Cytokine 120 (2019) 78–84

Contents lists available at ScienceDirect

Cytokine

journal homepage: www.elsevier.com/locate/cytokine

Review article

IL-23 and dendritic cells: What are the roles of their mutual attachment in immune response and immunotherapy?

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ARTICLE INFO

Keywords:
IL-23
IL-23R
Dendritic cells
T cell
Autoimmune diseases
Infection

ABSTRACT

Interleukin-23 (IL-23) is a cytokine that is composed of the subunits p19 and p40, while its receptor (IL-23R) consists of two subunits, that is, IL-23Rα and IL-12Rβ1. The interaction between IL-23 and IL-23R is necessary for exerting cardinal biological effects upon certain cell types, including promotion of memory T cell proliferation and Th17 cell-mediated IL-17 secretion. Accordingly, dendritic cells (DCs) are one of the main sources for IL-23 secretion. Interestingly, IL-23R is also present on the DC plasma membrane, suggesting that IL-23 potentially acts on DCs via an autocrine manner. In this review, we have summarized a variety of IL-23-mediated effects on the intracellular signaling pathways such as Janus kinase 2, tyrosine kinase 2, signal transducer and activator of transcription (STAT), mitogen-activated protein kinase signaling, and so forth, which may underlie numerous processes such as DC maturation, antigen presentation, T cell proliferation/activation, and cytokine secretion, which may be implicated in many immune-related diseases through IL-23/DC interactions. Accordingly, these signaling pathways are extensively involved in the pathogenesis and progression of numerous diseases, including autoimmune disease (e.g., atopic dermatitis, asthma, and multiple sclerosis) and infection (e.g., bacterial, fungal, and viral infections). Taken together, they are potentially applicable to novel but promising strategies for treating numerous diseases associated with the mutual attachment of IL-23 and DCs.

1. Introduction

Despite the fact that Oppmann and colleagues identified the cDNA sequence expressing interleukin-23 (IL-23) protein as early as the very beginning of the 21st century, a previous study had assumed that IL-23 alone has no detectable biological activity, since researchers originally believed that IL-23 was not only homologously related to IL-12 by sharing the p35 subunit in common, but also, in order to execute function, IL-23 had to form a complex comprising one of its subunits, p19, with another novel p40 subunit of IL-12 [1]. Given that the expression analysis of mouse cDNA libraries showed the presence of p19 mRNA in different cell types from various tissues [1], the highest level of IL-23 expression was found in polarized Th1 cells [2–5] and activated macrophages [6–10], among other cell types, which have been extensively studied since then. Accordingly, researchers started to consider that IL-23 alone, instead of IL-12 or their complex, is a more vital cytokine mediating certain functions in a specific region, for instance, autoimmune inflammation in the brain [11]. Additionally, a large amount of IL-23 secretion was also found in activated dendritic cells (DCs) in both mouse and human DCs derived from peripheral blood monocytes [1,12,13], but their mutual interactions have not been well defined yet. Basically, regarding IL-23 receptor (IL-23R) composed of two subunits, IL-23Rα and IL-12Rβ1, it is diversely expressed on DCs, macrophages, natural killer cells, and activated and/or memory T cells in humans [14,15]. It has been widely accepted that the affinitive binding between IL-23 and IL-23R is necessary for the normal biological activity implicated in all the relevant cell types [16–19]. Thus, the advances in the mutual attachment between IL-23 and related cell types of interest are described in brief as follows.

1.1. Memory T cells

IL-23 promotes the proliferation of memory T cells in a dose-dependent manner [1,15] as well as induces activation of memory T cells

Abbreviations: A/J, asthma-sensitive mice; CTL, cytotoxic T-lymphocyte; CD, cluster of differentiation; C3H, asthmatic mice; DC, dendritic cell; GP, glycoprotein; HIV-1, human immunodeficiency virus type 1; IFN, interferon; IL, interleukin; IL-23R, IL-23 receptor; MHC, major histocompatibility complex; OVA, ovalbumin; SOCS1, suppressor of cytokine signaling 1; STAT, signal transducer and activator of transcription; Th cells, T helper cells; TLR, Toll-like receptor; TNF, tumor necrosis factor

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https://doi.org/10.1016/j.cyto.2019.02.018
Received 19 September 2018; Received in revised form 21 February 2019; Accepted 22 February 2019
Available online 24 April 2019

for subsequent production of IL-17 and interferon (IFN)-γ [14]. Nevertheless, there is a diverse expression and a distinctive secretion pattern of IL-17 in different subsets of memory T cells. Accordingly, the IFN-γ expression and secretion also varies under different circumstances [20–25], especially under relatively complicated conditions during diseases such as Crohn's disease [24] and various types of autoimmune inflammation [20,23], regardless of the fact that IL-23 is not the only type of cytokine that induces memory T cells for IFN-γ production [15,26,27].

1.2. Th17 cells

IL-23 also promotes the differentiation of Th17 cells and Th17 cell-mediated IL-17 secretion. It has been well documented that the IL-23/Th17 cell axis plays an essential role in a number of diseases such as obesity-related metabolic syndrome [28] and inflammatory arthritis [29]. The latter one further includes inflammatory bowel disease [30,31], allergic airway inflammation [32], rheumatoid arthritis [33–35], adult-onset Still's disease [36], juvenile idiopathic arthritis [37–39], scleroderma [40–42], systemic lupus erythematosus [16,43–46], and psoriasis arthropathy or spondyloarthritis [33,47].

1.3. DCs

DCs are generally considered as the main source for IL-23 secretion, while IL-23R is present on the plasma membrane of DCs [48–50]. Given the involvement of IL-23 in the regulation of activities of numerous cell types in addition to the memory T cells and T17 cells mentioned above, IL-23 also acts on DCs along with macrophages in order to promote antigen presentation, followed by the production of various proinflammatory cytokines [51]. Interestingly, despite the genetic homogeneity of IL-23 and IL-12, they can be differentially regulated in their production, as for human DCs among other cell types, which are in turn involved in the activation and differentiation of these cell types [20,52,53]. Therefore, IL-23 not only connects innate immunity with adoptive immunity through its multiple roles, but it also particularly exerts a temporally and spatially varied effect on DCs in an autocrine manner [54]. Hence, it has become the main topic of interest, which is summarized below in this review.

2. DC-Secreted IL-23

IL-23 is produced by numerous cell types from various tissues. For instance, polarized Th1 cells and activated macrophages as well as keratinocytes in patients with psoriasis have been revealed to express high levels of IL-23p19 mRNA [55]. Another study has shown that large amounts of the IL-23 complex are produced by activated DCs. In addition, DCs derived from either human or mouse peripheral blood mononuclear cells also produce high levels of IL-23p19 mRNA. Therefore, based on multiple studies focusing on the signaling pathways that underlie IL-23 secretion and their related functional implications in many diseases, DCs are the major sources of IL-23 production [1]. In a mouse stroke model, interferon regulatory factor 4^+/cluster of differentiation (CD) $172\alpha^+$ type II DCs were found to be expressed most abundantly at the lesion site after cerebral ischemia. This specific DC subset was also considered as the major source of local IL-23 production at 24 h after stroke, thereby mediating neutrophil infiltration during the inflammatory response [56]. Additionally, IL-23 production in a variety of DC subsets was detected at the local lesion area in patients with plaque-type psoriasis [57]. Moreover, myeloid-derived DCs induced by *in vitro* serum-free culture conditions, i.e., serum-free DCs, were found to have a semi-mature phenotype in DCs, which produced large amounts of IL-23, but did not produce IL-12, when facing the threat of lipopolysaccharide challenge [58].

The role of IL-23 in DC-mediated protective immunity against bronchial asthma also has been reported. Ian and colleagues demonstrated the differences in the dysfunctional phenotypes of lung DC subsets in asthma-sensitive mice (A/J) and asthmatic mice (C3H) compared to control ones. They revealed that both antigen presentation of myeloid-derived DCs and Th17-mediated cytokine secretion, including both IL-23 and IL-6, are involved in bronchial airway hyperresponsiveness [54]. In addition, DC-mediated IL-23 secretion has been considered to be modulated by diverse biological processes. For instance, one study indicated that topical application of a Toll-like receptor (TLR) agonist alone promoted DC maturation and IL-23 production, while IL-4 overexpression reversed this particular effect mediated by TLR agonists [59]. Furthermore, it has been demonstrated as well that, roflumilast, also known as diesterase 4 inhibitor, promotes DC-mediated IL-23 secretion [60]. Meanwhile, prostaglandin E2 has been shown to increase IL-23 production in human DCs through the intracellular cyclic adenosine monophosphate signaling pathway [61]. In contrast, protein phosphatase 2A has been demonstrated to be involved in negative regulation of IL-23 production in DCs [62]. Accordingly, regarding antagonists against components of these signaling pathways, quite a few drugs, such as P2Y12 [63], galectin 3 [57], and morphine [64], have been screened for their involvement in suppression of IL-23 secretion in DCs. In particular, yohimibine, known as the dexmedetomidine inhibitor, has been demonstrated to suppress IL-23 secretion effectively from DCs that were originally derived from human umbilical cord blood mononuclear cells [65]. Taken together, even though DC-secreted IL-23 has not received less attention, the mutual interaction between IL-23 and DC, especially underlying signaling pathways, has not been extensively defined or clearly interpreted yet.

3. Functionally distinctive roles of DCs through IL-23-Induced activation of intracellular signaling pathways

It is well known that an increase in the local expression of IL-23 is commonly observed during pathological changes in numerous diseases [14,55]. Inflammatory cells are induced by IL-23 to initiate the selective expression of IL-23R. The affinitive binding between IL-23R and IL-23 subsequently mediates the activation of cell-type-specific expression of endogenous IL-23 during the immune response to these diseases [55] (Fig. 1). Both exogenous and endogenous IL-23 have been considered to be involved in binding to IL-23R on the cell membrane (p19 and IL-23R, p40 and IL-12Rβ1) to form a complex, which in turn activates intracellular signaling transduction pathways, namely, the Janus kinase pathway (IL-23R–Janus kinase 2) and the tyrosine kinase pathway (IL-12Rβ1–tyrosine kinase 2) [18] (Fig. 1). Activation of Janus kinase phosphorylates several tyrosine residues in the intracellular domain of IL-23R, which then activates downstream effectors including signal transducer and activator of transcription (STAT), mitogen-activated protein kinase, and phosphatidylinositol-3-kinase [18,66] (Fig. 1). Nevertheless, it also has been discovered that the tyrosine residues of catalytic subunits do not exist in the intracellular domain of human IL-12Rβ1, thereby suggesting that IL-23R is the main component of signal transduction in the complex [67] (Fig. 1).

3.1. DC maturation

It has been shown that myeloid-derived DCs transfected with IL-23-expressing plasmid started to display mature phenotypes, including acquisition of increased folds and irregular processes, abundant accumulation of mitochondria and endosome-associated complexes, and few lysosomes in the cytosol under electron microscopy [68]. Accordingly, a number of surface markers on the mature DCs, such as CD86, CD54, CD11b, major histocompatibility complex (MHC)-I, and MHC-II, can also be detected in comparison with those of immature or inactivated DCs [69–71] (Fig. 2). Interestingly, the expression levels of many surface markers on mature DCs were found to be almost unaffected, through suppression of either IL-23 secretion or IL-23p19 expression, by using specific drugs or antisense oligonucleotides [65,72]. These

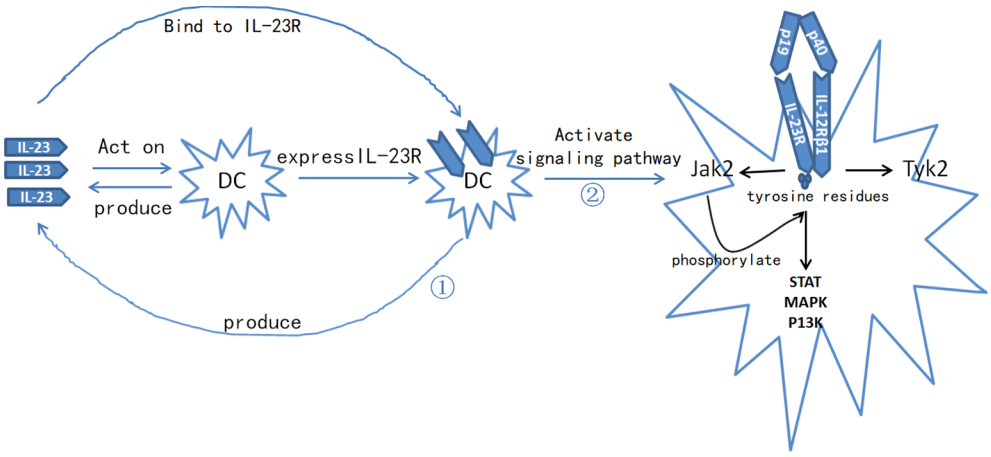

Fig. 1. Activation of IL-23-producing DCs via modulation of IL-23-dependent signaling pathways.

approaches, however, also have been proven to diminish IL-12 secretion effectively from DCs, thereby suggesting that the IL-12-producing potential may be a predictive hallmark for DC maturation [65]. In brief, these results have demonstrated that IL-23 is not necessarily involved in promoting DC maturation.

3.2. Enhanced immune response coupled with DC maturation

3.2.1. IL-23-mediated enhanced capacity of DC antigen presentation

Belladonna and colleagues carried out adoptive transfer skin experiments using two subsets of IL-23-expressing DCs, $CD8\alpha^-$ and $CD8\alpha^+$ DCs, which were loaded with tumor-specific peptides. As demonstrated by measuring the weight of each footpad 2 weeks following injection, footpad swelling did occur in mice inoculated with these DCs as expected, suggesting that IL-23 administration prompts antigen presentation of these DC subsets with high efficiency [73]. Similarly, Tan and colleagues transfected plasmids expressing IL-23 into myeloid-derived DCs, which were pulsed with tumor lysate. These antigen-sensitized DCs were in turn inoculated into mouse models of pancreatic cancer subcutaneously. Their results revealed that IL-23 administration indeed improved the tumor-specific antigen presentation of DCs [74] (Fig. 2).

In particular, IL-23 administration has been demonstrated to enhance the presentation of ovalbumin (OVA) peptides during an allergic reaction by DCs [75,76]. Moreover, IL-23p19 expression in DCs was discovered to be partially upregulated in a mouse model of atopic dermatitis as well as in patients with atopic dermatitis during clinical trials [75,76]. These DCs were isolated and cultured with rIL-23 for 24 h. After washing, they were then cocultured with naive $CD4^+$ OTII T cells in the presence of $OVA_{323\text{-}339}$ peptide [75,76]. IL-22 secretion by naive $CD4^+$ T cells was significantly increased, suggesting that IL-23 enhanced the capacity of DCs for antigen presentation of $OVA_{323\text{-}339}$ peptide to the naive $CD4^+$ T cells [55]. Therefore, OVA peptides have been commonly chosen for allergic sensitization and challenge in a mouse model of allergic asthma. However, further investigations are required to confirm whether IL-23 also enhances the presentation of OVA peptide by DCs in asthmatic mice.

3.2.2. IL-23-dependent and DC-mediated proliferation and activation of T cells: In particular, for cytotoxic T-lymphocyte (CTL) activation

DCs transfected with antisense oligonucleotides against IL-23p19 were cocultured with allogeneic $CD4^+$ T lymphocytes, and the results showed that the DC-induced proliferative capacity of these T cells was significantly diminished, whereas it was partially reversed by the addition of exogenous rIL-23, indicating that IL-23 strongly promotes DC-mediated T cell proliferation [77]. The mixed lymphocyte reaction test showed that the expression level of CD62L on the $CD4^+$ T lymphocytes could be used as an acute but novel plasma biomarker for the activation of T cells, due to the instability of CD62L, which was rapidly shed from the membrane during T cell activation [77]. Therefore, $CD4^+$ T cells with undetectable expression of endogenous CD62L were considered to be properly activated (Fig. 2).

Comparatively, DCs transfected with IL-23p19 antisense oligonucleotide, which specifically suppresses the expression of the IL-23p19 gene in DCs, were cocultured with allogeneic $CD4^+$ T cells [72]. The results showed that the number of $CD62L^+$ $CD4^+$ T cells from the oligonucleotide administration group was significantly higher (~42%) compared to that of the control group, suggesting that IL-23p19 antisense oligonucleotide effectively reduced the number of activated T cells [72]. Furthermore, DCs isolated from the lesion areas of patients

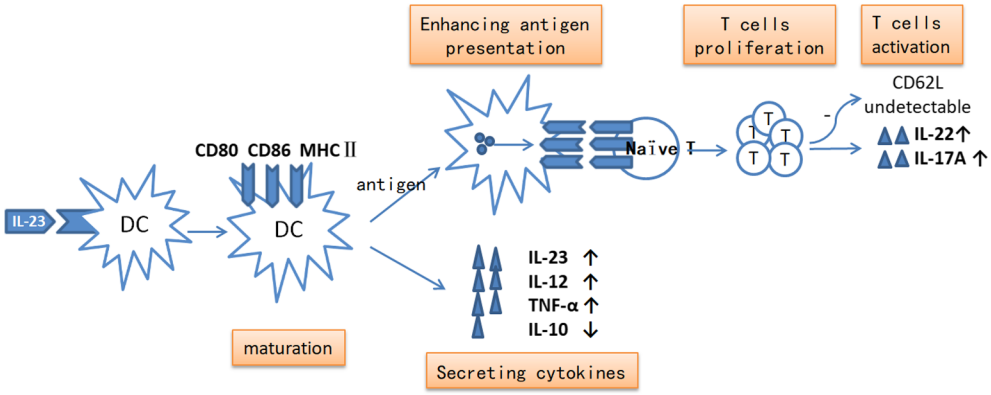

Fig. 2. Functional alterations in DCs through IL-23-induced activation of intracellular signaling pathways.

with atopic dermatitis were alternatively treated by rIL-23 mixed with naive $CD4^+$ T cells [55]. That study showed that IL-22 secretion was apparently increased by naive $CD4^+$ T cells; accordingly, the production of IL-17A detected in the culture medium was significantly increased [55]. Taken together, these studies demonstrated that IL-23 promotes DC-mediated activation of quite a few T cell subsets (Fig. 2).

3.2.3. IL-23-mediated DC activation: Alteration in cytokine secretion

DCs produce different cytokines in various microenvironments and mediate their corresponding biological functions. IL-23 exerts a beneficial influence on the secretion of DCs as follows (Fig. 2). (i) Promoting the secretion of endogenous IL-23: after mechanical damage in the skin, enhanced IL-23 released from the lesion site inevitably results in activation of DCs, followed by further production of more endogenous IL-23 [55]. (ii) Promoting the secretion of endogenous IL-12: IL-23 fusion protein induces $CD8\alpha^-$ and $CD8\alpha^+$ DC subsets for further production of IL-12. Moreover, DCs exogenously supplied with rIL-12 had an apparently increased expression level of IL-23p19 [55]. Therefore, it is highly likely that IL-23 and IL-12 are mutually regulated in DCs. (iii) Decreasing IL-10 while increasing tumor necrosis factor (TNF)-α secretion: suppression of IL-23p19 gene expression in DCs leads to a significant increase in the expression/secretion of IL-10 as well as a significant decrease in the expression/secretion of TNF-α [72]. Moreover, DCs supplemented with exogenous IL-23 rescued the expression/secretion of IL-10 and TNF-α, possibly due to the reduced amount of endogenous IL-23 [72]. (iv) Promoting IFN-γ secretion: DCs supplemented with IL-23-Ig efficiently induce the production of large amounts of IFN-γ, as shown in an *in vitro* study [55]. Collectively, IL-23 is involved in not only promoting DC maturation as well as enhancing the capacity of DC antigen presentation and their cytokine secretion, but also improving the proliferative capacity and the activation of T cells (Fig. 2).

4. Clinical implication and translational applications of intracellular signaling of IL-23 and/or DCs

There have been numerous studies focusing on preclinical and translational research on IL-23 and/or DCs. For example, it has been reported that the enhanced $CD4^+$ Th1-mediated immune response improved the viability of both DCs and Th1 cells in a tumor immunosuppressive microenvironment in an animal model [73]. Moreover, IL-23-Ig administration induced $CD8\alpha^+$ DCs to mediate the antigen presentation from the tumor *in vivo* as well as to increase the production of endogenous IL-12 and IFN *in vitro* [73].

Additionally, marrow-derived DCs that were previously transfected with IL-23 were loaded with different tumor-specific antigenic peptides, and then these DCs were inoculated into a mouse model of pancreatic cancer [73]. Accordingly, in vaccination-inoculated mice, there was undetectable tumor growth within 3 weeks, the tumor volume was obviously reduced, and the survival time of the mice was significantly prolonged [73]. Moreover, it also has been revealed that IL-23-transfected DCs migrated to the secondary lymph nodes and then to the spleen after subcutaneous injection [74]. Splenic T cells induced an effective concentration of IFN-γ upon stimulation. In addition, activated DCs stimulated T cells to express MHC-I, MHC-II, IL-12, IFN-γ, and other cytokines simultaneously after IL-23 transfection, eliciting a Th1 inflammatory immune response with CTL activation as well as suppressing tumor immune evasion [74]. Therefore, it has been regarded as an essential signaling pathway underlying basic features of immune response, which is thus widely applicable to the treatment of autoimmune disease (**4.1.1–4.1.3**) and infection (**4.2.1–4.2.4**) as follows.

4.1. Atopic dermatitis

Atopic dermatitis is a Th2-dominant inflammatory and chronic relapsing skin disease. IL-22 induces keratinocyte proliferation, which is elevated during inflammation in atopic dermatitis. In addition, skin-infiltrating Th22 cells are observed in atopic dermatitis lesions [55]. An animal model for atopic dermatitis revealed that endogenous TLR4 ligand-induced innate immunity promoted keratinocyte production and the release of IL-23, which led to the selective expression of IL-23R by a cutaneous administration of DCs to the mice [55]. Moreover, profound upregulation of endogenous IL-23 drove $CD4^+$ T cell subsets toward an inflammatory IL-22-positive phenotype [55]. Preclinical/clinical studies in patients with atopic dermatitis also showed that IL-23-induced polarization of cutaneous DCs elicited an immune response towards IL-22-mediated inflammation following mechanical scratching in the skin [55]. Hence, the occurrence of atopic dermatitis largely relies on IL-23/DC-mediated activation of T cell subsets and subsequent cytokine secretion.

4.2. Asthma

Genetic screening and functional analysis by Lan et al. compared lung DCs between an asthmatic A/J mouse model and an asthma-resistant C3H mouse model [78]. In their study, they found that allergen uptake by myeloid-derived DCs and the Th17-inducing cytokines IL-23 and IL-6 drove airway hyperresponsiveness in asthma-susceptible mice [78]. Meanwhile, resistance to asthma was associated with enhanced allergen uptake by plasmacytoid-derived DCs [78]. In addition, house dust mite-induced allergic asthma in a C3H mouse model revealed that this approach increased susceptibility to allergen-induced airway hyperresponsiveness through the profound upregulation of IL-17A in mouse lungs [78]. Therefore, these results demonstrated the involvement of DCs/Th17 cells in IL-23 secretion during asthma.

4.3. Multiple sclerosis

IL-23 as well as IL-12 are secreted mainly by activated DCs and macrophages, both of which induce T-cell subsets to secret IFN-γ among other cytokines [34]. Interestingly, IL-12-deficient mice displayed the phenotypes of multiple sclerosis and experimental autoimmune encephalomyelitis, which were not observed in mice that had specifically blocked expression of IL-23 and/or IL-12 *in vivo*, although DC expression of IL-23 indeed plays an important role in the pathogenesis of human autoimmune diseases including these diseases [79,80]. Another study has reported that there was an apparent increase in the mRNA expression levels of IL-23 and IL-23p19 in monocyte-derived DCs from patients with multiple sclerosis in comparison with those in healthy subjects [72]. Accordingly, enhanced expression and secretion of IL-17 were also observed in patients with multiple sclerosis [72]. Collectively, these results indicated an abnormal Th1 bias induced by IL-23 from DCs in clinical practice.

4.4. Citrobacter rodentium infections

Circulating monocyte-derived DCs and resident macrophages are involved in activation of immune responses in the intestinal mucosa [81,82]. For instance, CX3C chemokine receptor 1^+ mononuclear phagocytes have been reported to modulate the innate immune response to *C. rodentium* in infections and chronic inflammation of the colon [83]. Moreover, in the absence of IL-23, it was highly likely to be an acute lethal infection caused by a shortage of IL-22-producing macrophages and/or $CD11b^+$ DCs [83]. Thus, IL-12 or IFN-γ is commonly used to neutralize infection in animal models due to mechanisms underlying the acute lethality effects. In addition, studies have shown that mice were also rescued when the IL-12-deficient $CD103^+$ $CD11b^-$ DCs were rendered deficient by targeted gene manipulation. These findings also suggested that IL-12 production was repressed by IL-23 in colonic $CD103^+$ $CD11b^-$ DCs [83]. Besides the fact that it plays a certain role in inducing IL-22 production, it is widely accepted that IL-23, which is produced by either $CD103^-$ $CD11b^+$ DCs or macrophages,

is necessary for negative modulation of cytokine production, thereby effectively and efficiently avoiding deleterious accumulation of IL-12 secreted by $CD103^+$ $CD11b^-$ DCs [83]. Furthermore, impaired cross-talk between the mononuclear phagocytes and the infection source resulted in the generation of IFN-γ-producing Th17 cells, and eventually, lethal immunopathology [83]. Therefore, mutual attachment between IL-23 and specialized DC subsets plays a cardinal role in immune response against *C. rodentium* infections.

4.5. Human immunodeficiency virus type 1 (HIV-1) infection

Myeloid-derived DCs are associated with impaired T-cell function during HIV-1 infection [84,85]. HIV or glycoprotein (GP) 120 was found to inhibit lipopolysaccharide-induced myeloid-derived DC maturation and to cause defects in allogeneic T cell proliferation, IL-2/IFN-γ production, and phosphorylation and nuclear translocation of STATs [86–91]. For instance, GP120-induced myeloid-derived DCs down-regulated the proliferation and autologous T cell responses against defined peptides and subsequent IFN-γ production during the infection of chicken embryo fibroblast cells by cytomegalovirus, Epstein Barr virus, or influenza virus [86]. These T cell defects were associated with a decrease in the Th1-polarizing cytokine IL-12p70 and an increase in IL-23 production after GP120 administration in myeloid-derived DCs [86]. GP120-induced IL-23 upregulated the production of suppressor of cytokine signaling 1 (SOCS1) in T cells, while SOCS1 protein inhibited IFN-γ production and promoted the survival of chicken embryo fibroblast-pulsed monocytes [86]. Additionally, IL-23-induced SOCSl has been reported to bind and disrupt preexisting transcription complexes on actively transcribed IFN-γ genes, indicating that SOCS1 can be a potential target for immunotherapy in order to restore immune responses in HIV-infected patients [86].

4.6. Fungal infection

IL-17-producing Th17 cells contain a newly identified T-cell subset that potentially plays an essential role in the adaptive immune response to various fungal infections [92–94]. Opportunistic fungal pathogens including *Aspergillus* and *Rhizopus* induce a common innate pathway in human DCs compared to primary pathogenic fungi like *Histoplasma capsulatum*, resulting in a huge increase in IL-23 production and driving the Th17 cell-mediated immune response [95]. This process largely depends on selective exposure to fungal cell wall polysaccharides such as β-glucan and subsequent dectin-1 activation during invasive fungal infections [95]. Notably, changes in β-glucan caused drastic alterations in the cell wall of a *Histoplasma* mutant, not only abolishing the pathogenicity of the fungus but also triggering the activation of IL-23-producing DCs [95]. Taken together, sufficient exposure to β-glucans from the fungal cell wall is regarded as a prerequisite for activation of the IL-23/Th17 axis; hence, these results demonstrated that IL-23-producing DCs may be a key factor in the protective immunity against hypovirulent fungal strains but not nonpathogenic strains.

4.7. Listeria monocytogenes infection

The species-specific inflammatory response is characterized by the production of IL-12 and IFN-γ as well as $CD8^+$ T cell CTL-mediated protective immunity against *L. monocytogenes* infection [96,97]. These inflammatory cytokines may deeply affect the rate of memory $CD8^+$ T cell production and the total number of these short-lived effector cells [96,97]. For instance, Henry et al. sought to inoculate therapeutic vaccines derived from specific DC lines with the deletion of the IL-12 gene or the IL-12/23 genes in IL-12- and/or IL-23-deficient mice in order to monitor the role of IL-23 in *L. monocytogenes* infection [98]. They found that mice inoculated with wild-type or IL-12-deficient DCs were resistant to *L. monocytogenes* infection [98]. On the contrary, those that were inoculated with IL-12/23-deficient DCs exhibited enhanced susceptibility to its infection, possibly due to species-specific generation of T cell memory cell pools, when facing the threat of its infection [98]. Taken together, these results indicated that IL-23 plays at least a leading role in protective immunity against *L. monocytogenes* infection, especially in the absence of IL-12.

5. IL-23-mediated and DC-based novel translational approaches for human cancer immunotherapy

5.1. Gene-specific antisense oligonucleotides

Anti-IL-23p19 and anti-IL-12p35 antisense oligonucleotides were transfected into monocyte-derived DCs in mice as an animal model for multiple sclerosis [99]. These oligonucleotides effectively and specifically inhibited the expression of IL-23 and IL-12 genes; however, the viability of DCs and the DC maturation process were not obviously altered [72]. It has been widely accepted that lymphocytic chorionic meningitis virus infection in a mouse model specifically elicits an IL-23/IL-17-mediated pathological immune response [100,101]. The symptoms closely mimic the condition of viral hemorrhagic fever in patients. Antisense targeting of IL-23/IL-17 apparently reduces these symptoms and well demonstrates the importance of the IL-23/IL-17 signaling pathway in this mouse model. Thus, it is believed that this dysfunctional and pathological immune state is mediated by the involvement of IL-23/IL-17 signaling pathways [100,101]. Therefore, anti-IL-23 oligonucleotides are potentially applicable for targeting immune modulation through alteration of related gene expression of DCs and hence can be used to identify therapeutic treatments under a variety of inflammatory conditions that are potentially associated with IL-23/IL-17 signaling.

5.2. DC-based vaccines

5.2.1. DC-based vaccines against infection

Henry *et al.* inoculated IL-12/23-deficient DCs into mice that had been infected with *L. monocytogenes*. This DC-based vaccine partially compensated for deficiency of IL-12-induced T cell-mediated protective immunity against *L. monocytogenes* in the absence of IL-12 [98]. A more recent study also has shown that a DC-based vaccine was developed in order to enhance the protective immunity against pulmonary infection, whose causative agent was isolated and identified as a highly virulent *Cryptococcus gattii* strain in patients from Vancouver Island [102]. Accordingly, the administration of a DC-based vaccine obviously increased the expression and secretion of IL-17A-, IFN-γ-, and TNF-α-producing T cells in both the lungs and spleen, thereby ameliorating the fungal burden and mitigating the fatal outcome following infection [102]. By using this approach, DC-derived vaccines are basically pulsed with these pathogens and inoculate the animal models or even human subjects prior to infection, which leads to significant enhancement in the corresponding species-specific protective immunity.

5.2.2. DC-derived and peptide-based vaccines for tumor immunotherapy

Tan *et al.* reported that in an animal model of pancreatic cancer, a therapeutic vaccine comprised of DCs stably expressing IL-23 was used to target the proliferation of pancreatic cancer cell lines effectively, thereby offering a better long-term outcome for pancreatic cancer patients [74]. This study demonstrated the efficacy of DC-mediated immunotherapy for this particular type of cancer, which also accelerated the healing process of defective immune surveillance for pancreatic cancer, thereby inducing an antitumor immune response and inhibiting tumor growth [74]. Without a doubt, this method has great potential for *in vitro*-induced differentiation of DCs loaded with tumor-specific antigens to prime the CTL response in order for activity-specific immunotherapy against cancer. Hence, we would like to take advantage of this novel translational approach for immunotherapy against specific types of cancer in the future.

Acknowledgements

Declaration of interest: The authors declare that there are no conflicts of interest in this review.

References

[1] B. Oppmann, et al., Novel p19 protein engages IL-12p40 to form a cytokine, IL-23, with biological activities similar as well as distinct from IL-12, Immunity 13 (5) (2000) 715–725.
[2] H. Sophie, et al., Interleukin-23 drives innate and T cell-mediated intestinal inflammation, J. Exp. Med. 203 (11) (2006) 2473–2483.
[3] E. Imamura, et al., Anti-IL-23 receptor monoclonal antibody prevents CD4+ T cell-mediated colitis in association with decreased systemic Th1 and Th17 responses, Eur. J. Pharmacol. 824 (2018).
[4] J. Pidala, et al., In vivo IL-12/IL-23p40 neutralization blocks Th1/Th17 response after allogeneic hematopoietic cell transplantation, Haematologica 103 (3) (2018) p. haematol.2017.171199.
[5] J. Feng, et al., Interleukin-23 facilitates Th1 and Th2 cell differentiation in vitro following respiratory syncytial virus infection, J. Med. Virol. 149 (4) (2016) p. A81-A81.
[6] V. Fa, et al., Human IL-23-producing type 1 macrophages promote but IL-10-producing type 2 macrophages subvert immunity to (myco)bacteria, Proc. Natl. Acad. Sci. United States of America 101 (13) (2004) 4560–4565.
[7] Y. Rui, et al., Differential regulation of IL-23 production in M1 macrophages by TIR8/SIGIRR through TLR4- or TLR7/8-mediated signaling, Cytokine 99 (2017) 310–315.
[8] Y. Wang, et al., Macrophages play a pathogenic role in IL-23 mediated psoriasiform skin inflammation, 2017.
[9] F.M. Bloemendaal, et al., TNF-anti-TNF immune complexes inhibit IL-12/IL-23 secretion by inflammatory macrophages via an Fc-dependent mechanism, J. Crohns Colitis (2018).
[10] W. Nie, et al., Tumor-promoting effect of IL-23 in mammary cancer mediated by infiltration of M2 macrophages and neutrophils in tumor microenvironment, Biochem. Biophys. Res. Commun. 482 (4) (2016) 1400–1406.
[11] J.C. Daniel, et al., Interleukin-23 rather than interleukin-12 is the critical cytokine for autoimmune inflammation of the brain, Nature 421 (6924) (2003) 744.
[12] N.J. Wilson, et al., Development, cytokine profile and function of human interleukin 17-producing helper T cells, Nat. Immunol. 8 (9) (2007) 950–957.
[13] S. Aggarwal, et al., Interleukin-23 promotes a distinct CD4 T cell activation state characterized by the production of interleukin-17, J. Biol. Chem. 278 (3) (2003) 1910.
[14] Y. Li, et al., Silencing IL-23 expression by a small hairpin RNA protects against asthma in mice, Exp. Mol. Med. 43 (4) (2011) 197.
[15] N.J. Wilson, et al., Development, cytokine profile and function of human interleukin 17–producing helper T cells, Nat. Immunol. 8 (9) (2007) 950–957.
[16] A. Paradowskagorycka, et al., Impact of the IL-17F, IL-23 and IL-23R on susceptibility and phenotype of systemic lupus erythematosus, Autoimmunity 49 (6) (2016) 373–382.
[17] C. Lochmatter, et al., Integrative phosphoproteomics links IL-23R signaling with metabolic adaptation in lymphocytes, Sci. Rep. 6 (2016) 24491.
[18] C. Parham, et al., A receptor for the heterodimeric cytokine IL-23 is composed of IL-12Rβ1 and a novel cytokine receptor subunit, IL-23R, J. Immunol. 168 (11) (2002) 5699–5708.
[19] T.M. Hummel, et al., Synthetic deletion of the Interleukin 23 receptor (IL-23R) stalk region led to autonomous IL-23R homodimerization and activation, Mol. Cell. Biol. 37 (17) (2017) p. MCB.00014-17.
[20] A. Ziblat, et al., Interleukin (IL)-23 stimulates IFN-γ secretion by CD56 bright natural killer cells and enhances IL-18-driven dendritic cells activation, Front. Immunol. 8 (2017).
[21] J.I. Basile, et al., Mycobacterium tuberculosis multi-drug-resistant strain M induces IL-17+ IFNγ- CD4+ T cell expansion through an IL-23 and TGF-β-dependent mechanism in patients with MDR-TB tuberculosis, Clin. Exp. Immunol. 187 (1) (2017) 160–173.
[22] H.P. Lemos, et al., Prostaglandin mediates IL-23/IL-17-induced neutrophil migration in inflammation by inhibiting IL-12 and IFNγ production, Proc. Natl. Acad. Sci. U S A 106 (14) (2009) 5954–5959.
[23] J. Vilisaar, et al., Reciprocal regulation of substance P and IL-12/IL-23 and the associated cytokines, IFNγ/IL-17: a perspective on the relevance of this interaction to multiple sclerosis, J. Neuroimmune Pharmacol. 10 (3) (2015) 457–467.
[24] N. Kamada, et al., Unique CD14+ intestinal macrophages contribute to the pathogenesis of Crohn disease via IL-23/IFN-γ axis, J. Clin. Investig. 118 (6) (2008) 2269–2280.
[25] E.H. Mann, et al., Vitamin D counteracts an IL-23-dependent IL-17A+IFNγ+ response driven by urban particulate matter, Am. J. Respiratory Cell Mol. Biol. 57 (3) (2017).
[26] T. Hu, et al., Effects of IL-12 and IL-23 on CD4~+ memory T cells in gastric carcinoma tissues, Chin. J. Anat. (2009).
[27] H. Liu, C. Rohowsky-Kochan, Regulation of IL-17 in human CCR6+ effector memory T cells, J. Immunol. 180 (12) (2008) 7948–7957.
[28] L. Martins, et al., IL-23 promotes intestinal Th17 immunity and ameliorates obesity associated metabolic syndrome in a murine high-fat diet model, 2018.
[29] T. Yago, et al., IL-23 and Th17 disease in inflammatory arthritis, J. Clin. Med. 6 (9) (2017).
[30] N.D. De, et al., Targeting IL-23 and Th17-cytokines in inflammatory bowel diseases, Curr. Pharm. Des. 16 (33) (2010) 3656–3660.
[31] W. Shen, S.K. Durum, Synergy of IL-23 and Th17 cytokines: new light on inflammatory bowel disease, Neurochem. Res. 35 (6) (2010) 940–946.
[32] H. Wakashin, et al., Role of IL-23-Th17 cell axis in allergic airway inflammation, Int. Arch. Allergy Immunol. 149 (S1) (2009) 108–112.
[33] E. Baricza, et al., DistinctIn vitroT-helper 17 differentiation capacity of peripheral naive T cells in rheumatoid and psoriatic arthritis, Front. Immunol. 9 (2018) 606.
[34] M.T. Villanueva, Rheumatoid arthritis: IL-23 assists the transition from autoimmunity to inflammatory disease, Nat. Rev. Rheumatol. (2016).
[35] D.S. Zaky, E.M. Elnahrery, Role of interleukin-23 as a biomarker in rheumatoid arthritis patients and its correlation with disease activity, Int. Immunopharmacol. 31 (2016) 105–108.
[36] D.Y. Chen, et al., Potential role of Th17 cells in the pathogenesis of adult-onset Still's disease, Rheumatology 49 (12) (2010) 2305.
[37] S. Emami, et al., IL23R gene polymorphism with juvenile idiopathic arthritis and its association with serum IL-17A, Int. J. Rheumatic Diseases 19 (11) (2016) 1189–1196.
[38] H. Anne, et al., Subtype specific genetic associations for juvenile idiopathic arthritis: ERAP1with the enthesitis related arthritis subtype andIL23Rwith juvenile psoriatic arthritis, Arthritis Res. Therapy 13 (1) (2011) R12-R12 (2011-01-31).
[39] I.Z. Turtsevich, G.A. Novik, N.V. Bychkova, TH17-phenotypes of juvenile idiopathic arthritis, Pediat. Rheumatol. 12 (S1) (2014) 1–2.
[40] A. Yoshizaki, et al., Cell adhesion molecules regulate fibrotic process via Th1/Th2/Th17 cell balance in a bleomycin-induced scleroderma model, J. Immunol. 185 (4) (2010) 2502.
[41] W. Nakayama, et al., Dysregulated interleukin-23 signalling contributes to the increased collagen production in scleroderma fibroblasts via balancing microRNA expression, Rheumatology 56 (1) (2016).
[42] W. Nakayama, et al., Interleukin-23 signaling contributes to the increased collagen production in scleroderma fibroblasts, J. Dermatol. Sci. 69 (2) (2013) p. e6-e6.
[43] J. Yang, et al., Hydroxychloroquine inhibits the differentiation of Th17 cells in systemic lupus erythematosus, J. Rheumatol. (2018).
[44] C.K. Wong, et al., Hyperproduction of IL-23 and IL-17 in patients with systemic lupus erythematosus: implications for Th17-mediated inflammation in auto-immunity, Clin. Immunol. 127 (3) (2008) 385–393.
[45] V. Oke, et al., IFN-λ1 with Th17 axis cytokines and IFN-α define different subsets in systemic lupus erythematosus (SLE), Arthritis Res. Therapy 19 (1) (2017) 139.
[46] M. Zhao, et al., IL-6/STAT3 pathway induced deficiency of RFX1 contributes to Th17-dependent autoimmune diseases via epigenetic regulation, Nat. Commun. 9 (1) (2018) 583.
[47] C.A. Di, M.P. Di, F.O. Nestle, The IL-23/Th17 axis in the immunopathogenesis of psoriasis, J, Invest. Dermatol. 129 (6) (2009) 1339.
[48] D.A. Anderson, K.M. Murphy, C.G. Briseño, Development, diversity, and function of dendritic cells in mouse and human, Cold Spring Harb Perspect. Biol. (2017) p. a028613.
[49] X. Du, N.M. Chapman, H. Chi, Emerging roles of cellular metabolism in regulating dendritic cell subsets and function, Front. Cell Dev. Biol. 6 (2018) 152.
[50] B. Everts, E.J. Pearce, Metabolic control of dendritic cell activation and function: recent advances and clinical implications, Front. Immunol. 5 (2014) 203.
[51] N. Umezawa, et al., Interleukin-23 as a therapeutic target for inflammatory myopathy, Sci. Rep. 8 (1) (2018).
[52] O. Chijioke, C. Münz, Dendritic cell derived cytokines in human natural killer cell differentiation and activation, Front. Immunol. 4 (4) (2013) 365.
[53] G. Franca, et al., Differential regulation of interleukin 12 and interleukin 23 production in human dendritic cells, J. Exp. Med. 205 (6) (2008) 1447.
[54] K.R.B. Bastos, et al., What kind of message does IL-12/IL-23 bring to macrophages and dendritic cells? Microbes Infect. 6 (6) (2004) 630–636.
[55] J. Yoon, et al., IL-23 induced in keratinocytes by endogenous TLR4 ligands polarizes dendritic cells to drive IL-22 responses to skin immunization, J. Exp. Med. 213 (10) (2016) 2147–2166.
[56] M. Gelderblom, et al., IL-23 (Interleukin-23)-producing conventional dendritic cells control the detrimental IL-17 (Interleukin-17) response in stroke, Stroke 49 (1) (2018) 155–164.
[57] N. Yawalkar, G.G. Tscharner, R.E. Hunger, A.S. Hassan, Increased expression of IL-12p70 and IL-23 by multiple dendritic cell and macrophage subsets in plaque psoriasis, J. Dermatol. Sci. 54 (2) (2009) 99–105.
[58] S. Nagasaka, et al., Antigen-specific IL-23/17 pathway activation by murine semimature DC-like cells, Biochem. Biophys. Res. Commun. 387 (1) (2009) 52–57.
[59] R.E. Roses, et al., Differential production of IL-23 and IL-12 by myeloid-derived dendritic cells in response to TLR agonists, J. Immunol. 181 (7) (2008) 5120–5127.
[60] M. Bros, et al., The phosphodiesterase 4 inhibitor roflumilast augments the Th17-promoting capability of dendritic cells by enhancing IL-23 production, and impairs their T cell stimulatory activity due to elevated IL-10, Int. Immunopharmacol. 35 (2016) 174–184.
[61] Q. Shi, et al., PGE2 elevates IL-23 production in human dendritic cells via a cAMP dependent pathway, Mediators Inflamm. (8) (2015) 1–7 (2015-8-27).
[62] J.H. Chang, L.H. Glimcher, Interleukin-23 production in dendritic cells is negatively regulated by protein phosphatase 2A, Proc. Natl. Acad. Sci. USA 107 (18) (2010) 8340–8345.
[63] J. Zhang, et al., Knockout of P2Y12 aggravates experimental autoimmune encephalomyelitis in mice via increasing of IL-23 production and Th17 cell differentiation by dendritic cells, Brain Behav. Immun. (2016) 62.
[64] J. Wang, et al., Morphine inhibits murine dendritic cell IL-23 production by modulating Toll-like receptor 2 and Nod2 signaling, J. Biol. Chem. 286 (12)

(2011) 10225–10232.
[65] G. Chen, et al., Dexmedetomidine inhibits maturation and function of human cord blood-derived dendritic cells by interfering with synthesis and secretion of IL-12 and IL-23, Plos One 11 (4) (2016) e0153288.
[66] D.M. Floss, et al., Identification of canonical tyrosine-dependent and non-canonical tyrosine-independent STAT3 activation sites in the intracellular domain of the interleukin 23 receptor, J. Biol. Chem. 288 (27) (2013) 19386.
[67] D.M. Floss, et al., Insights into IL-23 biology: From structure to function, Cytokine Growth Factor Rev. 26 (5) (2015) 569–578.
[68] R.E.S. Caetano, Dendritic cells in a mature age, Nat. Rev. Immunol. 6 (6) (2006) 476–483.
[69] G. Ferlazzo, L. Moretta, Dendritic cell editing by natural killer cells, Crit. Rev. Oncog. 19 (1–2) (2014) 67.
[70] T. Worbs, S.I. Hammerschmidt, R. Förster, Dendritic cell migration in health and disease, Nat. Rev. Immunol. 17 (1) (2017) 30.
[71] H. Hasegawa, T. Matsumoto, Mechanisms of tolerance induction by dendritic cells in vivo, Front. Immunol. 9 (2018).
[72] A. Vaknin-Dembinsky, K. Balashov, H.L. Weiner, IL-23 is increased in dendritic cells in multiple sclerosis and down-regulation of IL-23 by antisense oligos increases dendritic cell IL-10 production, J. Immunol. 176 (12) (2006) 7768.
[73] M.L. Belladonna, et al., IL-23 and IL-12 have overlapping, but distinct, effects on murine dendritic cells, J. Immunol. 168 (11) (2002) 5448–5454.
[74] G. Tan, et al., Immunotherapeutic effects on murine pancreatic carcinoma by β-elemene combined with dendritic cells modified with genes encoding interleukin-23, Front. Med. China 1 (1) (2007) 41–45.
[75] T. Hilmenyuk, et al., Effects of glycation of the model food allergen ovalbumin on antigen uptake and presentation by human dendritic cells, Immunology 129 (3) (2010) 437–445.
[76] D. Pouniotis, et al., Vaccine delivery by penetratin: mechanism of antigen presentation by dendritic cells, Immunol. Res. 64 (4) (2016) 1–14.
[77] J. Kahn, et al., Membrane proximal cleavage of L-selectin: identification of the cleavage site and a 6-kD transmembrane peptide fragment of L-selectin, J. Cell Biol. 125 (2) (1994) 461–470.
[78] I.P. Lewkowich, et al., Allergen uptake, activation, and IL-23 production by pulmonary myeloid DCs drives airway hyperresponsiveness in asthma-susceptible mice, Plos One 3 (12) (2008) e3879.
[79] B. Gran, et al., IL-12p35-deficient mice are susceptible to experimental autoimmune encephalomyelitis: evidence for redundancy in the IL-12 system in the induction of central nervous system autoimmune demyelination, J. Immunol. 169 (12) (2002) 7104.
[80] G.X. Zhang, et al., Induction of experimental autoimmune encephalomyelitis in IL-12 receptor-beta 2-deficient mice: IL-12 responsiveness is not required in the pathogenesis of inflammatory demyelination in the central nervous system, J. Immunol. 170 (4) (2003) 2153–2160.
[81] P.B. Watchmaker, et al., Transcriptional and functional profiling of human intestinal dendritic cells reveals conserved specialization and a role for Bcl-6 and Blimp-1 in terminal subset differentiation, Nat. Immunol. 15 (1) (2014) 98–108.
[82] K. Bene, et al., Gut microbiota species can provoke both inflammatory and tolerogenic immune responses in human dendritic cells mediated by retinoic acid receptor alpha ligation, Front. Immunol. 8 (5) (2017) 427.
[83] T. Aychek, et al., IL-23-mediated mononuclear phagocyte crosstalk protects mice from Citrobacter rodentium-induced colon immunopathology, Nat. Commun. 6 (2015) 6525.
[84] A. Meropi, et al., PolyICLC exerts pro- and anti-HIV effects on the DC-T cell milieuin vitroand in vivo, Plos One 11 (9) (2016) e0161730.
[85] M. Sachdeva, A. Sharma, S.K. Arora, Increased expression of negative regulators of cytokine signaling during chronic HIV disease cause functionally exhausted state of dendritic cells, Cytokine 91 (2017) 118–123.
[86] A. Garg, P. Rawat, S.A. Spector, Interleukin 23 produced by myeloid dendritic cells contributes to T-cell dysfunction in HIV Type 1 infection by inducing SOCS1 expression, J. Infect. Dis. 211 (5) (2014) 755–768.
[87] J.G. Walker, et al., Expression of Jak3, STAT1, STAT4, and STAT6 in inflammatory arthritis: unique Jak3 and STAT4 expression in dendritic cells in seropositive rheumatoid arthritis, Ann. Rheum. Dis. 65 (2) (2006) 149.
[88] L.M. Johnson, P. Scott, STAT1 expression in dendritic cells, but not T cells, is required for immunity to Leishmania major, J. Immunol. 178 (11) (2007) 7259–7266.
[89] J. Horejshoeck, et al., Dendritic cells activated by IFN-γ/STAT1 express IL-31 receptor and release proinflammatory mediators upon IL-31 treatment, J. Immunol. 188 (11) (2012) 5319–5326.
[90] Y. Yang, et al., FC-98 regulates TLR9-mediated of CXCL-10 expression in dendritic cells via MAPK and STAT1 signaling pathway, Biomed Res. Int. 2014 (4) (2014) 926130.
[91] A. Masotti, et al., HIV-1 gp120 influences the expression of microRNAs in human monocyte-derived dendritic cells via STAT3 activation, BMC Genom. 16 (1) (2015) 480.
[92] G. André, et al., Cutting edge: IL-17-secreting innate lymphoid cells are essential for host defense against fungal infection, J. Immunol. 190 (2) (2013) 521–525.
[93] A. Gladiator, et al., Arming Th17 cells for antifungal host defense, Curr. Fungal Infect. Reports 7 (2) (2013) 138–143.
[94] A. Beringer, M. Noack, P. Miossec, IL-17 in Chronic inflammation: from discovery to targeting, Trends Mol. Med. 22 (3) (2016) 230–241.
[95] G. Chamilos, et al., Generation of IL-23 producing dendritic cells (DCs) by airborne fungi regulates fungal pathogenicity via the induction of TH-17 responses, Plos One 5 (9) (2010) e12955.
[96] D.G. Calame, S.L. Muellerortiz, R.A. Wetsel, Innate and adaptive immunologic functions of complement in the host response to Listeria monocytogenes infection, Immunobiology 221 (12) (2016) 1407–1417.
[97] V. Guariglia-Oropeza, et al., The Listeria monocytogenes bile stimulon under acidic conditions is characterized by strain-specific patterns and the upregulation of motility, cell wall modification functions, and the PrfA regulon, Front. Microbiol. 9 (2018).
[98] C.J. Henry, et al., The roles of IL-12 and IL-23 in CD8+ T cell-mediated immunity against listeria monocytogenes: insights from a DC vaccination model, Cell. Immunol. 264 (1) (2010) 23–31.
[99] A.H. Nuyts, et al., Dendritic cells in multiple sclerosis: key players in the immunopathogenesis, key players for new cellular immunotherapies? Multiple Sclerosis J. 19 (8) (2013) 995–1002.
[100] I. Yoichiro, I. Harumichi, The IL-23/IL-17 axis in inflammation, J. Clin. Investig. 116 (5) (2006) 1218.
[101] F.J. Schnell, et al., Antisense modulation of interleukins 17 and 23 signaling, US, 2016.
[102] K. Ueno, et al., Dendritic cell-based vaccine against fungal infection, Methods Mol. Biol. 1403 (2016) 537–549.