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Activation of the interleukin-23/interleukin-17 signalling pathway in autoinflammatory and autoimmune uveitis

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ABSTRACT

Uveitis is a group of diseases characterized by intraocular inflammation, of which some are driven by autoinflammatory or autoimmune responses, such as Vogt-Koyanagi-Harada disease, Behçet's disease, uveitis associated with spondyloarthritis, ocular sarcoidosis, sympathetic ophthalmia and birdshot chorioretinopathy. These entities have various clinical forms, but genetic and biomarker data suggest that they share a common molecular basis, activation of the Interleukin (IL)-23/IL-17 pathway. Multiple factors including genetic predisposition, various cytokine imbalances, infectious agents and gut alterations are found to trigger an aberrant response of this pathway. The enhanced activity of the IL-23/IL-17 pathway is committed to the expansion and pathogenicity of Th17 cells. Evidence from animal models demonstrates that the development of pathogenic Th17 cells is responsible for the induction of experimental autoimmune uveitis. Further findings indicate that retinal pigment epithelium (RPE) cells may be a target of IL-17. IL-17 triggers downstream inflammatory cascades and causes dysfunction of RPE cells, which may affect retinal barrier function and thereby promote intraocular inflammation. Currently, several emerging drugs blocking the IL-23/IL-17 pathway have been assessed for the treatment of uveitis in pilot studies. The purpose of this is to summarize updated biological knowledge and preliminary clinical data, providing the rationale for further development and evaluation of novel drugs targeting the IL-23/IL-17 pathway in autoinflammatory and autoimmune uveitis. Future studies may focus on translational medicine targeting the IL-23/IL-17 pathway for the improvement of diagnosis and treatment of uveitis. In conclusion, activation of the IL-23/IL-17 pathway is a critical biological event and can be an important target for the treatment of autoinflammatory and autoimmune uveitis.

1. Introduction

Uveitis is one of several vision-threatening diseases. Originally, uveitis refers to a collection of diseases characterized by intraocular inflammation that mainly affect the uvea, consisting of the iris, ciliary body and choroid. Uveitis also encompasses a range of entities involving inflammation of adjoining intraocular structures including the retina, vitreous and optic nerve (Krishna et al., 2017). According to the major site of inflammation, uveitis can be anatomically classified into anterior uveitis (inflammation of the iris and anterior chamber), intermediate uveitis (inflammation of the ciliary body and vitreous body), posterior uveitis (inflammation of the vitreous body, retina, choroid or even the optic disk) and panuveitis (a diffuse inflammation from the anterior through the posterior segment of the eye) (Tsirouki et al., 2018).

Uveitis can also be classified into two categories, infectious or non-infectious, and the standard treatments for the two categories are largely different. Infectious uveitis can be caused by a localized or systemic infection with a definite pathogens, such as cytomegalovirus, herpes simplex virus (HSV), *Toxoplasma gondii, Treponema pallidum* and *Mycobacterium tuberculosis*, which requires anti-infection therapy (Majumder et al., 2017). Non-infectious uveitis can be associated with systemic diseases including spondyloarthritis, Behçet's disease, Vogt-Koyanagi-Harada disease (VKH) and sarcoidosis. In addition, non-infectious uveitis may be confined to the eye with no apparent associated systemic diseases, such as sympathetic ophthalmia, birdshot chorioretinopathy, serpiginous choroiditis, or multiple evanescent white dot syndrome (Hsu et al., 2019). Most non-infectious uveitis entities are presumed to be an immune-related disorder, usually termed as autoinflammatory or autoimmune disease, which means a self-directed pathological process. In clinical practice, these entities are primarily treated with immunosuppressive agents to suppress the

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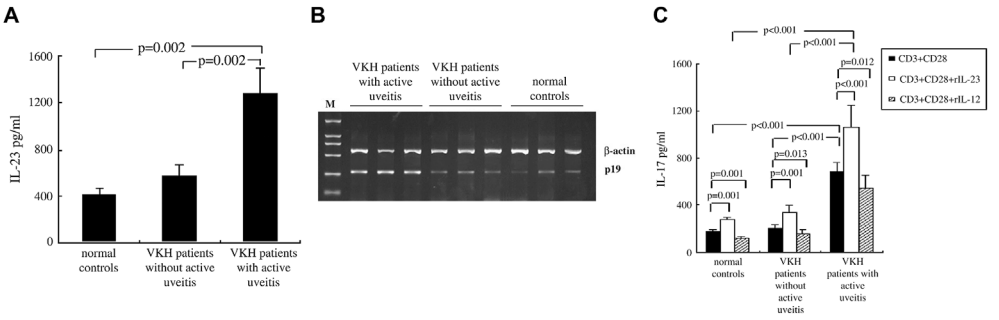


Fig. 1. Identification of the IL-23/IL-17 regulatory pathway in an autoimmune uveitis entity, Vogt-Koyanagi-Harada (VKH) disease. (A) Increased expression of IL-23 in the serum and supernatants of peripheral blood mononuclear cells (PBMCs) from patients with active VKH disease, as compared with those with inactive patients and normal control subjects. (B) Reverse transcription-polymerase chain reaction analysis showing the increased expression of IL-23 p19 in PBMCs from patients with active VKH disease stimulated by *Staphylococcus aureus* Cowan I. (C) Increased production of IL-17 produced by $CD4^+$ T cells from active patients with VKH disease, as compared with patients with inactive VKH disease and normal control subjects, cultured with anti-CD3 and anti-CD28 antibodies in the presence of recombinant IL-23. Figures and legends modified from (Chi et al., 2007) with permission from the copyright holder.

autoinflammatory or autoimmune responses (Jabs et al., 2000).

Non-infectious uveitis encompasses a wide range of heterogeneous entities, but the current understanding on the aetiology of uveitis and the heterogeneity of various uveitis phenotypes is still limited. Evidence suggests that a large number of uveitis entities within the context of autoinflammation and autoimmunity may share a common molecular and immunopathogenic basis, among which the activation of interleukin(IL)-23/interleukin(IL)-17 signalling pathway can be a critical biological event. Much knowledge has accrued that dysfunctional T cell dependent immunity strongly drives the inflammatory process of uveitis. Earlier findings suggested that T-helper type 1 (Th1) cells as well as its predominantly produced cytokine interferon-γ (IFN-γ) are primarily involved in the pathogenesis of uveitis (Hooks et al., 1988). But, it has recently been recognized that an important subgroup of $CD4^+$ T-helper cells, termed as Th17 cells, which primarily secrete the cytokine IL-17, may play a more dominant effect in driving autoimmunity in uveitis (Amadi-Obi et al., 2007). The first report that described the pro-inflammatory effect of the IL-23/IL-17 regulatory pathway to be implicated in an autoimmune uveitis entity, was published in 2007 (Fig. 1) (Chi et al., 2007). A subsequent study confirmed that IL-17 overexpression and Th17 cell expansion contributed to uveitis and scleritis in animal models (Amadi-Obi et al., 2007). Accumulated evidence from human samples of various autoimmune uveitis entities demonstrated the activation of the IL-23/IL-17 signalling pathway in these diseases (Chi et al., 2007, 2008; Facco et al., 2011; Furusato et al., 2011). Preclinical studies showed that blocking the IL-23/IL-17 signalling pathway can represent a novel therapeutic strategy for autoimmune uveitis, which highlighted the crucial role of the IL-23/IL-17 inflammatory axis in the disease (Hueber et al., 2010; Keino et al., 2008).

Currently, immunosuppressive therapy is the hallmark treatment for autoinflammatory and autoimmune uveitis, whereby the local or systemic use of corticosteroids remains the first-line mainstay of immunosuppression (Jabs et al., 2000). However, administration of corticosteroids can cause significant side effects or intolerance, which largely restricts its long-term use. Therefore, development of a more effective immunosuppressant that can etiologically treat the disease by a specific target is of utmost interest. Understanding the functional role of the IL-23/IL-17 pathway may help to determine drug targets for novel therapies. In this article, we provide genetic, immunological and medical contexts for elucidating the critical role of the Th17 cell mediated IL-23/IL-17 pathway in autoinflammatory and autoimmune uveitis. The purpose of the article is to provide the rationale for the further development and clinical research on novel drugs targeting the IL-23/IL-17 signalling pathway for the treatment of autoinflammatory and autoimmune uveitis entities.

2. Function and mechanism of the IL-23/IL-17 pathway under physiological conditions

2.1. Th1/Th2 balanced responses

The $CD4^+$ T lymphocytes play a pivotal role as helper cells to induce immune responses during the host defence and the pathogenesis of inflammatory diseases. Triggered in the presence of particular cytokine profiles, the naïve $CD4^+$ T cell will differentiate into diverse subsets such as Th1, Th2, Th17 and regulatory T cells (Tregs) (Fig. 2). The differentiation of Th1 and Th2 cells is mainly determined by the cytokines IL-12 and IL-4. When exposed to an antigen in combination with the stimulation of IL-12, secreted by antigen presenting cells (APC) such as macrophages or dendritic cells (DCs), a naïve $CD4^+$ T cell can differentiate into the Th1 phenotype (Mosmann et al., 1986). This process is critically dependent on the phosphorylation and homodimerization of signal transducer and activator of transcription (STAT) 4 as well as the activation of the T-box factor transcription family (T-bet) (Szabo et al., 2000). In contrast, if exposed to IL-4, the activated $CD4^+$ T lymphocyte may develop into the Th2 phenotype by the activation of transcription factors STAT6 and GATA binding protein 3 (GATA3) (Zheng and Flavell, 1997).

Th1 cells predominantly secrete IL-2 and IFN-γ to mobilize macrophages, natural killer (NK) cells and $CD8^+$ T lymphocytes, leading to the destruction of cells infected with virus and intracellular pathogens, eliminating cancer cells and inducing delayed-type hypersensitivity (Romagnani, 2000). On the other hand, Th2 cells mainly produce IL-4, IL-5, and IL-13, which may activate B cells and mast cells and drive humoral immunity, leading to the eradication of parasites or the induction of allergy (Romagnani, 2000). The differentiation of Th1 and Th2 cells can be reciprocally antagonized and self-reinforced, largely due to the mutual antagonistic function of IFN-γ and IL-4 (Larner et al., 1993; So et al., 2000) (Fig. 2).

For more than twenty years, Th1/Th2 responses had been thought to dominate the function of $CD4^+$ T helper cells. The IL-12 mediated Th1 cell pathway as well as its induced IFN-γ had long been assumed to be solely responsible for autoinflammatory disorders. The overactivated Th1 cell pathway was identified to explain certain animal autoinflammatory models, including experimental autoimmune encephalomyelitis (EAE), a mouse model for multiple sclerosis (Ando et al., 1989). However, some findings suggested that EAE could still be induced in IL-12 receptor-deficient mice or IFN-γ-deficient mice, indicating that the responsiveness of IL-12 and the expression of IFN-γ are not indispensable for the induction of EAE (Chu et al., 2000; Ferber et al., 1996; Zhang et al., 2003). The discrepancy was not fully explained until the finding that IL-12 is a heterodimeric molecule comprising two distinct subunits, p35 and p40. The p40 subunit is also a component of IL-23 which can play some biological activities similar with IL-12 (Oppmann et al., 2000). The perceived impact on autoimmune inflammation has been largely misinterpreted to be attributed

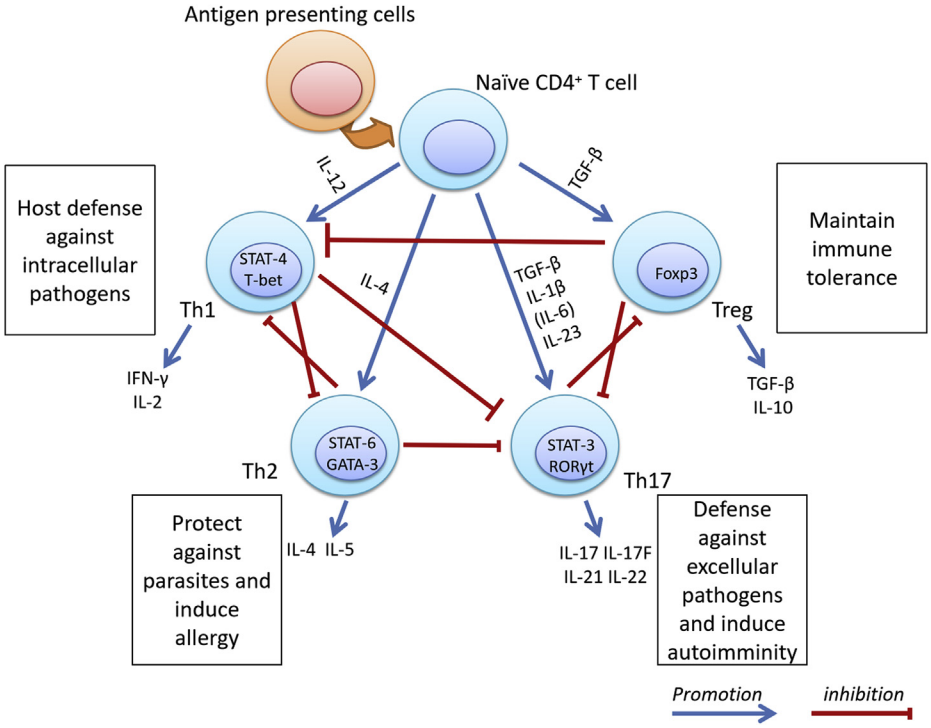


Fig. 2. Differentiation of naïve CD4$^+$ T cells stimulated with antigens by antigen presenting cells and with particular cytokines into diverse specific T helper effector cells. Figure drawn specifically for this paper.

solely to IL-12 before identifying the biological function of IL-23 (Cua et al., 2003). Actually, the newest indication from the EAE model showed that IL-23 could act as a key cytokine for the initiation of autoimmunity and autoinflammation (Cua et al., 2003).

2.2. Regulatory role of IL-23 on Th17 cells

IL-23 is a heterodimeric protein composed of p19 and p40 subunits. The p19 subunit is encoded by the gene *IL23A* at the location of 12q13.3, whereas the p40 subunit is encoded by the *IL12B* at 5q33.3 (Oppmann et al., 2000). IL-23 can be secreted by dendritic cells, monocytes, macrophages and activated myeloid cells. There is a similar biological activity of IL-12 and IL-23 in the generation of cellular immunity by inducing IFN-γ expression in a STAT4 dependent manner (Oppmann et al., 2000). However, the two cytokines bind different receptors. IL-12 can bind the IL-12 receptor comprising of two chains, IL-12Rβ1 and IL-12Rβ2, which are mainly assembled on the membrane of naïve CD4$^+$ T lymphocytes. IL-23 fails to interact with IL-12Rβ2, but can preferentially recognize a receptor consisting of IL-12Rβ1 and another unique chain named IL-23R, which are chiefly assembled on memory CD4$^+$ T cells. Thus, the IL-23 mediated production of IFN-γ is largely derived from a memory CD4$^+$ T cell rather than a naïve CD4$^+$ T cell (Oppmann et al., 2000).

Although the IL-23R is undetectable on the membrane of naïve CD4$^+$ T cells, the expression of IL-23R can be induced by the stimulation with transforming growth factor beta (TGF-β), thereby conferring responsiveness to IL-23 (Mangan et al., 2006). However, both Th1 and Th2 mediated IFN-γ and IL-4 can antagonize the action of TGF-β, thus providing a clue for the divergence of naïve CD4$^+$ T cells to a new lineage that is distinct from Th1 and Th2 cells (Mangan et al., 2006). It has currently become clear that TGF-β can promote the differentiation of naïve CD4$^+$ T cells into two disparate cell lineages, Th17 cells and Tregs, which are also maintained in a balance as mutual counterparts (Fig. 2). In this regard, TGF-β independently induces transcription factor FoxP3 expression to generate Tregs that are characterized by maintaining immune tolerance and possessing immunoinhibitory activities (Chen et al., 2003). Nevertheless, TGF-β, in synergy with IL-6 in mice and IL-1β in humans, may promote the differentiation cascade to another CD4$^+$ T cell lineage, Th17 cells, through the phosphorylation of STAT3, another transducer, that can up-regulate transcription factors such as ROR (retinoic acid receptor) family members, RORα and RORγt (Wilson et al., 2007; Yang et al., 2008b). Consequently, the expression of the downstream Th17 gene profile including IL-17 (also termed as IL-17A), IL-17F, IL-23R, IL-21, IL-22, CCL20 and CCR6 are transcriptionally triggered by RORα and RORγt (Castro et al., 2017). Moreover, when capturing the signals of IL-23 from antigen presenting cells, Th17 cells can in turn induce the expression of RORγt and IL-17 via STAT3 mediated signalling, and thereby progress to a pathogenic phenotype by reinforcing a positive feedback loop (McGeachy et al., 2009).

It has been recognized that not all IL-17-expressing T cells are capable of autoimmune mediated inflammation. A subpopulation of Th17 cells, characterized by the production of IL-17, IFN-γ, granulocyte- and granulocyte-macrophage colony-stimulating factor (G-CSF and GM-CSF) and IL-6, are closely associated with pathogenicity, whereby transformation to this phenotype is highly conditional on IL-23 signals for Th17 cells (Hirota et al., 2011). Although unlikely acting as a driver by itself for the initiation of Th17 cell differentiation from naïve CD4$^+$ T cells, IL-23 is critically committed to the expansion and pathogenicity of Th17 cells.

2.3. Function of IL-17

IL-17 (IL-17A) is a pro-inflammatory cytokine which is known to be released predominantly by activated Th17 cells but also by various other innate immune cells including invariant natural killer T (NKT) cells, mast cells, group 3 innate lymphoid cells (ILC3s) and neutrophils (Cua and Tato, 2010). These innate cell populations, residing in peripheral tissues, can become an early source of IL-17, following activation by key signals including IL-23 and IL-1β in the presence of stress, injury or pathogens (Cua and Tato, 2010). Members of the IL-17 family, from IL-17A through IL-17F, are homologous molecules, among which

Table 1
Comparison of autoimmunity and autoinflammation.

	Autoimmunity	Autoinflammation
Immune processes	The adaptive immune system activated to attack self-antigens and plays a major role in the eventual clinical expression of disease	Local triggering factors at disease-prone sites activate innate immune system, leading to self-directed inflammation and tissue damage
Immune response	Adaptive immunity	Innate immunity
Immune effector cells	B cells and T cells	Neutrophils, monocytes, macrophages or non-immune cells
Organ-specific autoantibodies	Yes	No
Antigen-specific T cells	Yes	No
Dominated in specific uveitis entities	Vogt-Koyanagi-Harada disease Sympathetic ophthalmia Birdshot retinochoroidopathy	Behçet's disease Uveitis associated with spondyloarthritis (ankylosing spondylitis, reactive arthritis, juvenile idiopathic arthritis, psoriatic arthritis, enteropathic arthritis or inflammatory bowel disease)

IL-17A and IL-17F exist in the form of homodimers or as heterodimers and can display similar functions (Wright et al., 2007).

IL-17 can generate the transcription of an inflammatory target gene signature. IL-17 signalling starts with the recruitment of Act1, an E3 ubiquitin ligase, to activate TNF receptor associated factor (TRAF) members (Zhang et al., 2013). Therein, activated TRAF6 can function as a signal transducer in triggering of nuclear factor kappa B (NF-κB), CCAAT/enhancer-binding protein (C/EBP) and mitogen-activated protein kinase (MAPK) pathways (Huang et al., 2015; Maitra et al., 2007; Shen et al., 2006). These pathways induce the expression of multiple inflammatory cytokines such as IL-1β, IL-6, G-CSF, GM-CSF and tumor necrosis factor alpha (TNF-α), chemokines such as C-X-C motif ligands and C–C motif chemokine ligands, anti-microbial peptides such as β-defensins and S100 family members, and matrix metalloproteinases (MMPs) (Awane et al., 1999; Fossiez et al., 1996; Liang et al., 2006; Sylvester et al., 2004). Besides turning on a core gene profile via *de novo* transcription, another mechanism for promoting the expression of IL-17 target gene signature can be attributed to controlling mRNA transcript stability mediated by IL-17 alone or in cooperation with other cytokines such as TNF-α (Hartupee et al., 2007; Karlsen et al., 2010). This process is critically dependent on the phosphorylation of Act1 to favor the recruitment of TRAF2 and TRAF5. The Act1-TRAF2-TRAF5 complex can sequester the RNA decay factor (Splicing factor 2, SF2) away from the 3′ untranslated region (UTR) of the transcript, and can thus impede the degradation of the mRNA (Sun et al., 2011). In addition, the Act1-TRAF2-TRAF5 complex can activate the RNA binding protein Human Antigen R (HuR) by polyubiquitination to further competitively interfere with SF2 binding on mRNA 3′ UTR (Herjan et al., 2013). Consequently, the improvement of transcript stability in the cytoplasm provides favourable conditions for the stable and rapid translation of IL-17-mediated inflammatory gene profiles.

Under physiological conditions, IL-17 is responsible for mucosal immunity against microbial infection in the skin, oral cavity, lungs, airway, gastrointestinal tract and vagina, whereby cutaneous and mucosal epithelial cells of these organs broadly express the IL-17 receptor (IL-17R) (Chen et al., 2011a; Veldhoen, 2017). By inducing anti-microbial peptides such as β-defensins and S100 proteins in mucosal epithelial cells, IL-17 in cooperation with IL-22 maintains epithelial barriers through direct clearance of pathogens or the prevention of microbial invasion (Liang et al., 2006). Nevertheless, when the barrier is eventually breached, IL-17 can promote the recruitment of neutrophils, monocytes and macrophages (chemokines) and facilitate the recruitment by maintaining cell survival and activity (G-CSF and GM-CSF) and enhancing access to the inflammatory site (MMPs) (Veldhoen, 2017). Moreover, IL-17 can induce the expression of pro-inflammatory cytokines including IL-1β, IL-6 and TNF-α, and these cytokines in turn enhance the production and strengthen the effects of IL-17, through the activation of STAT3 and the NF-κB pathway (Ogura et al., 2008; Veldhoen, 2017). Taken together, IL-17 has a powerful capacity of recruiting immune cells as well as creating an inflammatory microenvironment. Details on how dysregulation of the IL-23/IL-17 pathway contributes to uveitis, is described for clinical human uveitis in Chapter 3 and its role in experimental models is dealt with in Chapter 4.

3. Dysregulation of the IL-23/IL-17 pathway in autoinflammatory and autoimmune uveitis entities

Autoimmunity and autoinflammation are currently considered as the driving forces in most non-infectious uveitis entities. Although both autoinflammatory and autoimmune processes can be simultaneously involved in a certain uveitis entity, it is generally believed that there is a predominant component between the two processes that is associated with its pathogenesis (Forrester et al., 2018). Autoimmunity involves activation of the adaptive immune system, in which B and T lymphocytes are implicated in the inflammatory response through the recognition of specific self-antigens (McGonagle and McDermott, 2006). Current knowledge recognizes some antigens in the retina as the target of autoreactive T lymphocytes in uveitis, such as melanocyte-associated antigens, retinal soluble antigen (S–Ag) and interphotoreceptor retinoid-binding protein (IRBP) (Kawashima et al., 1991; Maezawa and Yano, 1988; Mattapallil et al., 2011). Several uveitis entities are considered to be dominantly mediated by an adaptive immune response directed against retinal antigenic targets (Table 1). Another condition is related to the pathogenesis of autoinflammation, whereby the innate immune cells are aberrantly provoked by endogenous danger signals, metabolic mediators or cytokines to cause local tissue damage in lack of a definite antigenic target (Table 1) (McGonagle and McDermott, 2006).

Although uveitis due to autoimmune and autoinflammatory mechanisms may be heterogeneous in clinical manifestations and includes a range of different clinical entities, many studies now show that these entities share the dysregulation of the IL-23/IL-17 signalling pathway at the genetic and molecular level. The following sections describe the evidence of an aberrant IL-23/IL-17 signalling pathway with implications for some common autoimmune and autoinflammatory uveitis entities such as Vogt-Koyanagi-Harada disease, Behçet's disease, uveitis associated with spondyloarthritis, birdshot chorioretinopathy, sympathetic ophthalmia and ocular sarcoidosis. In this review we will focus on the entities named above, since various reports have been published on the link between the IL-23/IL-17 pathway and these common uveitis entities, which may provide an indication for targeted therapies for these diseases. Little is known about the role of the IL-23/IL-17 pathway in entities such as serpiginous choroiditis, multiple evanescent white dot syndrome, tubulointerstitial nephritis and uveitis (TINU) syndrome and relapsing polychondritis, and these entities are therefore not addressed in detail.

3.1. Dysregulation of the IL-23/IL-17 pathway in Vogt-Koyanagi-Harada disease

Vogt-Koyanagi-Harada (VKH) disease is an autoimmune disease characterized by bilateral granulomatous panuveitis (diffuse choroiditis

and anterior uveitis) commonly associated with vitiligo, poliosis, alopecia, auditory-vestibular disorders as well as nerve system abnormalities (Yang et al., 2007). The incidence of VKH disease varies greatly worldwide, whereby VKH disease primarily affects Asian, Hispanic, American Indian and Middle Eastern populations and is rarely seen among European and African populations (Du et al., 2016). The pathogenesis of VKH disease is related to autoimmune responses to several organs and tissues expressing antigenic peptides, such as the eye, skin, meninges and auditory system. Self-antigens including melanin associated antigen, retinal S-antigen and interphotoreceptor retinoid-binding protein have been shown to be associated with VKH disease (de Smet et al., 1990; Descamps et al., 2008; Norose and Yano, 1996). Systemic corticosteroids combined with immunosuppressive agents are currently used to treat VKH disease (Yang et al., 2018).

VKH disease has been shown to be associated with several gene polymorphisms including the human leukocyte antigens such as DR4 and DRw53 (HLA-DR4 and HLA-DRw53), in Chinese, Japanese and Hispanic populations (Ohno, 1981; Weisz et al., 1995; Zhao et al., 1991). Although the precise mechanisms underlying the association with HLA gene regions remains to be elucidated, it has been suggested that viral and microbial infection may exert a triggering role of the disease in a genetically susceptible host (Sugita et al., 2006, 2007; Ye et al., 2020). A genome-wide association study (GWAS) analysis showed that in addition to susceptibility in HLA-DRB1/DQA1, two novel genetic loci, ADO-ZNF365-EGR2 and IL23R–C1orf141, were also associated with VKH disease in Han Chinese (Fig. 3) (Cao et al., 2016; Hou et al., 2014). Several candidate genes linked with IL-23/IL-17 signalling and its downstream pathway were identified to confer susceptibility to VKH disease, including JAK1 (Janus kinase 1), IL23A, IL23R, IL17F, IL12B, STAT4, TNFSF4 (Tumor necrosis factor superfamily 4), TNFAIP3 (TNF alpha induced protein 3), TRAF5 (TNF receptor associated factor 5) and TRAF3IP2 (TRAF3 interacting protein 2, members of TNF receptor associated factor family) (Hou et al., 2015; Hu et al., 2010, 2013; Jiang et al., 2010b; Li et al., 2013b, 2014b; Lu et al., 2016; Shu et al., 2010; Xiang et al., 2014).

At the molecular level, an enhanced production of IL-23 was observed in serum and supernatants of peripheral blood mononuclear cells (PBMCs) obtained from patients with active VKH disease (Chi et al., 2007). Moreover, the IL-23R level was also found to be significantly elevated in PBMCs, suggestive of an enhanced responsiveness to IL-23 signalling in VKH (Wang et al., 2018). Recombinant IL-23 protein could up-regulate the IL-17 expression in PBMCs and $CD4^+$ T cells, and that IL-17 expressed by these activated cells was markedly increased in patients with active VKH in comparison with those with inactive disease or healthy individuals (Fig. 1) (Chi et al., 2007). Analysis of peripheral Th cell subsets in active VKH disease showed a substantial expansion of Th17 cells as well as an elevated level of Th17 related cytokines (TGF-β, IL-6, IL-23 and IL-17), as compared with inactive VKH and healthy controls (Liang et al., 2019). Further evidence showed the aberrant expression and function of the IL-23/IL-17 downstream regulatory network involving IFN-γ, IL-7, IL-6, IL-10, IL-21, IL-25, IL-27, IL-35, IL-37 and Disabled-2 in VKH disease, which supported the overactivation of the IL-23/IL-17 pathway and the involvement of pathogenic Th17 cells in the development, chronicity and recurrence of VKH disease (Hu et al., 2019; Li et al., 2010; Norose et al., 1994; Wang et al., 2012; Xu et al., 2014; Yang et al., 2012; Ye et al., 2014b; Yi et al., 2018).

3.2. Dysregulation of the IL-23/IL-17 pathway in Behçet's disease

Behçet's disease (BD) is a systemic vasculitis involving frequent relapsing episodes of oral ulcers, ocular inflammation, multiform skin lesions, genital ulcerations, and even occasionally manifests as a cardiovascular, gastrointestinal or neurological abnormality (Deuter et al., 2008). Ocular lesions typically present as scleritis and non-granulomatous uveitis involving the anterior segment, the posterior segment or both (panuveitis) (Yang et al., 2008a). Behçet's disease is globally distributed with an overall prevalence of 10.3/100,000 persons and can be more frequently seen in the Middle East and Asia (Maldini et al., 2017). The precise aetiology and pathophysiology of Behçet's disease is still not clear, but it has been theorized that a source of infectious agents and environmental factors, such as seasons, climates and habitation, combined with a genetically predisposed background leads to this disease (Deuter et al., 2008; Lee et al., 2015). Combination of corticosteroids with immunosuppressive drugs can be effective in the treatment of Behçet's disease (Yang et al., 2008a). In recent years, biologicals such as TNF blockers and IFN-α have been introduced as novel therapies for Behçet's disease (Atienza-Mateo et al., 2019; Yang et al., 2019a).

Behçet's disease has been demonstrated to be in a strong association with the MHC gene region (Fig. 4) (Hou et al., 2012). HLA-B51, an MHC class I molecule, has a high frequency in Behçet's disease, ranging between 45% and 60% in a variety of races including Asian and Eurasian populations from Japan through the Middle East (Ohno et al., 1982). A close interaction of the HLA-B51 molecule was observed with the endoplasmic reticulum aminopeptidase (ERAP) 1 and/or 2 molecules, of which polymorphisms were also shown to increase the risk of Behçet's disease (Kirino et al., 2013; Zhang et al., 2015b). The function of ERAP1/2 involves trimming of peptides that are then loaded onto the MHC class I molecule, in this case dealing with processing of specific HLA-B51:01 ligands (Guasp et al., 2019).

Besides the strong genetic predisposition of HLA-B51 to Behçet's disease, genome-wide association and replication analyses showed significant associations with genes encoding molecules related to the IL-23/IL-17 signalling pathway, such as IL23A, IL23R, IL12A, IL12B, IL12RB2, IL17A, IL17F, IL18RAP, IL6, IL10, IL37, STAT3, STAT4 and TNFAIP3 (Hou et al., 2012, 2015; Hu et al., 2010, 2012, 2015; Jiang et al., 2010a, 2015; Kappen et al., 2015; Kim et al., 2012; Li et al., 2013a, 2014b; Remmers et al., 2010; Tan et al., 2016; Yu et al., 2017). More importantly, the expressions of IL-23, IL-23R, IL-17, IFN-γ, IL-6 and TNF-α were observed to be considerably up-regulated in Behçet's disease (Çavuş et al., 2014; Chi et al., 2008). Further analyses showed that gene polymorphisms in the IL23R-IL12RB2 region can promote the expression of IL-23R as well as the production of pro-inflammatory cytokines such as IL-17, TNF-α and IL-6, indicating that those identified genetic variations in Behçet's disease are critically involved in the regulation of the IL-23/IL-17 pathway and therefore predispose to the development of the disease (Çavuş et al., 2014; Jiang et al., 2015). In addition, *in vitro* assays confirmed that recombinant IL-23 could promote IL-17 production in polyclonally stimulated PBMCs from patients with Behçet's disease, and furthermore indicated that IL-17 production by stimulated T lymphocytes was higher in Behçet's disease as compared with healthy individuals (Chi et al., 2008). The IL-23/IL-17 pathway mediated Th17 cell expression profiles were also correlated with the clinical activity of Behçet's disease and associated with the activation of early innate immunity as well as neutrophil and monocyte infiltration (Na et al., 2013). The findings mentioned above support the hypothesis that overactivation of the IL-23/IL-17 signalling pathway plays an important role during the autoinflammatory process in Behçet's disease.

3.3. Dysregulation of the IL-23/IL-17 pathway in uveitis associated with spondyloarthritis

Spondyloarthritis (SpA) refers to a cluster of several closely related but phenotypically different diseases, such as ankylosing spondylitis, reactive arthritis, psoriatic arthritis, arthritis associated with inflammatory bowel disease and a subgroup of juvenile idiopathic arthritis (Dougados M and Baeten D, 2011). It is considered to be appropriate to classify these diseases together into one entity due to the fact that they can be present in the same patient or in family members at the same time or in a sequential order (Dougados M and Baeten D, 2011). The typical clinical manifestations of spondyloarthritis are

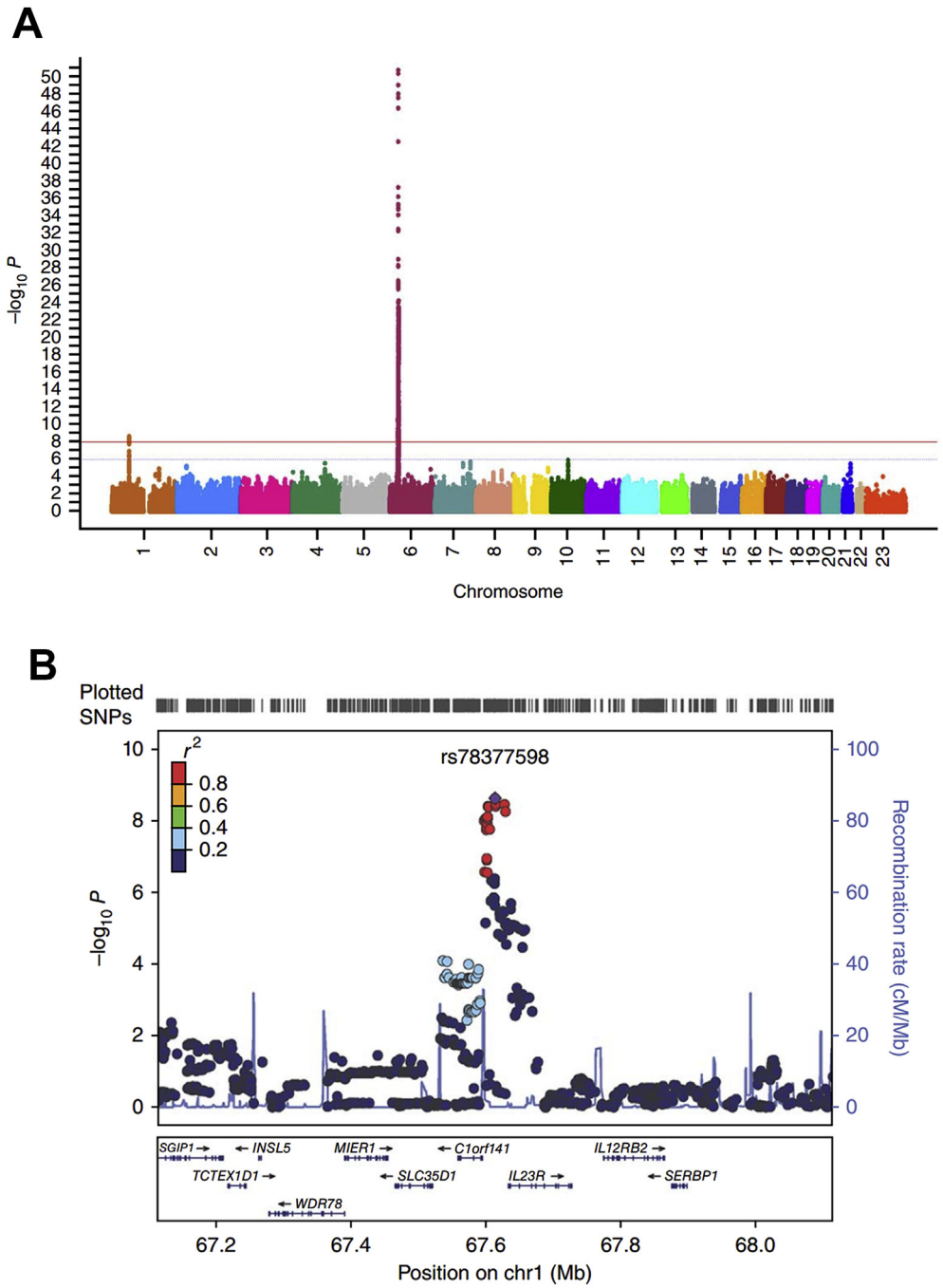


Fig. 3. Genome-wide association results showing strong signals of genetic variants associated with Vogt-Koyanagi-Harada disease in the Chromosome 6 HLA gene region and the Chromosome 1 IL23R gene region. (A) Manhattan plot of P values on the -log10 scale for 2,208,258 SNPs in the GWAS stage (774 cases and 2,009 controls). (B) Regional plots of association results for the two newly identified susceptibility loci for VKH syndrome at 1p31.2. Figures and legends modified from (Hou et al., 2014) with permission from the copyright holder.

spinal or axial involvement, peripheral arthritis, enthesopathy and extra-articular lesions such as uveitis, psoriasis and inflammatory bowel disease (Jhaj and Kopplin, 2018). The most frequently encountered form of ocular involvement is an acute anterior uveitis; while, scleritis, chronic anterior uveitis, or posterior segment involvement can also be observed, and are especially more common in inflammatory bowel disease, psoriatic arthritis and juvenile idiopathic arthritis (Jhaj and Kopplin, 2018). Local or systemic corticosteroids, disease modifying antirheumatic drugs (DMARDs) and TNF blockers are recommended for the treatment of ocular lesions as well as systemic symptoms (Jhaj and Kopplin, 2018).

Advances in our knowledge of the genetics also support the recognition of spondyloarthritis diseases as one entity, since they are predominantly associated with HLA-B27, an MHC class I molecule (Hammer et al., 1990; Said-Nahal et al., 2000). The underlying mechanism of HLA-B27 in spondyloarthritis is not clear, but it has been proposed that the HLA-B27 molecule may trigger an abnormal innate immune response to danger signals (Dougados M and Baeten D, 2011). There might also be an epistatic interaction between HLA-B27 and ERAP1, whereby ERAP1 allotypes related to enhanced catalytic activity are associated with the development of spondyloarthritis (Seregin et al., 2013). In addition, several reports have shown that HLA-B27 has the ability to form heavy-chain homodimers as well as heavy-chain misfolding (Kollnberger et al., 2004; Turner et al., 2005). Upon stress or

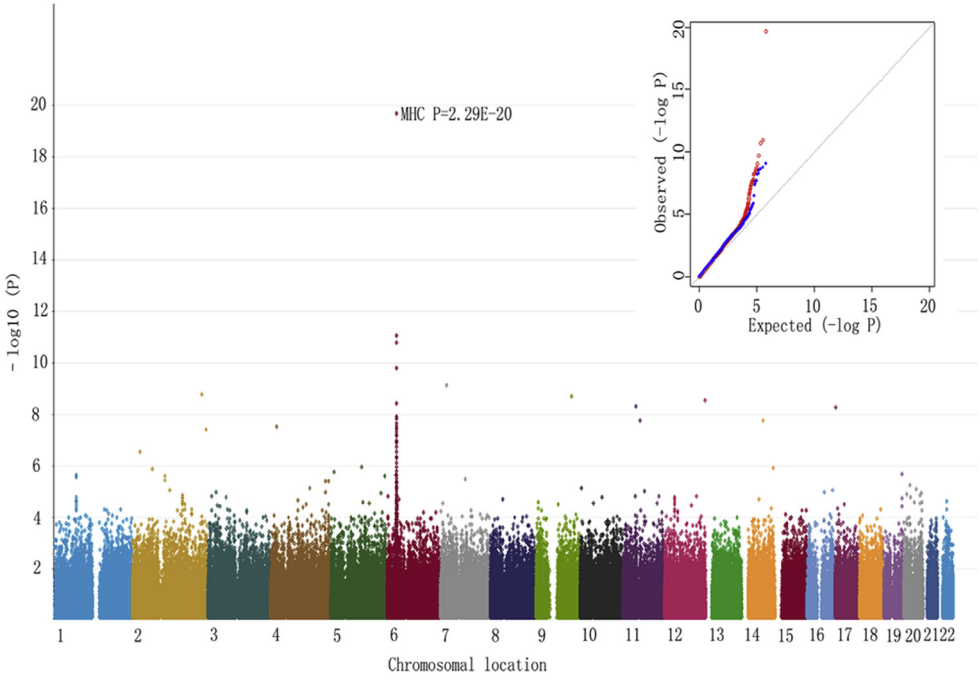


Fig. 4. Genome-wide association analysis showing strong signals of genetic variants associated with Behçet's disease in the Chromosome 6 HLA gene region. Figure and legend modified from (Hou et al., 2012) with permission from the copyright holder.

bacterial infections, HLA-B27 misfolding and the unfolded protein response can cause an enhanced induction of IL-23 and IL-17 as well as activation of Th17 cells (DeLay et al., 2009).

Genome-wide association studies have shown that the IL23R gene, a critical determinant of IL-23 responsiveness, can be a common susceptibility factor for spondyloarthritis including nearly all the different spondyloarthritis subtypes (Huang et al., 2017; International Genetics of Ankylosing Spondylitis Consortium et al., 2013; Robinson et al., 2015; Stuart et al., 2015). Further studies demonstrated that the risk polymorphisms are located in the regulatory regions of the IL23R gene and are causally associated with an elevated expression of IL-23R and a higher activity of IL23/IL-17 signalling, thereby conferring an increased risk for spondyloarthritis (Sode et al., 2018; Sun et al., 2018). In addition, expansion of Th17 cells and up-regulation of pro-inflammatory cytokines including IL-6, TGF-β, IL-23, IL-17, TNF-α and IFN-γ are observed in patients with HLA-B27 associated uveitis and correlated with the disease activity (Zhuang et al., 2017). These findings support a functional role for the overactivation of the IL-23/IL-17 pathway in the pathophysiology of spondyloarthritis as well as its associated uveitis.

3.4. Dysregulation of the IL-23/IL-17 pathway in birdshot chorioretinopathy

Birdshot chorioretinopathy (BSCR) is a chronic intraocular inflammation involving the choroid, retinal pigment epithelium and retina, which predominantly affects the middle aged and elderly white population (Kuiper et al., 2015). The typical manifestations of the disease include bilateral vitritis, retinal vascular leakage and distinctive multiple choroidal hypopigmented lesions, and immunosuppressive therapies are the mainstay of treatment for this disease (Shao et al., 2014).

Birdshot chorioretinopathy is strongly associated with HLA-A29, an MHC class I molecule (Levinson et al., 2004). Although the exact mechanism remains to be elucidated, it has been proposed that prior microbial infections could trigger the disease through exerting molecular mimicry and inducing an HLA-A29 cross reactive responses directed against retinal targets (Kuiper et al., 2015). A genome-wide association study additionally identified functional genetic variants nearby the ERAP2 gene that were correlated with the expression of ERAP2 and predisposed to the disease (Kuiper et al., 2014b). Dysfunction of ERAP1 and ERAP2 isoforms might affect peptide processing or antigen presentation, leading to an altered immune response in birdshot chorioretinopathy (Kuiper et al., 2014b, 2018).

For a long time, the pathogenesis of birdshot chorioretinopathy was thought to be driven by T cells, while recently, the identification of the role of the IL-17 pathway in this disease has further improved our knowledge concerning the underlying mechanisms (Kuiper et al., 2011, 2014a). The increased intraocular expression of pro-inflammatory and Th17 cell related cytokines including IL-21, IL-23, IL-17 and TGF-β1 has been observed in patients with birdshot chorioretinopathy (Molins et al., 2016; Yang and Foster, 2013). Dysregulation of the IL-23/IL-17 signalling pathway and Th17 cell immunity may be a key pathogenic mechanism in the development of this chronic ocular disease.

3.5. Dysregulation of the IL-23/IL-17 pathway in sympathetic ophthalmia

Sympathetic ophthalmia (SO) is a bilateral granulomatous panuveitis that develops due to an autoimmune response against ocular antigens induced by ocular injury or surgery (Chu and Chan, 2013). Sympathetic ophthalmia shares identical clinical and histopathological manifestations with Vogt-Koyanagi-Harada disease, such as granulomatous inflammation in the choroid with exudative retinal detachment (Goto and Rao, 1990). Patients with sympathetic ophthalmia often have a definite history of ocular trauma, less frequent systemic manifestations but a worse visual prognosis, as compared with Vogt-Koyanagi-Harada disease (Yang et al., 2019b).Therapeutic strategies are currently restricted to surgical removal of the injured eye and immunosuppressive therapies (Chu and Chan, 2013).

Sympathetic ophthalmia was found to be linked with the HLA antigens DRB1, DR4, DRw53, DQA1, DQB1, A11, B40 and Bw54 (Davis et al., 1990; Reynard et al., 1983; Shindo et al., 1997). There are similarities between sympathetic ophthalmia and Vogt-Koyanagi-Harada disease concerning shared associations with HLA-DR4, HLA-DRw53 and HLA-Bw54 (Davis et al., 1990). It has been proposed that ocular injuries could lead to a reverse of immune tolerance by introducing exogenous antigen to the ocular microenvironment, triggering an autoimmune

response against intraocular antigenic proteins in a genetically susceptible host (Goto and Rao, 1990). A recent study evaluated the genetic associations of non-HLA-region genes with sympathetic ophthalmia, but most susceptible loci identified in Vogt-Koyanagi-Harada disease such as IL23R–C1orf141, IL-17F, TRAF5 and IL-12B were not significantly associated with sympathetic ophthalmia (Deng et al., 2017). Although there are not sufficient studies to show a definite role for Th17 cells in sympathetic ophthalmia, evidence has been established regarding the up-regulation of IL-23 and IL-17 in granulomatous lesions, suggesting a role for an overactivation of the IL-23/IL-17 signalling pathway in the pathogenesis of the disease (Furusato et al., 2011). Further biological and genetic studies are warranted to clarify the underlying mechanisms.

3.6. Dysregulation of the IL-23/IL-17 pathway in ocular sarcoidosis

Sarcoidosis is a systemic inflammatory disorder which can involve almost any organ system but most frequently affects the lungs (Valeyre et al., 2014). A population-based study determined that ocular involvement occurs in 7% of sarcoidosis patients (Ungprasert et al., 2019). The typical clinicopathological characteristic of sarcoidosis is the presence of non-caseating epithelioid cell granulomas in affected tissues. Systemic corticosteroids and immunosuppressant drugs remain the standard treatment (Valeyre et al., 2014).

The major genetic contributor to sarcoidosis has been mapped to HLA class II alleles including HLA-DRB1 and HLA-DPB1 (Rossman et al., 2003). The aetiology of sarcoidosis is not well understood, but it has been suggested to be associated with a complex combination of genetic predisposition and environmental triggers such as infectious agents (Valeyre et al., 2014). Histologic observations suggested that the formation of granulomas and fibrosis were associated with the activation of Th1 cells, monocytes and macrophages and the overproduction of IFN-γ, IL-2, TNF-α, IL-15 and CCL20 (Agostini et al., 1996, 1999; Facco et al., 2007). A recent study reported that Th17 cells participated in the infiltration and localization around and inside the granuloma (Facco et al., 2011). Genetic analyses also established that IL23R polymorphisms were associated with the susceptibility to sarcoidosis, especially ocular sarcoidosis (Kim et al., 2011). Additionally, increased expressions of IL23R, IL-17 and RORγt in patients with active sarcoidosis suggest the involvement of the IL-23/IL-17 signalling pathway in this disease (Facco et al., 2011).

Based on the evidence as mentioned above, we can draw several major implications. First, these common autoimmune and autoinflammatory uveitis entities can fall into the concept of multifactorial disease to which multiple genes and environmental factors have contributed. We developed a database, UVEOGENE (http://www.uvogene.com), which identified 1,612 genetic associations of 370 genes and 918 single nucleotide polymorphisms covering 14 uveitis entities and 40 ethnic populations (Fig. 5) (Wang et al., 2019). This database provides an informative resource for understanding multiple genetic effects on autoimmune and autoinflammatory uveitis. Second, almost all these autoimmune and autoinflammatory diseases are thought to have a strong association and most probably a causal relation with specific HLA molecules. This highlights that the interaction of host genetics and infectious agents may have a profound impact on the triggering of these diseases (Tian et al., 2017). Third, from a genetic perspective, IL23R may be the most prominent factor and causal contributor to the development of autoimmune and autoinflammatory uveitis among these non-HLA disease susceptibility genes. We have observed that nearly all the common uveitis entities are associated with the genetic susceptibility factor IL23R (Table 2). These risk variants are likely to function as the *cis*-regulator to affect the transcriptional level of the gene, influence the activation of IL-23/IL-17 signalling, and therefore contribute to the development of the disease (Sode et al., 2018; Sun et al., 2018). Existing evidence supports the hypothesis that an up-regulation of IL-23R in these diseases (Table 3), may lead to an increased IL-23 responsiveness, which subsequently acts as a driver for the overactivation of the IL-23/IL-17 signalling pathway. Taken together, the current knowledge concerning the role of the IL-23/IL-17 signalling pathway in these autoimmune and autoinflammatory uveitis entities, strongly suggests that it may be a suitable target for intervention and prevention strategies.

4. Activation of the IL-23/IL-17 pathway in experimental uveitis animal models

To better understand pathogenic processes of autoimmune and autoinflammatory uveitis, several animal models have been established for experimental research. A widely used model is Endotoxin induced uveitis (EIU), which can be induced in some strains of rats or mice by a systemic or local intraocular injection of lipopolysaccharide (LPS), the principal outer cell wall component of gram-negative bacteria (Rosenbaum et al., 1980). This model is characterized by an acute anterior uveitis of rapid onset and short duration, and partially supported the view that bacterial infections could trigger innate inflammatory responses and cause sterile intraocular inflammation (Li et al., 2007). Although the EIU model has provided great insight into mediators involved during intraocular inflammation, it differs largely from human uveitis which is known to be rarely seen in individuals exposed to LPS. Another model is Experimental autoimmune uveitis (EAU), which is induced by immunizing animals with retinal antigens such as interphotoreceptor retinoid-binding protein (IRBP) in complete Freund's adjuvant containing heat-killed *Mycobacterium tuberculosis* strain (MTB) that triggers innate pro-inflammatory signals to polarize the adaptive immune T cells towards an autoreactive response (Silver et al., 1999). In addition, the EAU model can be adapted by genetic manipulation to create autoreactive T cells with specific T-cell receptors against IRBP in gene-edited spontaneous uveitis mice (DeVoss et al., 2006). The pathogenesis of the EAU model shows a relatively good resemblance to human autoinflammatory and autoimmune uveitis because it also involves a dysfunctional T cell dependent immunity.

Content	Number
Diseases	14 (Behcet's disease, Vogt–Koyanagi–Harada disease, intermediate uveitis, acute anterior uveitis, Fuchs uveitis syndrome, pediatric uveitis, juvenile idiopathic arthritis, toxoplasmosis, sympathetic ophthalmia, Birdshot chorioretinopathy, multifocal choroiditis, sarcoidosis, idiopathic uveitis, and punctate inner choroidopathy)
Genes	370
SNPs	918
Populations	40
Associations	1,612
Year	January 2001 to March 2018 (289 publications)

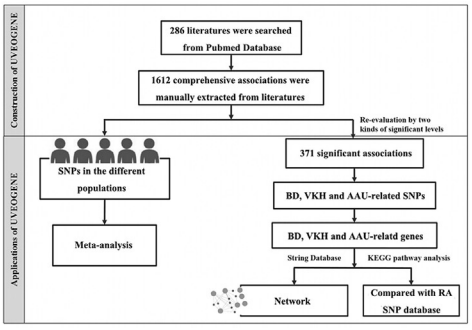


Fig. 5. Content and work flow of the UVEOGENE database. A total of 1,612 associations of single nucleotide polymorphisms with uveitis covering 14 different entities and 40 ethnic populations were included in the UVEOGENE database. The data can be viewed and downloaded from the web database UVEOGENE (http://www.uvogene.com). Figure and legend modified from (Wang et al., 2019) with permission from the copyright holder.

Table 2
Genetic susceptibility of IL-23/IL-17 pathway related genes in common autoinflammatory and autoimmune uveitis entities.

Entity	*IL23A*			*IL23R*			*IL17A*			*IL17F*		
	Ethnicity	Method	Reference	Ethnicity	Method	Reference	Ethnicity	Method	Reference	Ethnicity	Method	Reference
Ankylosing spondylitis	Not reported	–	–	European and Asian	GWAS	International Genetics of Ankylosing Spondylitis Consortium et al. (2013)	Chinese	Genotyping	Yang et al. (2017)	Not reported	–	–
Psoriasis	European	GWAS	Stuart et al. (2015)	European	GWAS	Stuart et al. (2015)	Indian	Genotyping	Kaur et al. (2018)	Korean and Indian	Genotyping	(Kaur et al., 2018; Kim et al., 2017)
Ulcerative colitis	Not reported	–	–	European and Asian	GWAS	Liu et al. (2015)	Caucasian and Asian	Genotyping	Li et al. (2014a)	Caucasian and Asian	Genotyping	Li et al. (2014a)
Crohn's disease	Not reported	–	–	Europea Asian, and African American	GWAS	(Brant et al., 2017; Liu et al., 2015)	Not reported	–	–	Not reported	–	–
Juvenile idiopathic arthritis	Not reported	–	–	Caucasian and Iranian	Genotyping	(Emami et al., 2016; Hinks et al., 2011)	Not reported	–	–	Not reported	–	–
Behçet's disease	Chinese	Genotyping	Hou et al. (2015)	Turkish, Iranian, Japanese, Korean and Chinese	GWAS and genotyping	(Kim et al., 2012; Takeuchi et al., 2017; Yu et al., 2017)	Korean	Genotyping	Kim et al. (2012)	Chinese and Korean	Genotyping	(Hou et al., 2015; Jang et al., 2008)
Vogt-Koyanagi-Harada disease	Chinese	Genotyping	Hou et al. (2015)	Chinese	GWAS	Hou et al. (2014)	Not reported	–	–	Chinese	Genotyping	Hou et al. (2015)
Birdshot chorioretinopathy	Not reported	–	–	Not reported	–	–	Not reported	–	–	Not reported	–	–
Sympathetic ophthalmia	Not reported	–	–	Not reported	–	–	Not reported	–	–	Not reported	–	–
Ocular sarcoidosis	Not reported	–	–	Caucasian	Genotyping	Kim et al. (2011)	Not reported	–	–	Not reported	–	–

GWAS, genome-wide genotyping and association study. Genotyping, candidate-gene genotyping and association study.

Table 3
Expression of mediators in IL-23/IL-17 signalling pathway in autoinflammatory and autoimmune uveitis entities.

Entity	IL-23		IL-23R		IL-17 (IL-17A)		IL-17F	
	Expression	Reference	Expression	Reference	Expression	Reference	Expression	Reference
Ankylosing spondylitis	Up-regulation	Rezaiemanesh et al. (2017)	Up-regulation	Kenna et al. (2012)	Up-regulation	Sode et al. (2018)	Not reported	–
Psoriasis	Up-regulation	Yawalkar et al. (2009)	Up-regulation	Benham et al. (2013)	Up-regulation	Johansen et al. (2009)	Up-regulation	Johansen et al. (2009)
Ulcerative colitis	Up-regulation	Youssef et al. (2018)	Up-regulation	Kobayashi et al. (2008)	Up-regulation	Zhang et al. (2016a)	Up-regulation	Iboshi et al. (2017)
Crohn's disease	Up-regulation	Höltta et al. (2008)	Up-regulation	Kobayashi et al. (2008)	Up-regulation	Höltta et al. (2008)	Up-regulation	Seiderer et al. (2008)
Juvenile idiopathic arthritis	Not reported	–	Not reported	–	Up-regulation	Kessel et al., 2017)	Not reported	–
Behçet's disease	Up-regulation	Chi et al. (2008)	Up-regulation	Jiang et al. (2015)	Up-regulation	Chi et al. (2008)	Up-regulation	Sonmez et al. (2018)
Vogt-Koyanagi-Harada disease	Up-regulation	Chi et al. (2007)	Up-regulation	Wang et al. (2018)	Not reported	–	Up-regulation	Hou et al. (2015)
Birdshot chorioretinopathy	Up-regulation	Yang and Foster (2013)	Not reported	–	Up-regulation	Yang and Foster (2013)	Not reported	–
Sympathetic ophthalmia	Up-regulation	Furusato et al. (2011)	Not reported	–	Up-regulation	Furusato et al. (2011)	Not reported	–
Sarcoidosis	Not reported	–	Up-regulation	Facco et al. (2011)	Up-regulation	Facco et al. (2011)	Not reported	–

4.1. Pathogenic driving effects of IL-17 and Th17 cells

As mentioned above, the prevailing evidence shows an activation of autoreactive Th1 and Th17 cells during ocular inflammation suggesting that both Th1 and Th17 cells mediated immune responses can function as pathogenic effectors involved in uveitis. Recent studies however suggested that of these two cell types, the Th17 cells seem to play a more definite pathogenic role. Although the Th1 cell profile cytokines such as IFN-γ and IL-12 were highly up-regulated in clinical and experimental uveitis, experimental models in EAU mice showed that IL-12 and IFN-γ provided by Th1 cells could also play an inhibitory effect against autoimmunity and autoinflammation (Caspi et al., 1994; Tarrant et al., 1999). Treatment by the neutralization of IFN-γ could exacerbate inflammation in EAU mice and could also confer the induction of experimental ocular inflammation in several EAU-resistant strains of mice (Caspi et al., 1994). Consistently, administration of IL-12 led to increased levels of innate IFN-γ, but failed to cause disease-promoting effects in EAU-resistant strains and actually inhibited disease induction in EAU-susceptible mice (Tarrant et al., 1999). However, treatment with an antibody to IL-17 was able to prevent and ameliorate EAU (Amadi-Obi et al., 2007; Luger et al., 2008). Further evidence in IFN-γ knockout mice suggested that despite the absence of IFN-γ, EAU could still be induced by IL-17-producing T cells (Luger et al., 2008). In addition, Th17 cells were thought to be responsible for ocular inflammation in the early phase of EAU, while Th1 cell activation was correlated with the late stage and regression of inflammation (Amadi-Obi et al., 2007). In view of the findings mentioned above, it has been proposed that IL-17 predominantly secreted by Th17 cells has a definite promoting role for autoinflammation and autoimmunity in uveitis, whereas the increased IFN-γ expressed by Th1 cells may arise due to inverse feedback and have an antagonistic effect against IL-17 mediated autoinflammation. Findings from human samples also suggested that both neutralization of IFN-γ and treatment of recombinant IL-23 could promote the production of IL-17 in polyclonally stimulated PBMCs from Behçet's disease patients (Chi et al., 2008). Therefore, inhibition of IL-23/IL-17 but not of IFN-γ can be a more reliable strategy for the treatment of autoimmune and autoinflammatory uveitis.

4.2. Regulatory roles of multiple mediators on the IL-23/IL-17 pathway

Numerous cytokines and mediators have been identified in different autoimmune animal models that show the importance of the IL-23/IL-17 signalling pathway and maturation of pathogenic Th17 cells, either via direct effects or interacting pathways. The upstream cytokines such as IL-1β, IL-6 and TGF-β are believed to be initiating modulators for the IL-23/IL-17 signalling, and mediators that affect the expression of these upstream cytokines may have important regulatory potential. The role of some of these has been determined and validated in experimental or clinical autoimmune uveitis. It was observed that the expression of molecules such as IL-7, IL-21, C4 (Complement component 4), C3aR (Complement 3a receptor), Hes-1, Notch 1, NOD1, NOD2, TLR2, TLR3, TLR4, Leptin, and ROS-NLRP3 was significantly up-regulated in the serum of patients with active Vogt-Koyanagi-Harada disease, Behçet's disease or EAU mice (Deng et al., 2016; Hou et al., 2013; Li et al., 2010; Liang et al., 2015; Liu et al., 2008; Qi et al., 2014; Wang et al., 2017; Yang et al., 2012). These mediators can promote PBMC proliferation and might be associated with the activation of NLRP3, Notch, p38 MAPK and NF-κB signalling in antigen-presenting cells, leading to increased production of IL-1β and IL-6 that positively regulate the IL-23/IL-17 pathway (Hou et al., 2013; Liang et al., 2013; Qi et al., 2014; Wang et al., 2017; Wei et al., 2014). On the other hand, down-regulated expression of mediators such as IL-25, IL-27, IL-35, IL-37, IFN-α, miR-155, miR-146a, A20 and Disabled-2 have been observed in patients with autoimmune and autoinflammatory uveitis entities (He et al., 2018; Hu et al., 2019; Plskova et al., 2006; Wang et al., 2014; Xu et al., 2014; Ye et al., 2014b; Yi et al., 2018; Zhou et al., 2012, 2014).

Evidence suggests that these molecules might inhibit the proliferation of PBMC, down-regulate the expression of IL-6 and IL-1β, increase the production of inhibitory cytokine IL-10 and inversely regulate the activation of Th17 cells (Hu et al., 2019; Liu et al., 2011; Shao et al., 2012; Tian et al., 2011, 2012; Wang et al., 2012; Ye et al., 2014a; Yi et al., 2018; Zhou et al., 2012). Although the full regulatory profile and precise mechanism have not yet been fully elucidated, these findings support the existence of a complex regulatory network involving a balance of multiple mediators, which eventually leads to the activation of the IL-23/IL-17 signalling and the development of pathogenic Th17 cells.

4.3. Triggering role of infectious agents in the activation of the IL-23/IL-17 pathway

Clinical observations suggest that microbial or viral infection precede the onset of diseases such as Vogt-Koyanagi-Harada disease, Behçet's disease and uveitis associated with ankylosing spondylitis, supporting the potential causal association between infections and the development of autoimmune and autoinflammatory uveitis (Lindström et al., 2016; Yoshino et al., 2018; Zhang et al., 2015a). Nevertheless, the underlying mechanisms are poorly understood. Previous theories have proposed a cross-reactive mechanism by which the resemblance of the exogenous antigens of an infectious source with the host endogenous peptides will lead to molecular mimicry (Oldstone, 1987). Therefore, an autoimmune response will be triggered by the shared autoantibodies or T cell receptors that could cross-react with the pathogen-derived antigens and endogenous self-peptides (Oldstone, 1987). This mechanism might be more dominant in some autoimmune uveitis entities such as Vogt-Koyanagi-Harada disease. In autoinflammatory uveitis, the inflammation and tissue damages may not be driven by adaptive T cell reactivity directly towards self-antigens, but may be caused by a hyperreactivity of innate immunity against exogenous antigens. Within this context, Toll-like receptor (TLR) signalling might have important implications. The Toll-like receptors belong to a large family of pattern-recognition receptors (PRRs), which is responsible for the recognition of infectious products to initiate innate immune responses and steer subsequent adaptive immune responses (Kaisho and Akira, 2006). A variety of genetic variations in TLR2, TLR3, TLR4 and TLR7 have been identified to confer susceptibility for a range of different clinical uveitis entities (Fang et al., 2013, 2015; Liang et al., 2015). Increased expression of TLR2 and TLR4 in the autoinflammatory uveitis can promote the activation of the NLRP3 inflammasome and the maturation of IL-1β and reactive oxygen species (ROS) in monocyte-derived macrophages when stimulated with peptidoglycan (PGN)/lipopolysaccharide (LPS) (Liang et al., 2013). Activation of NLRP3 inflammasome and up-regulation of IL-1β have been shown to be responsible for the enhanced IL-23/IL-17 signalling and Th17 response (Lalor et al., 2011).

As mentioned earlier, a variety of infectious agents can directly cause uveitis and these entities can successfully be treated with appropriate anti-viral, anti-parasitic and anti-bacterial drugs. On the other hand, microbes may also be involved in the so called non-infectious uveitis entities, whereby the role of the microbiome in triggering autoimmune or autoinflammatory reactions is currently receiving a lot of attention. Emerging studies on the microbiome composition have provided important indications that infectious agents from the gut can trigger autoimmune uveitis (Horai et al., 2015; Ye et al., 2018). Metagenomic studies, 16s rDNA sequencing and metabolomics analyses have shown differentially abundant gut microbiota composition as well as specifically altered metabolites in Vogt-Koyanagi-Harada disease, Behçet's disease and acute anterior uveitis (Figs. 6–8) (Huang et al., 2018; Ye et al., 2018, 2020). Transplantation of fecal samples from active Behçet's disease could promote the expression of IL-17 and exacerbate EAU activity (Fig. 9), which indicates that gut microbes might be involved in the regulation of IL-23/IL-17 signalling and therefore contribute to the disease (Ye et al., 2018). Moreover, gut microbiota

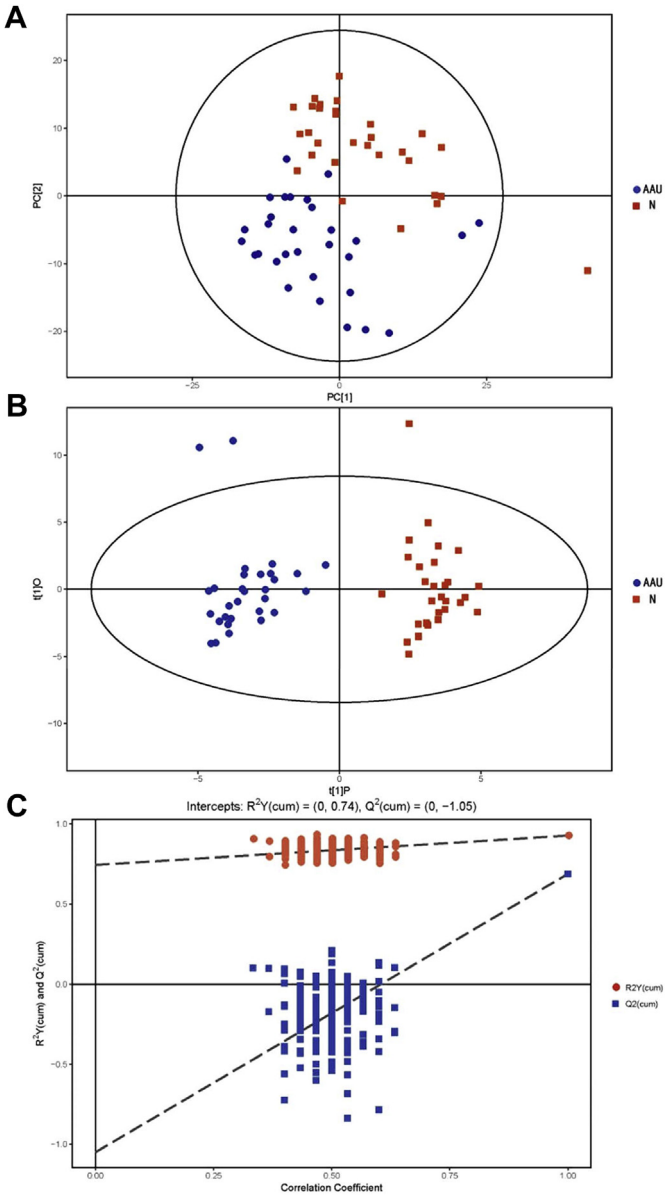


Fig. 6. Alteration of metabolites between acute anterior uveitis (AAU) patients and healthy controls detected by Gas chromatographic mass spectrometry (GC-MS). (A) Principal component analysis of fecal samples from AAU patients (blue circle) and healthy controls (orange square). (B) Orthogonal projections to latent structures discriminate analysis (OPLS-DA) of fecal samples from AAU patients (blue circle) and healthy controls (orange square). (C) Validation of OPLS-DA model (using 200 random permutations). Figures and legends modified from (Huang et al., 2018) with permission from the copyright holder. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

could provide a source of cross-reactive antigen peptides that could propel autoreactive T cells to trigger autoimmune uveitis (Horai et al., 2015). This finding indicates that gut microbiota may be pathogenic through antigenic mimicry, but the exact mimic has yet to be identified. Despite lack of direct evidence in uveitis, it has been theorized that a perturbed microbiota composition might contribute to ocular autoinflammation and autoimmunity via the production of pro-inflammatory metabolites and peptides, altering intestinal permeability and inducing translocation of intestinally-derived innate immune stimulus or inflammatory cells to the eye (Rosenbaum and Asquith, 2018).

In summary, infectious agents can be a triggering factor for the development of autoimmune and autoinflammatory uveitis. The

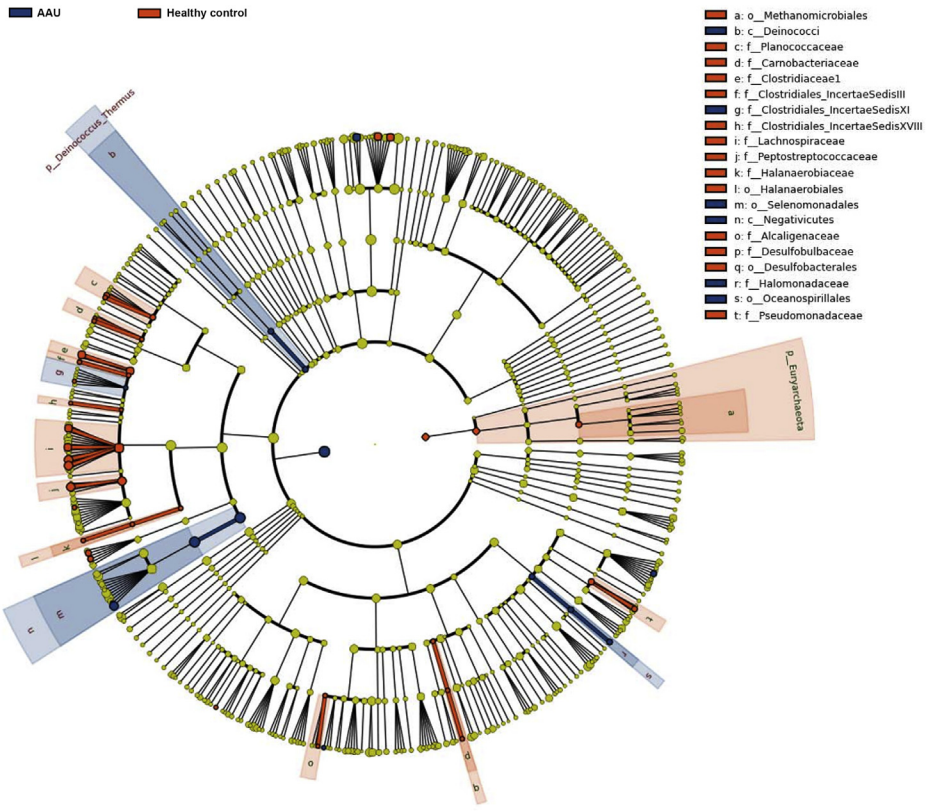


Fig. 7. Differentially abundant taxa of gut microbiota composition in acute anterior uveitis (AAU). The cladogram shows six different taxonomic levels (from kingdom to genus) detected by 16s rDNA sequencing. Orange circles and shadings show the significantly enriched bacterial taxa obtained from healthy controls. Blue circles and shadings show the significantly enriched bacterial taxa obtained from patients with AAU. Figure and legend modified from (Huang et al., 2018) with permission from the copyright holder. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

underlying mechanisms are complicated, which is different from the direct toxicity of a living pathogen that usually causes an acute or chronic infectious disease clinically treated with appropriate antibiotics. Nevertheless, the triggering role of microorganisms and commensals in autoimmune and autoinflammatory uveitis may possibly depend on their living organisms, derivatives, metabolites or even purified peptides that can implicate the activation of innate or adaptive immunity, essentially through stimulating immunoregulatory pathways such as the Toll-like receptor signalling and the IL-23/IL-17 pathway. Therefore, immunosuppressive therapies are the mainstream strategy for autoimmune and autoinflammatory uveitis, whereby the IL-23/IL-17 pathway may be a useful drug target.

4.4. Dysfunction of retinal pigment epithelium cells as the target of IL-23/IL-17 signalling

Besides acting on a diverse set of immune cells such as neutrophils, monocytes and macrophages, IL-17 also plays a pro-inflammatory role by targeting retinal pigment epithelium (RPE) cells, which may facilitate the development of an inflammatory microenvironment in the eye. The neuroectodermally-derived retinal pigment epithelium is a major component of the blood-retinal barrier, which is essential to protect eyes as an immune-privileged organ and to maintain normal visual function (Cunha-Vaz et al., 2010). Under physiological conditions, the retinal pigment epithelium contributes to T cell anergy by directly presenting extracellular peptides to naive $CD4^+$ T cells via MHC class II (Gregerson et al., 2007). The stimulation of the retinal pigment epithelium and breakdown of the blood-retinal barrier will facilitate the inflammatory process, counteract immunological tolerance, expose more antigenic targets and finally cause tissue damage (Forrester et al., 2018). It has been demonstrated that the human primary retinal pigment epithelium cells constitutively express IL-17RA and IL-17RC for IL-17 responsiveness (Zhang et al., 2016b). Upon receiving the IL-17 signals from activated Th17 cells, retinal pigment epithelium cells show an induction of downstream Erk1/2, p38 MAPK, PI3K-Akt and NF-κB signalling pathways and the formation of NLRP3 inflammasome (Chen et al., 2011b; Zhang et al., 2016b). The stimulated retinal pigment epithelium cells can then express pro-inflammatory cytokines and chemokines including IL-1β, IL-6, CXCL8 and CCL2 to recruit neutrophils, monocytes and macrophages (Fig. 10) (Chen et al., 2011b, 2011c; Zhang et al., 2016b). In addition, *in vitro* experiments showed that IL-17 and IL-17F could lead to abnormally enhanced transepithelial electrical resistance and transepithelial permeability (Fig. 11) (Chen et al., 2011c). The tight junction molecules such as ZO-1 and Occludin in retinal pigment epithelium cells can be markedly down-regulated and aberrantly distributed, leading to an impaired integrity of the basement membrane and barrier (Fig. 12) (Chen et al., 2011c). The breakdown of blood-retinal barrier may lead to retinal fluid accumulation and macular edema formation in the retina (Klaassen et al., 2013). Evidence also showed that the stimulated retinal pigment epithelium cells could interact with choroidal endothelial cells or microglia cells to induce the secretion of cytokines including IL-1β, IL-6, IL-8, IL-18, MCP-1 (monocyte chemoattractant protein-1), CXCL1, CCL2, GM-CSF and VEGF, which promotes retinal and choroidal neovascularization (Chen et al., 2018; Holtkamp et al., 2001; Mohr et al., 2015; Wu et al., 2017). One should note that some of the studies were performed with the ARPE-19 cell line (Chen et al., 2011b, 2011c) and controversy exists in the literature whether these cells are a true and reliable representative of the original RPE layer in the eye (Mannermaa et al., 2010). Taken together, the observations mentioned above suggest that the dysfunction of retinal pigment epithelium cells as the target of IL-23/IL-17 signalling may contribute to posterior segment inflammation of the eye. Further *in vivo* experiments are warranted to investigate the pathophysiological conditions and functions of the retinal pigment epithelium when responding to a dysregulated IL-23/IL-17 signalling.

We thus propose a potential mechanism whereby intraocular inflammation is triggered by pathogens and mechanical stress in genetically susceptible individuals (Fig. 13 and Fig. 14). During this process, multiple abnormal events such as pathogen-associated molecular pattern recognition, MHC molecule predisposition, antigen presentation

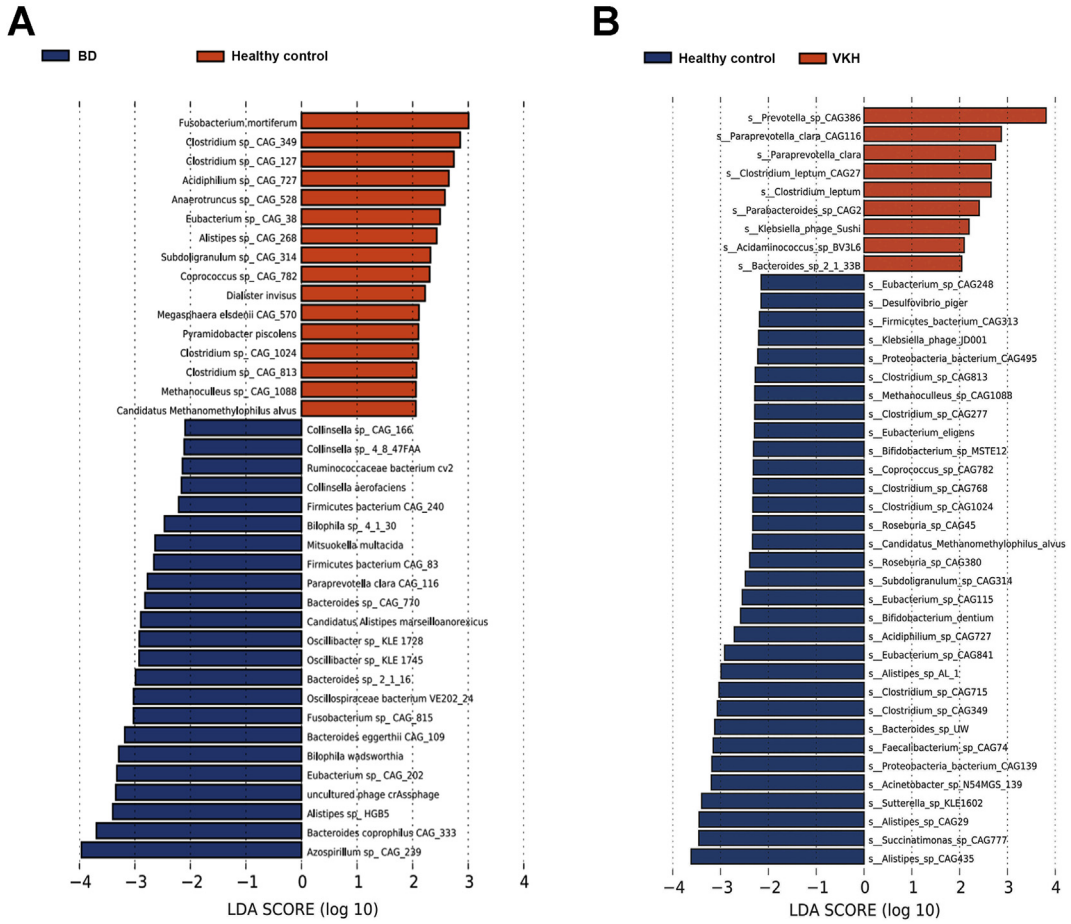
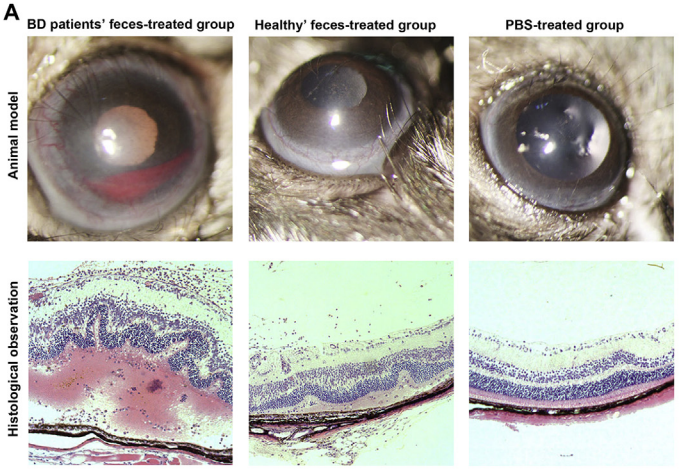


Fig. 8. Metagenomic analysis of differentially abundant taxa of gut microbiota composition in Behçet's disease (BD) (A) and Vogt-Koyanagi-Harada disease (VKH) (B), as compared with healthy controls. The X-axis shows the log linear discrimination analysis (LDA) scores. Figures and legends modified from (Ye et al., 2018, 2020) with permission from the copyright holder.

and genetically determined IL-23 responsiveness may all contribute to the pathogenesis whereby the central event appears to be the over-activation of the IL-23/IL-17 signalling pathway.

5. Targeting IL-23/IL-17 signalling for treatment

Inhibition of the IL-23/IL-17 pathway and Th17 cell response can be a promising therapeutic strategy for those uveitis entities that have been found to be associated with activation of the IL-23/IL-17 pathway. Many widely used agents such as Cyclosporin A, Prednisone,



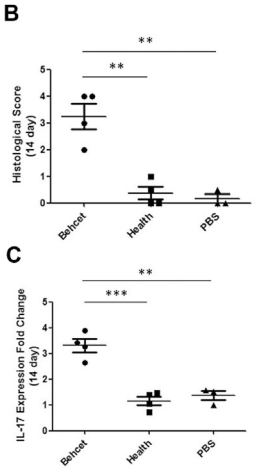


Fig. 9. Effect of transplantation of feces from Behçet's disease (BD) patients on experimental autoimmune uveitis (EAU). Pooled feces from active BD patients transferred to B10RIII mice by oral gavage. EAU was induced by immunization with IRBP161-180. Pooled feces from healthy individuals or phosphate buffer saline (PBS) were transferred to mice as the control groups. (A) Representative images of animal model and histological observation on day 14 after EAU induction. (B) Increased histological score in the BD patients' feces-treated group as compared with controls, showing exacerbated EAU activity. (C) Real-time polymerase chain reaction assays showing the increased mRNA expression of IL-17 of the spleens of EAU mice in the BD patients' feces-treated group as compared with controls. Figures and legends modified from (Ye et al., 2018) with permission from the copyright holder.

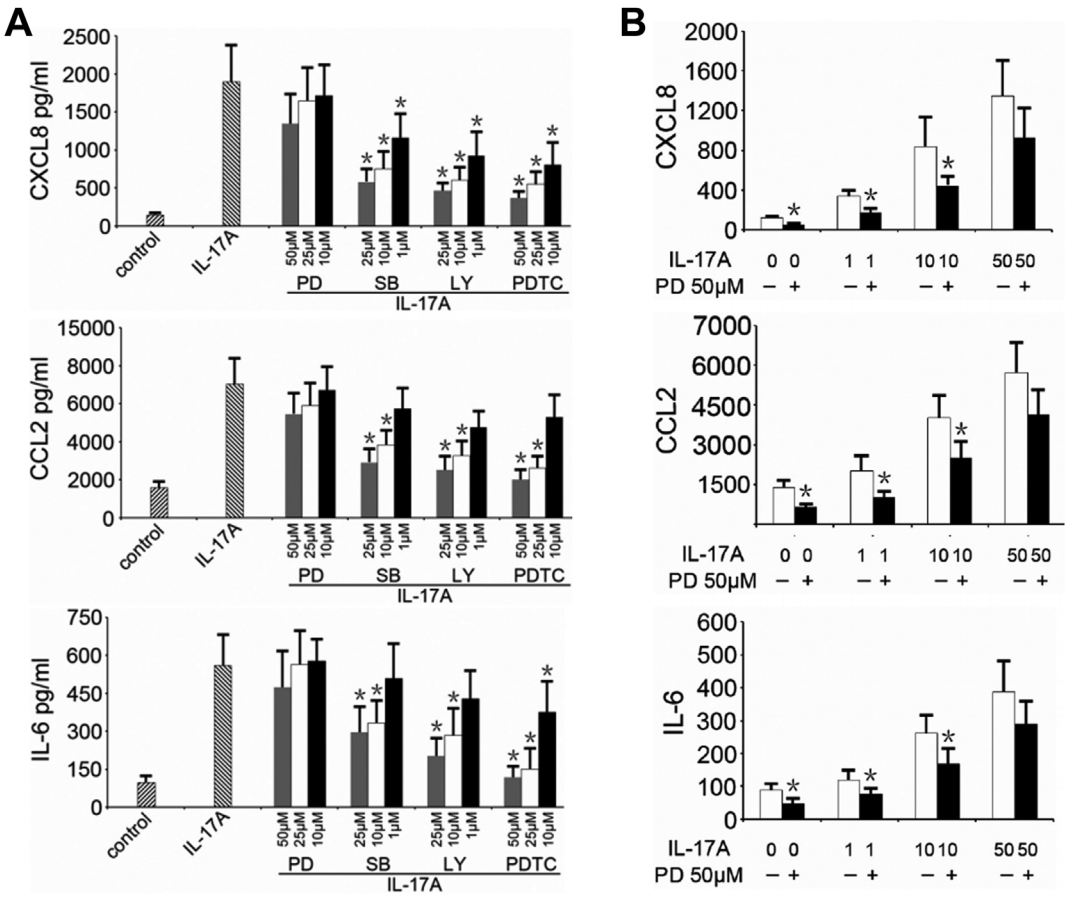


Fig. 10. Effect of IL-17A on the production of pro-inflammatory cytokines and chemokines of ARPE-19 cells. (A) Increased expression of CXCL8, CCL2 and IL-6 in cell supernatants determined by ELISA in the group treated with 100 ng/ml IL-17A, as compared with the control group and those groups pre-treated with the Erk1/2 signalling inhibitor PD98059 (PD), the p38 MAPK signalling inhibitor SB203580 (SB), the PI3K signalling inhibitor LY29400 (LY) or the NF-κB signalling inhibitor PDTC at the indicated concentrations. (B) Effect of different concentrations of IL-17A and the Erk1/2 signalling inhibitor (PD) on the expression of CXCL8, CCL2 and IL-6 of cell supernatants determined by ELISA. Data are expressed as the mean ± SD of four independent experiments.*$p < 0.05$. Figures and legends modified from (Chen et al., 2011b) with permission from the copyright holder.

Dexamethasone and IFN-α for uveitis can cause a significant inhibitory effect on IL-17 (Fig. 15) (Chi et al., 2010; Liu et al., 2009, 2011; Tian et al., 2011; Yang et al., 2009). Moreover, a preclinical study provided evidence from the EAU animal model supportive of the theory that specific inhibition of IL-23 as well as the downstream signalling by small molecules is effective for the suppression of intraocular inflammation (Keino et al., 2008). Several biological agents are now developed, including monoclonal antibodies that can specifically block mediators such as the IL-23 p40 subunit, p19 subunit, IL-17A, IL-17F and IL-17RA, respectively (Fig. 16). The following sections introduce these biological agents as well as their efficacy and safety profiles on uveitis and uveitis related systemic diseases such as ankylosing spondylitis and psoriasis.

5.1. Targeting the p40 subunit

The p40 subunit is a shared component for IL-23 and IL-12 and at present, two monoclonal antibodies, Ustekinumab (Janssen Biotech Inc) and Briakinumab (Abbott), can neutralize the biological activity of the p40 subunit. Ustekinumab has shown efficacy and safety in confirmatory Phase III clinical trials and is now the first-line biologic therapy for patients with psoriasis and psoriatic arthritis (Griffiths et al., 2010; Leonardi et al., 2008; McInnes et al., 2013). In addition, administration of Ustekinumab yields significant improvements in clinical response and remission rates in patients with moderately to severely active Crohn's disease including cases not responding to conventional or biological anti-TNF drugs (Feagan et al., 2016; Sandborn et al., 2012). Nevertheless, disappointing results have been reported in relapsing-remitting multiple sclerosis, possibly due to the blood-brain barrier that does not allow drug access to the central nervous system as readily as it does to the skin and gut (Segal et al., 2008). Similarly, another monoclonal antibody against the p40 molecule, Briakinumab, has been demonstrated efficacy for moderate to severe plaque psoriasis and Crohn's disease, but this drug has not yet been approved due to reports on increased cancer incidence and major adverse cardiac events (Langley et al., 2013; Panaccione et al., 2015; Reich et al., 2011).

Case reports have been published on successful treatment with Ustekinumab in Behçet's disease, uveitis associated with Crohn's disease and psoriasis as well as psoriatic arthritis (Baerveldt et al., 2013; Chateau et al., 2019; Mugheddu et al., 2017). In addition, a prospective single arm study involving 14 patients with active Behçet's disease suggested that Ustekinumab appeared to be efficient and safe for patients with refractory oral ulcers (Mirouse et al., 2017). Furthermore, Phase II trials are now being conducted to evaluate the proof of concept of efficacy of Ustekinumab for Behçet's disease (STELABEC; ClinicalTrials.gov ID: NCT02648581) and for those with non-infectious severe uveitis (USTEKINISU; ClinicalTrials.gov ID: NCT03847272). Another non-randomized, uncontrolled, pilot study is also ongoing to determine the efficacy of Ustekinumab for active intermediate uveitis, posterior uveitis or panuveitis (ClinicalTrials.gov ID: NCT02911116). As yet, no randomized clinical trials have been published that show

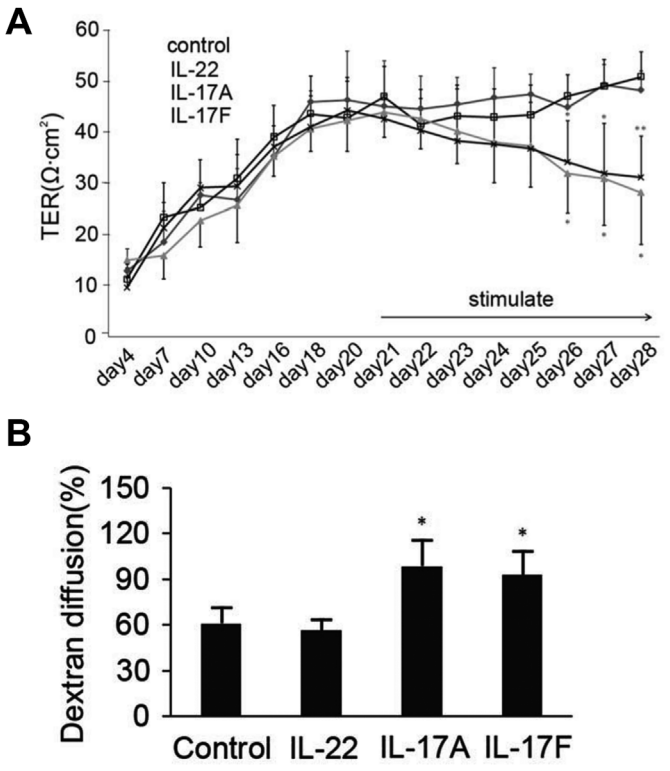


Fig. 11. Effect of IL-17A, IL-17F or IL-22 on transepithelial electrical resistance (TER) and transepithelial permeability. (A) Effect on TER of cultured ARPE-19 monolayer. Monolayers were cultured for 21 days, where after the various stimuli were added. Incubation of ARPE-19 monolayers with 50 ng/ml IL-17A or IL-17F induced a gradual decrease of TER, and a significant effect occurred 5 days ($p = 0.019$, $p = 0.045$) after stimulation. The continuous decreases were also observed 6 days ($p = 0.01$, $p = 0.016$) and 7 days ($p = 0.023$, $p = 0.008$) after stimulation. IL-22 had no effect on TER. (B) Effect on transepithelial diffusion rate of FITC-dextran in ARPE-19 monolayer. Stimulation of ARPE-19 monolayer with 50 ng/ml IL-17A or IL-17F for 6 days induced a higher FITC-dextran diffusion rate at 24 h compared with the control group. IL-22 had no effect on diffusion rate. Data are shown as the means ± SEM of four independent experiments.*$p < 0.05$ versus the control group. Figures and legends modified from (Chen et al., 2011c) with permission from the copyright holder.

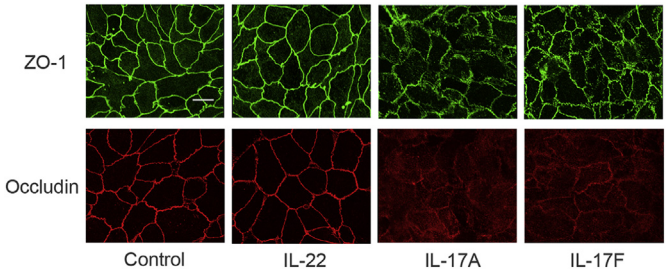


Fig. 12. Effect of IL-17A, IL-17F or IL-22 on the distribution of junction proteins in ARPE-19 monolayer. Cells were incubated with or without 50 ng/ml IL-17A, IL-17F or IL-22 for 6 days, then fixed and immunolabeled with ZO-1 or Occludin. Immunostaining for ZO-1 and Occludin in untreated or IL-22-treated ARPE-19 monolayer showed a continuous labelling in the region of cell-cell contact. Incubation with IL-17A or IL-17F caused a marked disruption of ZO-1 and Occludin staining. Scale bar = 15 mm. Figures and legends modified from (Chen et al., 2011c) with permission from the copyright holder.

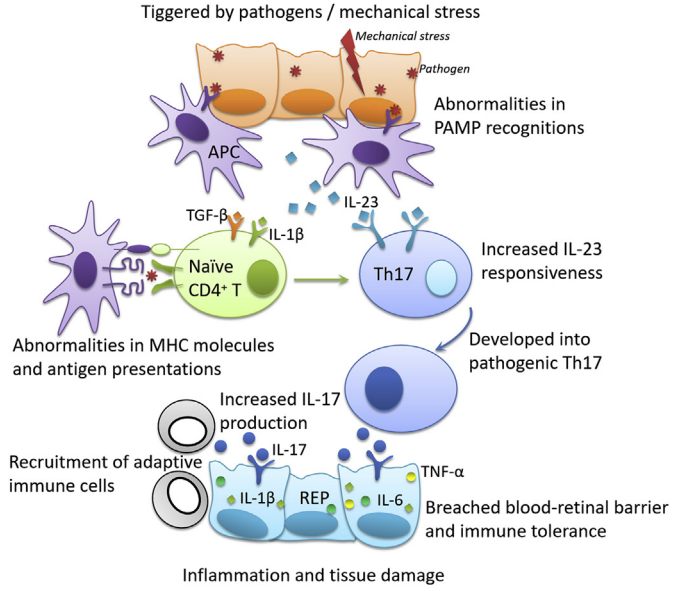


Fig. 13. Proposed mechanism and pathogenic events centered around the activation of the IL-23/IL-17 signalling pathway in multifactorial triggered autoinflammatory and autoimmune uveitis. APC, antigen presenting cells; PAMP, pathogen-associated molecular pattern; REP, retinal pigment epithelium. Figure drawn specifically for this paper.

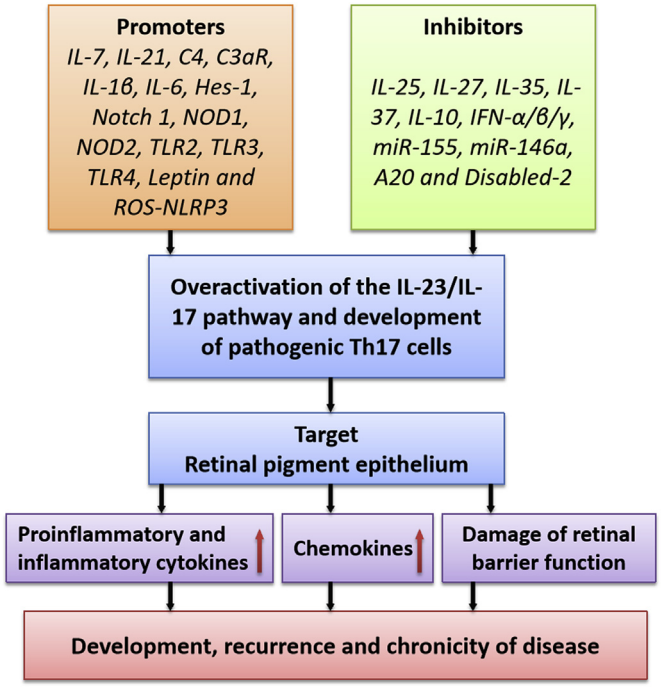


Fig. 14. Identified regulatory mediators and their functional roles on the IL-23/IL-17 signalling pathway and the development of autoimmune and autoinflammatory uveitis. Figure drawn specifically for this paper.

clinical benefits of Ustekinumab in the control of intraocular inflammation.

5.2. Targeting the IL-23 p19 subunit

More recently, several novel monoclonal antibodies such as Guselkumab (Johnson & Johnson Janssen Biotech), Tildrakizumab (Merck), Risankizumab (AbbVie) and Brazikumab (Allergan) have been developed to selectively bind the target of the IL-23 p19 subunit, among

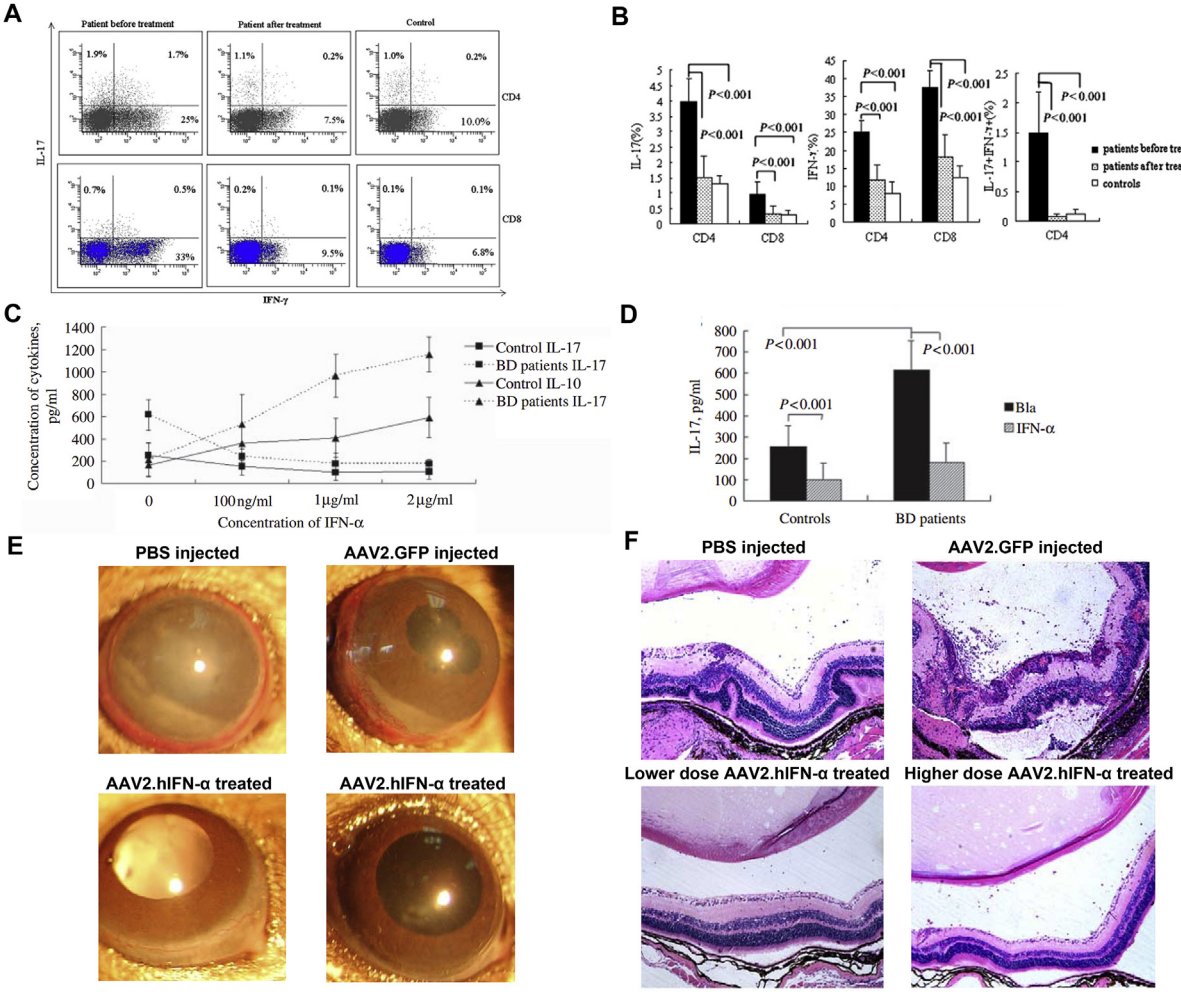


Fig. 15. Treatment of Cyclosporin A, Prednisone or IFN-α on IL-17 and uveitis disease activity. (A) Detection of IL-17 and IFN-γ expressing T cells ($CD4^+$ or $CD8^+$) in peripheral blood mononuclear cells (PBMCs) from patients with Vogt-Koyanagi-Harada disease (VKH) (n = 8) before and after systemic treatment with Cyclosporin A (CsA) and Prednisone and from normal control subjects (n = 8) by intracellular cytokine staining assay and fluorescent-activated cell sorting (FACS) analysis. (B) Quantitative analysis showing decreased IL-17- and IFN-γ-expressing T cells in VKH patients after systemic treatment with Cyclosporin A (CsA) and Prednisone. Data are expressed as mean ± SEM. (C) Dose-related effect of recombinant human interferon (rhIFN)-α2a on IL-17 and IL-10 production by PBMCs in Behçet's disease (n = 8) and healthy controls (n = 8) stimulated with anti-CD3 and anti-CD28 antibodies measured by ELISA. (D) Decreased IL-17 production in the supernatants of cultured PBMCs in Behçet's disease with rhIFN-α2a at a concentration of 1 mg/ml plus anti-CD3 and anti-CD28 antibodies measured by ELISA. Bla means PBMCs were cultured without rhIFN-α2a. (E) Evaluation of adeno-associated virus 2 (AAV2) based human interferon-α (AAV2.hIFN-α) gene therapy on experimental autoimmune uveitis (EAU) activity. Two doses of AAV2.hIFN-α were subretinally injected into the eye. Phosphate buffer saline (PBS) and AAV2. Green fluorescent protein (GFP) was used as controls. Three weeks after injection, EAU was induced by immunization with IRBP161-180 and ocular inflammation was examined by slit lamp microscopy. Images show significantly severe inflammation in the PBS and AAV2.GFP injected eyes as compared to the AAV2.hIFN-α treated eyes. (F) Histological examinations on day 14 of EAU. Images of histological analysis show obvious iris thickening, severe retinal folding, destruction, damage of the photoreceptor layer and massive inflammatory cell infiltration in the iris, vitreous, retina, and subretinal space, as well as intensive vasculitis formation in PBS injected eye and AAV2.GFP injected eyes. However, a minor infiltration of inflammatory cells was observed in the vitreous and retina in both lower and higher doses of AAV2.hIFN-α treated eyes. Figures and legends modified from (Liu et al., 2009, 2011; Tian et al., 2011) with permission from the copyright holder. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

which only Guselkumab, Tildrakizumab and Risankizumab have so far been assessed in Phase III clinical programmes. Results of Phase III trials demonstrated that Guselkumab, Tildrakizumab and Risankizumab had a favourable efficacy and safety profile for moderate to severe chronic psoriasis (Blauvelt et al., 2017; Reich et al., 2017, 2019). Moreover, for those patients with a poor response to Ustekinumab, treatment switching to Guselkumab has shown clinical benefits in plaque psoriasis (Langley et al., 2018). In addition, head-to-head comparisons demonstrated that Guselkumab could lead to a higher proportion of complete clearance of lesions of psoriasis than Adalimumab, a monoclonal antibody against TNF-α (Foley et al., 2018; Gordon et al., 2015). Adalimumab is an effective agent for the relief of active non-infectious uveitis and for the long-term maintenance of disease inactivity (Jaffe et al., 2016; Nguyen et al., 2016). There are only limited reports on the therapeutic use of Guselkumab for autoimmune or autoinflammatory uveitis. One case report showed a poor control of sarcoidosis-related panuveitis with Guselkumab in a patient with refractory disease who was previously treated with various biologicals including Adalimumab and Ustekinumab (Thomas and Rosenbaum, 2019).

5.3. Targeting IL-17A

Two monoclonal antibodies with affinity to IL-17A, Ixekizumab (Eli Lilly) and Sekukinumab (Novartis) have been developed and have advanced to the stage of Phase III clinical trials. Significant therapeutic effects and generally good tolerances have been observed in suppressing inflammation of plaque psoriasis and psoriatic arthritis for both

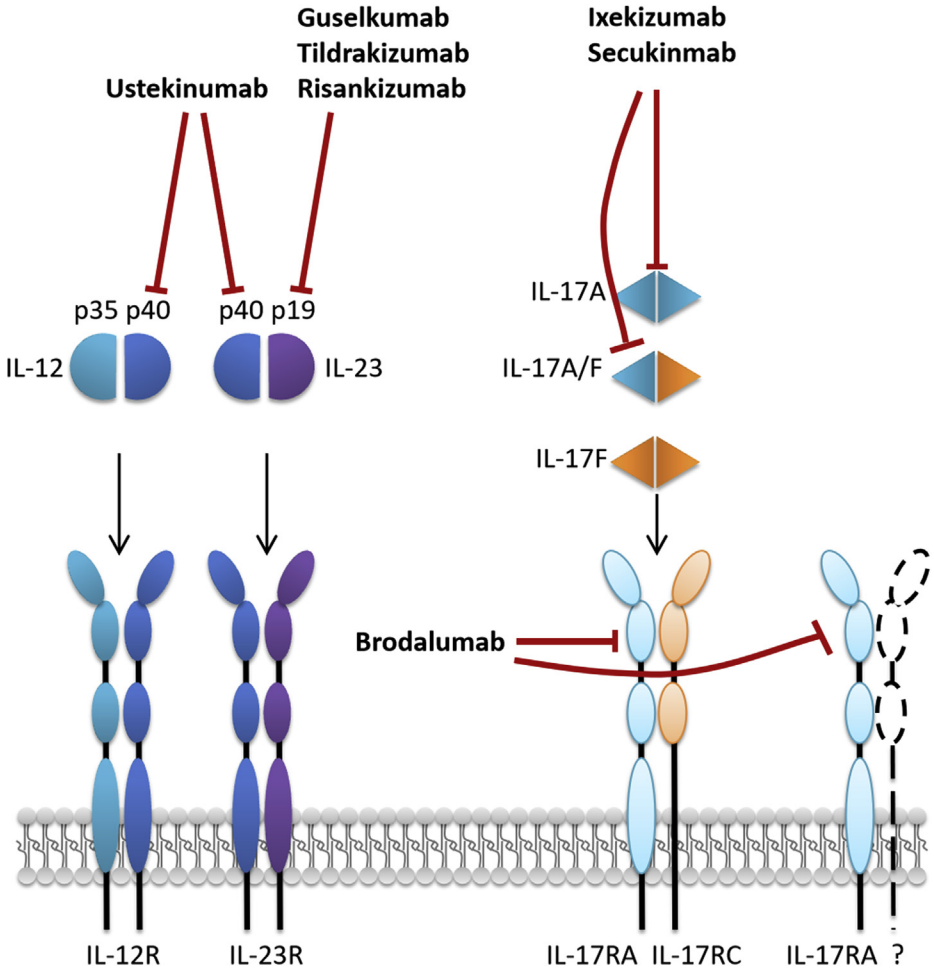


Fig. 16. FDA approved monoclonal antibodies specifically targeting the component of IL-23/IL-17 signalling pathway for inhibition. Figure drawn specifically for this paper.

Ixekizumab and Sekukinumab in Phase III trials (Griffiths et al., 2015; Langley et al., 2014; Mease et al., 2015; Nash et al., 2017). Additionally, Secukinumab showed efficacy in the relief of the signs and symptoms of ankylosing spondylitis, especially in patients in whom previous anti-TNF-α treatment had failed (Baeten et al., 2015). Efficacy of Secukinumab has also been demonstrated for active rheumatoid arthritis patients showing an inadequate response to anti-TNF therapy (Huang et al., 2019).

An initial study in a small number of chronic non-infectious uveitis patients reported that blocking of IL-17A with Secukinumab could lead to either the improvement of visual acuity or reduction in intraocular inflammation (Hueber et al., 2010). However, analyses of several subsequent randomized, double-masked, placebo-controlled trials (ClinicalTrials.gov ID: NCT00995709, NCT01032915, NCT01095250) involving 274 subjects provided disappointing results. No statistically significant differences were detected regarding the uveitis recurrence rate in subcutaneously administered Secukinumab groups compared to placebo (Dick et al., 2013). Nevertheless, exploratory analyses of this study indicated that treatment with Secukinumab had beneficial effects in shortening the use of concomitant immunosuppressive agents (Dick et al., 2013). In addition, a multicenter, randomized, double-masked, dose-ranging trial (ClinicalTrials.gov ID: NCT00685399) showed that intravenous Secukinumab was effective and well tolerated in corticosteroid-sparing treatment for active non-infectious intermediate uveitis, posterior uveitis, or panuveitis (Letko et al., 2015). This study indicated that patients might not have received a sufficiently high drug dose when Secukinumab had been administered subcutaneously. Taken together, Secukinumab may be a promising therapeutic option for uveitis treatment.

5.4. Targeting the IL-17 receptor

Brodalumab (Amgen and MedImmune) is the first monoclonal antibody that can block IL-17RA, which in theory, could be superior over those therapies only targeting IL-17A since it also blocks the action of other members of the IL-17 cytokine family, such as IL-17C and IL-17F. However, due to the broad action of the drug, abrupt cessation of Brodalumab may cause a rebound effect, even in those patients who experienced complete remission (Masson Regnault et al., 2017). To date, Phase III trials have proven that treatment with Brodalumab can lead to clinical improvement with an acceptable safety profile for moderate to severe chronic plaque psoriasis, and therefore, Brodalumab has been licensed and approved by the FDA for the first-line use in psoriasis (Lebwohl et al., 2015). As yet, no studies have commenced using Brodalumab for the treatment of uveitis.

A variety of monoclonal antibodies have emerged as effective blockers of the IL-23/IL-17 signalling pathway for the suppression of inflammatory responses. Trials with these novel monoclonal antibodies are now registered on the ClinicalTrials.gov website for the treatment of uveitis, showing the scientific merits and general belief that this pathway plays an important role in the pathogenesis of uveitis (Table 4).

Currently, head-to-head comparisons of anti-IL-23/IL-17 antibody drugs with conventional immunosuppressants and TNF inhibitors for

Table 4
Results and status of clinical trials of treatment with monoclonal antibodies for uveitis.

Trial	Agent	Target	Study design	Participant	Primary efficacy outcome and status of the study	ClinicalTrials.gov ID and publication
STELABEC	Ustekinumab	p40 subunit	Phase II, open-label, single group assignment	16 subjects with Behçet's disease, including patients with oral ulcers and those with active posterior uveitis or panuveitis	Number of oral ulcers at week 24 compared to baseline Number of uveitis or retinal vasculitis remission Study ongoing	NCT02648581
STAR Study	Ustekinumab	p40 subunit	Phase II, open-label, sequential assignment	Estimated 11 subjects with active intermediate uveitis, posterior uveitis or panuveitis	Number of participants who experience treatment response by week 16 Study ongoing	NCT02911116
USTEKINISU	Ustekinumab	p40 subunit	Phase II, single-arm, proof-of-concept	Estimated 29 subjects with non-infectious severe uveitis	Percentage of remission and percentage of patients free of relapse between week 6 and week 24 Study ongoing	NCT03847272
SHIELD	Secukinumab	IL-17A	Phase III, multicenter, randomized, double-masked, placebo controlled,	125 Behçet's disease with posterior or panuveitis	Rate of recurrent ocular exacerbations in the study eye during 24 weeks Study completed, showing no significant effects on primary outcome as compared with the placebo group	NCT00995709 (Dick et al., 2013)
SHIELD Extension Study	Secukinumab	IL-17A	Phase III, 38-week extension to a 24-week multicenter, randomized, double-masked, placebo controlled study	59 Behçet's disease with posterior or panuveitis	Rate of recurrent pcular exacerbations in Behçet's disease Study terminated due to core study in Behçet's disease with mostly active uveitis did not meet its primary endpoint	NCT01093846
INSURE	Secukinumab	IL-17A	Phase III, multicenter, randomized, double-masked, placebo controlled, dose-ranging	30 subjects with intermediate uveitis, posterior uveitis, or panuveitis requiring systemic immunosuppression	Mean change in vitreous haze grade in the study eye from baseline to 28 weeks or at time of rescue Study terminated due to the fact that Behcet's disease with mostly active uveitis did not meet its primary endpoint	NCT01095250 (Dick et al., 2013)
ENDURE	Secukinumab	IL-17A	Phase III, multicenter, randomized, double-masked, placebo controlled, dose-ranging	125 subjects with quiescent, non-infectious intermediate, posterior or panuveitis	Time to first recurrence in any eye of active intermediate, posterior, or panuveitis from baseline Results of a planned interim analysis showing no significant effects on any primary or secondary endpoint	NCT01032915 (Dick et al., 2013)
Safety and Efficacy of AIN457 in Noninfectious Uveitis	Secukinumab	IL-17A	Phase II, open-label proof-of-concept study with a double-masked, dose-ranging component	76 subjects with active intermediate uveitis, posterior uveitis or panuveitis	Number of responders at day 57 Study completed, showing that Secukinumab 30 mg/kg iv and 10 mg/kg iv, compared with the 300 mg sc dose, produce significantly higher responder rates and remission rates	NCT00685399 (Letko et al., 2015)

Abbrevation: iv, intravenous; sc, subcutaneous. ClinicalTrials.gov website assessed on March 6, 2020.

the treatment of uveitis are still lacking. However, results from trials in psoriasis suggested that anti-IL-23/IL-17 therapies are superior to immunosuppressive drugs such as Methotrexate as well as TNF blockers such as Etanercept and Adalimumab (Foley et al., 2018; Griffiths et al., 2015; Reich et al., 2011). The IL-23/IL-17 pathway plays an important role in the regulation of Th17 cell activation and downstream TNF-α production. Accordingly, molecular targeted treatments through this pathway are likely to have greater effects and to provide additional benefits for those resistant to anti-TNF therapies. However, the disadvantage is also evident that a broad immunosuppressive action of anti-IL-23/IL-17 agents may raise potential safety issues such as infection and cardiovascular events, which may lead to a discontinuation due to side effects (Cui et al., 2018).

With the release of data from ongoing studies, we expect to witness a promising prospect for therapies targeting the IL-23/IL-17 pathway for the first-line clinical uses in uveitis. However, a number of questions remain to be solved. First, although antagonism of IL-23/IL-17 signalling has great potential to improve systemic inflammatory conditions, extrapolation of the effectiveness for intraocular inflammation is still weak. A complicating factor may be caused by drug access through the blood-retinal barrier and the complexity of the intraocular immune microenvironment. It is not clear whether the treatment for uveitis requires a different route of administration or a higher dose of anti-IL-23/IL-17 drugs, and whether such dosages might be associated with more frequent adverse events and intolerability. In addition, in view of the fact that uveitis is a heterogeneous group of intraocular inflammatory entities, it is possible that some subgroups of uveitis patients with special disease conditions may not respond to a specific IL-23/IL-17 blocker, and there remain medical needs for therapeutic options with different drug targets in this pathway. We expect that novel drugs will soon be designed and find their way to clinical trials, such as small molecules targeting other components of the IL-23/IL-17 pathway including RORγt inhibitors, JAK inhibitors and especially IL-23R blockers such as PTG-200 (an orally bioavailable antagonist of the IL-23R) (Cheng et al., 2017; Morelli et al., 2018; Sasaki et al., 2018).

6. Conclusion and future studies

Autoinflammatory and autoimmune mechanisms are the main cause of non-infectious uveitis, whereby immunosuppressive therapy is currently the hallmark treatment. Many uveitis patients however still lose their visual function and a search for novel therapies is of utmost importance. Great progress in immunological and genetic research has allowed an improved understanding of the multifactorial aetiology of the disease, such as genetic predisposition, infectious triggers, gut microbiome status, various cytokine imbalances and retinal barrier dysfunctions. The activation of the IL-23/IL-17 pathway as well as the development of pathogenic Th17 cells appears to be a critical event that is shared by most clinical autoimmune and autoinflammatory uveitis entities. IL-17 is an important cytokine that regulates mucosal immunity, whereby dysregulation of IL-17 responses may lead to destructive autoimmunity and tissue inflammation. Existing clinical data on the efficacy of anti-IL-23 or anti-IL-17 drugs in uveitis associated systemic diseases such as ankylosing spondylitis, psoriasis and Crohn's disease further support the functional role of the IL-23/IL-17 signalling in autoinflammation and autoimmunity. This article provides extensive biological knowledge and preliminary clinical data to support the further development and evaluation of novel drugs targeting the IL-23/IL-17 pathway for autoimmune and autoinflammatory uveitis.

Accumulated findings in the molecular pathology of uveitis over the years have made a great contribution to the management of this disease. Genetic approaches such as HLA typing have been applied to facilitate the diagnosis, especially for HLA-B27 associated uveitis and ankylosing spondylitis. Novel drugs such as TNF inhibitors have significantly improved the prognosis of some refractory uveitis entities such as Behçet's disease, and therefore open up a broad field for emerging biological therapies. However, there are still a number of challenges in clinical and translational medicine with regards to targeting the IL-23/IL-17 pathway in uveitis. First, as a multifactorial disease, our understanding of the pathophysiology of uveitis is still limited. It has been recognized that activation of the IL-23/IL-17 pathway is critically involved in the development of uveitis, whereby multiple genetic and environmental factors contribute to the dysregulation of the pathway. Nevertheless, the precise mechanisms underlying the contribution have not been well characterized especially in *in vivo* experiments. Second, the diagnosis of uveitis entities is currently restricted to clinical manifestations, and few studies have commenced employing the genetic and biomarker data related to molecules in the IL-23/IL-17 pathway to improve the diagnostic criteria for a specific uveitis entity and which might lead to a further sub-classification. It is still a long way before we will be able to use genetic or biomarker based diagnostic tests for uveitis in clinical practice. Third, clinical trials of several drugs targeting the IL-23/IL-17 signalling for uveitis are ongoing. The efficacy of these drugs has not yet been confirmed and will need further fine tuning. Although some drugs have shown limited effects, it is possible to obtain additional benefits by changing delivery routes, adjusting drug doses or combining them with other agents, which warrants further study. In biological science, future studies in autoimmune and autoinflammatory uveitis should aim at identifying novel triggering factors or mediators, which may further elucidate the exact mode of action of the IL-23/IL-17 pathway in this disease. In clinical areas, future investigations, on one hand, may focus on genetic and biomarker assays to improve uveitis diagnosis in different ethnical populations or to determine the proper indication for anti-IL23/IL-17 therapies. On the other hand, larger trials are expected to further assess the efficacy and safety of novel targeted drugs or combined regimens for the disease. Based on our advanced knowledge concerning the IL-23/IL-17 pathway in uveitis, we expect to witness novel diagnostic or therapeutic approaches that can significantly change the clinical practice in the future.

Declaration of competing interest

The authors declare no competing financial interests.

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