anti-IL-23 therapy reduced the serum levels of IL-17 as well as CNS expression of IFN-γ, IL-17, IL-6 and TNF α and ameliorated EAE (Chen et al. 2006). In addition, IL-23-stimulated peripheral blood $CD4^+$ lymphocytes are potentially efficient at penetrating brain derived microvascular endothelial monolayers in vitro (Kebir et al. 2007). This could be secondary to IL-23 driven upregulation of adhesion molecules on $CD4^+$ T cells that enhance their interactions with endothelium. IL-23 could also stimulate $CD4^+$ T cells to secrete soluble factors and/or upregulates cell surface adhesion molecule expression on endothelial cells, or disrupt junctions between endothelial cells, in their vicinity. IL-23 could influence T cell trafficking by modulation of chemokines receptor profiles.

Effects of IL-23 cannot be explained by actions of IL-17 alone because anti-IL-17 treatment did not prevent the onset and relapse of EAE with the same efficiency as anti-IL-23p19 or

anti IL-12/IL-23p40 treatment. IL-23 may directly activate a subset of mouse macrophages and dendritic cells expressing IL-23R, resulting in the production TNF-α and IL-1 (Cua et al. 2003). IL-6 and IL-1 likely play role in the development of EAE since IL-$6^{-/-}$ and IL-$1^{-/-}$ mice are significantly resistant and IL-1 receptor antagonist deficient mice are more susceptible to EAE (Chen et al. 2006). In the EAE model, it was shown that DCs also expressed IL-17R and secreted IL-23 in responses to IL-17, which was enhanced by LPS and blocked by addition of IL-17RFc. Furthermore, DCs expressed IL-1β, IL-6, TGF-β, CCL2, and CXCL10 in response to IL-17 alone or in synergy with a TLR agonist. These findings demonstrate that γδ T cell-derived IL-17 promotes further IL-17 production by Th17 cells, both directly by interacting with IL-17R on $CD4^+$ T cell and indirectly by enhancing the production of IL-23 and other cytokines and chemokines from DCs that promote the development, expansion, and recruitment of Th17 cells in the brain (Sutton et al. 2009).

LPS-stimulated human microglial cells efficiently express IL-23p19 as well as perivascular dendritic cells in areas affected by MS. Effective treatment of MS patients with type 1 interferon-beta reduced the expression of IL-23p19 (Li et al. 2003; Sonobe et al. 2005; Xu and Drew 2007).

Though there was considerable progress made in delineating the pathophysiology of EAE, the animal model of MS, and having preclinical studies using animal models yielded promising results, translation into the clinic was disappointing (Codarri et al. 2010). So, further understanding of pathophysiology is required at this stage to be able to translate the knowledge into clinical practice successfully. MS is one of several autoimmune diseases, where different types of blocking therapeutic antibodies for IL-23 and IL-23p19 were used (Kasper et al. 2006; Wittig 2007; Segal et al. 2008; Kurzeja et al. 2011).

CNS viral infections

IL-23 is also involved in the control of viral infections in the brain. First it was shown for experimental ocular herpes simplex virus type 1 (HSV-1) infection in mice (Kim et al. 2008), where upregulation of IL-23p19 was detected as soon as 3 days post infection in trigeminal ganglia (Broberg et al. 2002, 2004). In West Nile virus (WNV), a mosquito-transmitted single-stranded RNA (ssRNA) flavivirus, causes human CNS disease of variable severity, TLR7 and IL-23-dependent responses represented a vital host defense mechanism (Town et al. 2009). In autoimmune demyelinating disease following Theiler's virus (TMEV) infection Thomas M. Petro and co-authors have shown that TLR3 and TLR7 contribute to IL-23 p19 expression during challenge of macrophages with TMEV (Al-Salleeh and Petro 2007, 2008).

CNS HIV-1 infection

HIV-1 infects brain mononuclear phagocytic cells (MP, macrophages/micrglia) and activated MP are tightly associated with the development of neurologic complications in infected patients (Price et al. 1988; Budka 1990; Gendelman and Tardieu 1994; Newton 1995; Antinori et al. 2007; Yadav and Collman 2009). However, involvement of IL-23 in pathogenesis of such conditions is not clear. The peripheral immune cells, which pass through the BBB and scatter through the brain parenchyma (white matter tracts) or become entrapped in perivascular spaces, can activate microglial cells. Activated microglia can persistently contribute to the loss of neuronal function, with or without productive HIV-1-infection (Spencer and Price 1992; Kielian 2004). Microglial cells are the major sensor of the neuronal microenvironment and respond to neuronal dysfunction by multiple mechanisms (Kramer-Hammerle et al. 2005; Yadav and Collman 2009). The ability of activated lymphocytes, primarily functionally mature CD4 T helper 1 (Th1) T cells and

$CD8^+$ cytotoxic lymphocytes, NK (Shieh et al. 2001; Clements et al. 2002; Bissel et al. 2008; Sadagopal et al. 2008), and to a lesser extent in HIV-1/SIV brain infection, NK T cells and γ δ T cells, to prime microglial cells via IFNγ is part of the cascade of cytokines and events associated with the adaptive immune response. Activated microglia by IL-23 secretion can stimulate T cells differentiation into Th17 (IL17-, IL-21- and IFNγ producing cells), which contribute to inflammation in the brain (Gottfried-Blackmore et al. 2009; Goverman 2009; Louis et al. 2010); and play a significant role in protecting the host from opportunistic bacterial infections (Jin et al. 2004; Khader et al. 2005; Desvignes and Ernst 2009; Dietlin et al. 2009; Martin et al. 2009; Meeks et al. 2009; Riol-Blanco et al. 2010). The decline of protective HIV-1-specific $CD4^+$ cells due to HIV-1 infection may be associated with increased migration and local CNS expansion of antiviral/antibacterial T cells, which produce IL-17 and IFNγ in response to damage signals that destroy infected cells by MHC-independent mechanisms (Fenoglio et al. 2009). The presence and dynamics of these cell populations (NK T cells and T cells) in the brain during HIV-1/SIV infection has not been vigorously investigated. Moreover, in the brain, the balance between effector and regulatory $CD4^+$ cells, which are susceptible to HIV-1 infection and could contribute to the brain inflammatory responses is unknown.

IL-23 and tumors

Many cancers arise from the sites of infection, chronic irritation and inflammation, caused by infectious agents such as *Helicobacter pylori* and hepatitis viruses or non-infectious agents such as asbestos etc. Inflammatory cells in tumor microenvironment play a significant role in the neoplastic process by altering proliferation and survival of tumor cells (Coussens and Werb 2002). Innate immune cells in chronically inflamed tissues secrete several cytokines and metalloproteinases, along with factors affecting angiogenesis, such as vascular endothelial growth factor, thereby altering tumor growth. Locally expressed cytokines and various growth factors may not only aid in tissue remodeling and angiogenesis, but also protect the tumor from immune mediated elimination (Ganss et al. 2004). In contrast, tumor infiltrating T cells and intraepithelial lymphocytes provide immune surveillance by eliminating early malignant lesions (Dunn et al. 2004). HIV-1-induced immunodeficiency significantly increases development of malignancies, such as Kaposhi sarcoma, non-Hodgkin lymphoma and other different types of carcinomas (De Vuyst et al. 2008; Silverberg et al. 2009).

Infectious inflammation is associated with the secretion of several cytokines by innate immune cells in response to pathogen-associated molecular stimuli. Recent studies showed that IL-23, and not IL-12, is over-expressed by macrophages and DCs in human and mouse tumors and antagonistically regulates local inflammatory responses in the tumor microenvironment and infiltration of intraepithelial lymphocytes. IL-23 upregulates proinflammatory cytokines IL-17 and IL-22, matrix metalloproteinase MMP9 and increases angiogenesis. In addition, IL-23 reduces tumor infiltration of $CD8^+$ T cells. In contrast, IL-12 promotes infiltration of cytotoxic T cells. Genetic deletion or antibody-mediated elimination of IL-23 leads to increased infiltration of cytotoxic T cells into the transformed tissues, thus protecting against chemically induced carcinogenesis (Langowski et al. 2006). In addition, mice depleted for IL-23 or IL-23R showed restricted growth in transplanted tumors (Langowski et al. 2006). It was also shown that Th17 cells are gradually increased in the tumor microenvironment during tumor development (Kryczek et al. 2007) and that IL-17 upregulates the production of a variety of proinflammatory cytokines (Kolls and Linden 2004) and proangiogenic factors (Takahashi et al. 2005) to promote tumor development (Numasaki et al. 2003). Therefore, the activation of the IL-23/IL-17 pathway promotes the incidence and growth of tumors by inducing local inflammatory responses (Shime et al. 2008). The relationship between microbial stimulation, inflammation and cancer was in deep

review by (von Hertzen et al. 2011). In addition, in murine models it was shown that IL-23p19 suppressed controlled by NK cell-mediated immunity. In particular, NK cell perforin and IFN-γ effector functions appear to be suppressed by host IL-23p19, and suppression was independent of host IL-17A (Teng et al. 2010).

Conclusions

The actual involvement of IL-23 in controlling OI and cancer in AIDS remains understudied. Taking the fact that the most powerful inducers of this cytokine are bacterial/fungal products, the microbial/fungal local persistence is impossible due to strong innate immunity mediated by microbicidal peptides at all external body barriers. The deficiency of the barriers and translocation of bacterial/fungal products in systemic lymphatic tissues should continuously stimulate macrophages/DC to produce IL-23/IL-12 and support the innate barrier protection with $CD4^+$ IL-17-producing cells as well as all arms of adaptive immunity until complete resolution. In HIV-1 infection, overproduction of IL-23 should counterbalance the anti-bacterial/fungal protection by stimulation of local accumulation of innate immune cells. Unfortunately, in the absence of Th1 and Th2 types effectors these cells do not have the power to compensate adaptive immunity, but will attract more granulacytes/macrophages with high tissue destructive potential. Schematic representation of this hypothesis is shown on Fig. 1. Another arm of immune suppression and actual reduction of IL-23 production by activated macrophages in chronic HIV-1 infection could be disproportional accumulation of IL-10-producing Treg and/or changes in macrophage polarization from M1 IL-23-producing to M2 IL-10-producing cells. Antiretroviral treatment induced restoration of $CD4^+$ cell (Th1) system may not come with the restoration of IL-23 production as was shown by a few humans and SIV-infected monkey observations.

Based on reviewed findings we suggest that overproduction of IL-23 by activated macrophages, DC and brain resident microglial cells could be a pathogenetic factor and a therapeutic target for prevention of HIV-1-induced immune activation, inflammation, neurodegeneration and tumorogenesis. However, down regulation of IL-23 expression in advanced HIV/SIV infection raised the question of the mechanisms involved in regulation of its production by cells of myeloid lineage (macrophages and dendritic cells) and capability to support the protective antibacterial/antifungal function of Th17 cells as well as all other IL-23R expressing populations. All these aspects require attention and thoughtful investigation.

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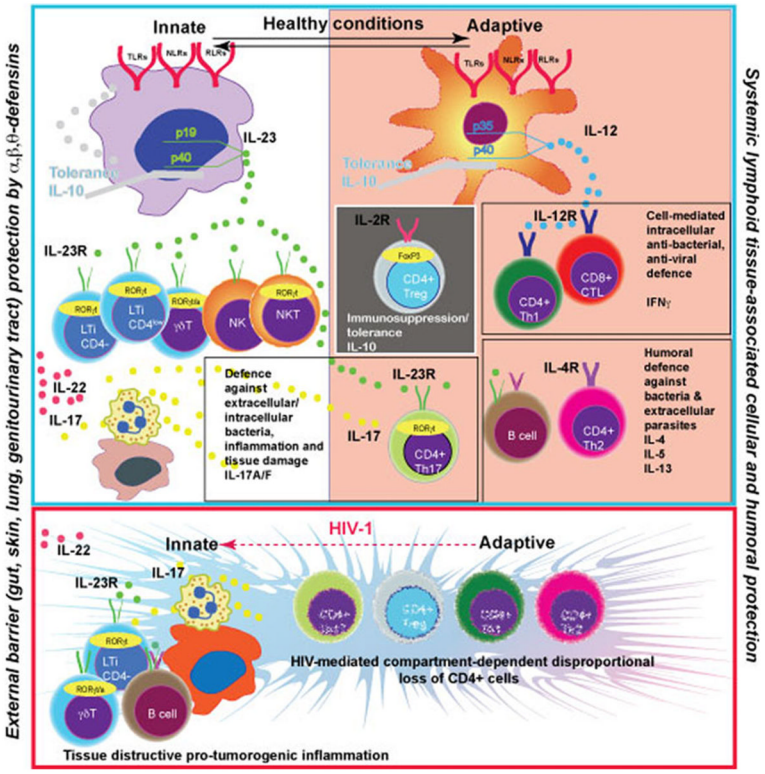

Fig. 1.

IL-23 is a key cytokine produced by macrophages at the external body barriers – gut, skin, lung, genitourinary tract. IL-23 stimulates the protective function in a variety of innate immune cells. It includes IL-17, IL-22 secretion, granulocytes attraction and the release of bactericidal peptides. The barrier prevents generalization of bacterial/fungal infections and maintains the balance with systemic lymphoid tissue associated IL-12→IFNγ and IL-4 axis of the Th1/Th2 mediated adaptive immune system. The protection generated by T cells of adaptive immunity (antibody production and cytotoxic T cells) at external barriers now includes $CD4^+$ IL-17 producing cells. These cells are in a balance with immunosuppressive Treg. Microbial environment at the external barriers and cytokine milieu induced by microbiota dictates the organ-specific balance between Th17 and Treg cells. The transcriptional factors FoxP3 and RORγt are involved in phenotypic control of these cells. There is ongoing loss of $CD4^+$ T cells and an associated adaptive immunity contribution in antibacterial/antifungal control during HIV-1 infection. External barrier macrophages upregulate expression of IL-23 in response to pathogens and attract more innate immune cells, B cells and neutrophils to generate a new type of barrier (tertiary lymphoid structures in bowel, lung, skin). Expanded proliferation of epithelial cells and tissue destruction (inflammation) is a pro-tumorogenic environment. Anti-retroviral treatment will induce partial restoration of Th1/Th2 immune responses and such inflammation could be increased. However, it will not compensate the innate immune cell protective function. The secretion of IL-23 will be reduced as a result of a combination of several negative regulatory factors, such as IL-10, IFNγ and IL-4, and facilitate the development of opportunistic infections