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Abstract

Aim: To investigate the role of interleukin-17 in ocular surface disease. Ocular surface disease is a leading cause of blindness and is an ongoing challenge to the public health sector to implement effective therapies. The majority of cells in corneal lesions are derived primarily from neutrophils that induce inflammatory events that lead to tissue damage. One of the key pro-inflammatory cytokines is IL-17, and it has been investigated in order to facilitate the understanding of the pathogenesis of ocular surface lesion development. Results: IL-17 has been shown to exacerbate viral and bacterial keratitis lesion severity, although it was found to be protective for Acanthamoeba. Antibodies developed to neutralise IL-17 have shown some promise in reducing the severity of some diseases. Conclusion: IL-17 plays a role in the pathogenesis of ocular surface disease and targeting this cytokine may provide a useful treatment option in the future.

Key words

keratitis, ocular surface disease and bacterial or fungal or viral or acanthamoebal or dry eye

Introduction

Across the globe corneal infections remain a leading cause of blindness and thus pose a challenge for public health policies to select and implement targeted and effective therapies.[1, 2] Infective keratitis (caused by bacterial, fungal, amoebal or viral infection) treatment is based on the aetiology and usually involves topical or in some cases, systemic medications.[3-5] Infective keratitis resulting in corneal inflammation, necrosis and scarring, can lead to significant vision loss.[6] In situations where effective treatment for infective keratitis is delayed or not commenced at all, the sequelae can result in loss of the eye itself from corneal perforation and endophthalmitis. In a small proportion of severe cases, despite correct and prompt treatment, serious sequelae such as perforation can occur. Ongoing studies in animal models and cell lines to elucidate the pathogenesis of keratitis have focused on the relationship between host and pathogen and the various signalling pathways. An understanding of this relationship, and who this then effects is crucial, as the biochemical pathways would allow for the development of novel modes of treatment that may be efficacious clinically, however more studies are needed in this area, particularly human studies.[7]

Of interest in this discussion is interleukin (IL)-17 (IL-17) and its role in ocular surface disease and infective keratitis. The major cellular component of corneal lesions, at all of the phases of keratitis pathogenesis, are derived primarily from neutrophils that induce inflammatory events that lead to tissue damage (Figure 1).[8, 9]

Figure 1: Function and induction of IL-17. Adapted from Matsuzaki *et al*.[10]

The prominence of neutrophils in keratitis lesions and their expression of the recently identified pro-inflammatory cytokine IL-17 has led to the possibility that investigation of this could facilitate understanding of the pathogenesis of ocular surface lesion development. The IL-17 family is comprised of six members, where the most understood are IL-17A and IL-17F. Although there is some redundancy between IL-17A and IL-17F, there are also some differences in regulation, receptor binding and post receptor signal transduction that are highlighted in different disease processes.[11, 12] IL-17 works indirectly to aid neutrophil survival and promote tissue infiltration of neutrophils, whilst further inducing cells to synthesise and secrete destructive molecules including matrix metalloproteinases and reactive oxygen species.[13-16] The production of matrix metalloproteinases breaks down the extracellular and basement membrane of the corneal epithelium. This, combined with dysregulated reactive oxygen species, induces apoptosis of ocular surface cells and causing disruption of the corneal epithelium function. Once this barrier has started to erode, the host is more susceptible to ocular surface disease for instance being seeded with pathogens. Then the extrinsic (tumour necrosis factor-mediated) and intrinsic (mitogen-activated protein kinase) apoptotic pathways are activated to induce cell death at the ocular surface.[17, 18]

In the instance of inoculation with extracellular pathogens, the infected epithelial cells induce neutrophil recruitment through IL-8 production and both epithelial cells and fibroblasts become activated themselves via secretion of proinflammatory cytokines including IL-1, TNFα and IL-6.[10] In infection and autoimmunity, the accepted role for IL-17 is to attract neutrophils once it has been produced by Th17 (adaptive immune system lymphoid cell) or Natural Killer (NK) T cells and γδ T cells (innate immune system lymphoid cells). For the innate immune system NK T cells have been reported to secrete IL-17 and γδ T cells can potentially be stimulated by IL-23 although self-antigen recognition as a means of inducing IL-17 production. The tissue resident fibroblasts and epithelial cells are known to

constitutively express receptors for the subunits IL-17RA and IL-17RC.[19] Ocular epithelial cell damage and microbicidal action is the result of neutrophil recruitment, which is mediated by the production of pro-inflammatory and chemotactic cytokines initially induced by IL-17A. [20-22] Preliminary studies of IL-17 in autoimmune and chronic inflammatory diseases were shown to promote a proinflammatory response.[23] As research has advanced, there has been evidence to suggest that IL-17 plays an additional role in host defence against infections from fungus, bacteria and protozoa.[24-26] Furthermore, observing intestinal inflammation caused by T cells, a recent study has shown that IL-17 may play a protective role in the pathophysiology of the diseases.[27] Another study found that IL-17 promoted an IgA response to infections in the intestine and that a correlation between levels of IL-17 and IgA were seen in synovial fluid in patients with arthropathies.[28, 29] This review will focus on bacterial, fungal, viral, Acanthamoebal keratitis and dry eye and what role IL-17 plays in the pathogenesis of each disease.

Bacterial

Bacterial keratitis is responsible for the majority of new cases of microbial keratitis.[30] Previous results disagree on the most common organisms that cause bacterial keratitis, but the most common in developed countries are *Staphylococci* and *Pseudomonas* species.[31] The most common risk factors for bacterial keratitis include ocular trauma, surgery, concurrent ocular surface disease, immunosuppression and the use of contact lenses.[7, 32] Similar to other bacterial infections, the pathogenesis of bacterial keratitis (caused primarily by extracellular bacteria) is dependent on the species of the bacteria, the virulence factors and host immune response.[33] Heimer *et al.* (Table 1) investigated the gene expression of human corneal epithelial cells secondary to infection with *Staphylococcus aureus*. The study found that of the inflammatory mediators assessed (IL-1β, IL-2, IL-4, IL-10, TNF-α, CSF-2, IL-6, IL-8, IL-17 and IFN-γ) in epithelial cells, IL-6, IL-8, IL-17 and IFN-γ showed the greatest expression rate. For IL-8 and IFN-γ, release was not affected by the *Staphylococcus aureus* strain used. In comparison IL-17 was increased and IL-6 was decreased in the non-toxigenic strain when compared to the toxigenic variant.[34] Zaidi *et al*. (Table 1) investigated IL-17 in pseudomonas infection in mouse corneal cells *in vivo*. Results showed that neutrophil infiltration was decreased if the receptor for IL-17 was knocked out in mice infected with *Pseudomonas aeruginosa*. Further IL-17R knockout mice had less severe corneal pathology and intracellular bacterial levels regardless of pseudomonas strain tested (clinical isolate strains were 6294 (ExoS producing) and 6077 (ExoU producing)). Topical antibodies to IL-

17 applied to the cornea of mice were found to reduce neutrophil infiltration and lower the level of IL-17 in the cornea itself.[35]

Fungal

Fungal keratitis is caused by filamentous fungi (Aspergillus species and Fusarium species) and yeast (Candida species).[36] The risk factors for fungal keratitis are ocular surgery, ocular surface disease, topical or systemic steroid use and contact lens wear. In developing nations fungal keratitis is primarily from ocular trauma in the agricultural setting.[37] In industrialised countries, wearing contact lenses is the primary risk factor.[38, 39] Infiltration of innate immune cells and upregulation of pro-inflammatory, chemotactic, and regulatory cytokines is the vigorous immune response that patients with keratitis mount to Aspergillus and Fusarium hyphae formation.[7] Studies have shown that individuals with a compromised IL-17 response, primarily as a results of autoantibodies against IL-17, are more vulnerable to yeast fungal infections, particularly candidiasis at mucosal surfaces.[40, 41] Other studies have shown that mutations in the STAT3 gene, which is required for the production of IL-17, increase the susceptibility of individuals to infections with Candida.[42, 43]

Taylor *et al*. in one of their 2014 studies, observed the effect of *Aspergillus fumigatus* and *Fusarium oxysporum* on mice corneas by flow cytometry, PCR and immunoassay.[44] (

Table 2) Taylor *et al*. found that mice had increased levels of local and systemic IL-17 and IFN-γ but did not increase neutrophil infiltration in the cornea if they were immunised with fungal conidia. In mice corneas that were immunised, neutrophils were found to be an early source of IL-17. The study found that IL-17 rather than IFN-γ was required for a protective immune response that was able to limit fungal progression.[44]

Further studies by Taylor *et al*. performed on murine neutrophils, splenocytes and corneas, and human neutrophils (

Table 2) reiterated that IL-6 is required for IL-17 production *in vivo*, although other cytokines are also thought to mediate production of IL-17. The study went on further to observe mediators of IL-17 production post fungal infection using Western blots and confocal microscopy. Results showed that neutrophils were seen to produce IL-17 and express IL17R post IL-6 and IL-23 stimulation. The transcription factor RORγt translocates to the nucleus, which was demonstrated by confocal microscopy, Western blot and electrophoretic mobility shift assay, and is able to bind to the promoter sequence for IL-17 post IL-6 and IL-23 stimulation.[22] In a subsequent study by Taylor *et al.* in 2016, the group observed JAK/STAT regulatory pathways in mouse corneal cells infected with *Aspergillus fumigatus*.[45] The study used JAK1,2 inhibitor Ruxolitinib, STAT3-SH2 inhibitor Stattic and RORγt inhibitor SR1001. The inherent ability of peripheral neutrophils to clear fungal infection was impaired in subjects treated with the previously mentioned inhibitors. This could be related to the fact that these cells then produce decreased levels of reactive oxygen species (ROS), IL-17 and RORγt translocation to the nucleus. Further, the neutrophils' ability to increase secretion of the enzymes elastase and gelatinase once stimulated by IL-6 and IL-23 was decreased by Ruxolitinib and Stattic (6-Nitrobenzo[*b*]thiophene-1,1-dioxide).[45]

Zhang *et al*. (

Table 2 2) found that nude mice (i.e. mice lacking a thymus, hence impaired immune systems) inoculated with candida blastospores did not display significant fungal proliferation or structural damage in comparison to immunocompetent mice.[46] In immunocompetent mice, it was observed that IL-17 was raised acutely post inoculation. Neutralisation here is used broadly to include increased clearance of the cytokine *via* antibody-antigen complexes or inhibition of ligand receptor binding. Further experiments showed that IL-23 neutralised mice and nude mice did not induce IL-17 and did not develop keratitis. Furthermore, in immunocompetent mice, those treated with anti-CD4 antibodies were more resistant to keratitis compared to those treated with anti-CD25 and anti TCRγδ antibodies which did not change the course of infection. Mice that underwent neutrophil depletion did not develop candida keratitis. Further depletion of IL-17 or IL-23 in immunocompetent mice reduced candida keratitis induction. Pseudohyphae were more common in immunocompetent mice than in nude mice post inoculation. PCR studies showed that chemokines (CXCL12, CXCL10, CXCL2, CXCL1, and CCL2) and also IL-6 were upregulated in immunocompetent mice. Further CXCL2 was able to restore the neutrophils' ability to infiltrate into the corneas of nude mice and interestingly CXCL2 co-administration with blastopores in immunocompetent mice worsened the severity of the keratitis and increased corneal neutrophil infiltration. The effect on IL-17 neutralisation was not only explored in the cornea but also on the skin. It was found that neutralisation also inhibited leukocyte infiltration at the skin, but this then led to fungal expansion.[46] Karthikeyan *et al*. (

Table 2) found that individuals with fungal keratitis or exposed to fusarium or aspergillus have a greater number of IL-17-expressing neutrophils in their peripheral blood.[47] Although, it is interesting to note that humans with depleted CD4+ T cells due to human immunodeficiency virus infection were more likely to develop fungal keratitis.[48] This highlights the difference in host immunity and antimicrobial mechanisms between humans and mice.

Viral

The most common ocular viral infection is with herpes simplex virus-1 (HSV-1).[49] The reactivation of latent herpes virus situated in the sensory neurons of the trigeminal ganglion is the major cause of corneal HSV-1 infection rather than primary ocular infection. Due to the nature of recurrent dormant disease, the prevalence of HSV-1 keratitis is relatively high being 149 per 10^5 of the population in developed nations,[5, 50] whereas incidence is between 6 and 20 per 10^5 of the population per year.[5, 50] Individuals with corneal epithelial infection from HSV-1 can develop stromal disease. When the stroma is infiltrated, it is known as herpes stromal keratitis and can occur with or without damage to overlying corneal epithelium.[51]

In a 2002 study by Maertzdorf *et al*. on corneal fibroblasts and intracorneal T cell lines of humans infected with HSV-1, IL-17 increased the level of MMP-1 in combination with IFN-γ but slightly decreased its effect when combined with IL-1 or TNF-α.[52] Neutrophil infiltration was decreased by anti-IL-8 antibody. Neither IL-6 nor IL-8 levels were increased by stimulation of IL-17 or IFN-γ individually or in combination. Both IL-6 and IL-8 were increased by stimulation with IL-1 and TNF-α. In isolation, IL-17 did not change expression of IL-6 or IL-8 but in combination with TNF-α, IL-6 and IL-8 levels increased. Neutralisation with anti-IL-17 antibodies reduced the synergistic expression of IL-6 and IL-8 in cells treated with a combination of IL-17 and TNF-α. Dexamethasone almost entirely suppressed the induced expression of IL-6 and IL-8 to 1.6 times the control and 3.3 times the control, respectively.[52]

The results by Suryawanshi *et al*. (

Table 3) of mouse corneal cells inoculated with HSV1 have shown there is a biphasic expression of IL-17 and that γδ T cells were seen to contribute to the early secretion of IL-17.[53] IL-6 and TGF-β expression were seen to be raised initially, and then decreased over the twenty-one days of the study. CCL20 was also seen to be expressed during the later stage (between seven and fifteen days) of herpetic infection. This expression during the late stage of herpes stromal keratitis could be responsible for the migration of Th17 cells during this phase. This study found that Th1 cells were the primary cell type during the acute phase and hence the main immune cell component of the stromal keratitis lesion and this then changed to both Th1 and Th17 cells during the chronic phase. The study showed that the Th1 cells primed the environment of the stroma through upregulation and expression of cytokines and chemokines which then generated the migration of Th17 cells. The Th17 cells are seen to maintain the inflammation and damage through the secretion of IL-17.[53]

Severity of herpes stromal keratitis lesions were studied by the same group, with mouse corneal cells neutralisation of IL-17 at early (days eight to fifteen) and late stages (day twenty one) of disease progression.[53] Systemic anti-IL-17 antibodies commenced before and during infection showed an overall reduced severity of disease. Neutralisation at the later stage of herpes stromal keratitis was examined using local anti-IL-17 antibody. The study found that once herpes stromal keratitis lesions had become evident, anti-IL-17 antibodies were able to reduce the severity of the disease. Histologically, the corneas themselves had developed reduced fibrosis of stromal tissue and little if any epithelial layer hypertrophy and also there were fewer infiltrating neutrophils. Studies undertaken with IL-17 knockout mice showed a delay in herpes stromal keratitis development and an overall reduced severity. Similarly to antibody treated specimens, knockout mice had histologically less fibrosis and fewer infiltrating neutrophils in the stromal tissue.[53]

Suryawanshi *et al*. (

Table 3) undertook further studies in mice investigating corneal vascularisation and IL-17. IL-17 was seen to stimulate VEGF-A production thus facilitating corneal neovascularisation. It was observed from the study of neovascularisation that the degree of induction of VEGF-A could be increased significantly when the cells were also exposed to IL-6 and IL-1α. It was postulated that IL-17 increased expression of MMPs that degrade VEGFR-1 and increased VEGF-A, thus increasing angiogenesis. Cells treated with IL-17 and IL-6 produced increased expression of CXCL1/KC. The use of anti-IL-17 antibodies were able to inhibit the effect of IL-17 compared to anti-IL-6R antibody which did not affect IL-17. Neutralisation of IL-17 in *in vivo* studies of HSV-1 inoculated mice produced corneas with decreased neutrophil infiltration.[54]

Molesworth-Kenyon *et al*. (

Table 3) found in murine corneal cells that there was a synergy noted between IL-1 and IL-17 which increased the production of IL-6 and CXCL2 when compared to IL-17 alone.[55] After the acute phase of infection, there was no difference in neutrophil infiltration in the cornea between IL-17 receptor knockout mice and corresponding WT control. Initially MIP-1 and -2 levels were lower in IL-17 receptor knockout mice but as time progressed, these levels increased above that of the control. The ability of IL-17 receptor knockout mice to clear HSV-1 infection was comparable to that of control. In IFN-γ knock out mice there were elevated levels of IL-17 and the development of corneal opacity was accelerated compared to the control.[55]

Acanthamoeba

Free living protozoa of genus Acanthamoeba can precipitate a debilitating, extremely painful and vision-impairing infection of the cornea.[56] In individuals that are immunocompetent, the cornea is the most susceptible tissue to infection by Acanthamoeba. The pathogenic mechanism by which Acanthamoeba leads to keratitis has not yet been fully elucidated.[57] The leading risk factor for Acanthamoeba keratitis in developed countries is contact lens wear and, in developing nations, is trauma in an agricultural setting. [4, 56, 58, 59] In the 2015 study by Suryawanshi *et al*., mouse corneas and associated lymph nodes were examined by flow cytometry, immunoassay and phase-contrast microscopy. The draining lymph nodes were examined during the study (Table 4) and it was found that T helper (Th) 1, Th17 and Th2 cell populations were expanded during infection. After day five of the experiment, Th1 and Th17 cells increased along with the severity of the keratitis. In the acute stage of keratitis there was an increase in the number of CD45 cells and neutrophils. As the severity of the keratitis decreased so did the levels of CD45 cells and neutrophils. Acanthamoeba infection induced a regulatory T cell response in the cornea and draining lymph nodes after acute infection. The study noted that IL-17 neutralisation increased keratitis and increased the time needed to reduce the corneal opacification from the infection. The neutralisation of IL-17 also resulted in an increase in amoeba and decrease in infiltrating neutrophil numbers although not statistically different from the control group. IL-17 knockout mice were seen to have increased disease severity.[60] In the 2017 study by Carnt *et al*., cytokine levels were investigated in the tears produced by contact lens wearers with and without Acanthamoeba

keratitis in human subjects. This study utilised ELISA and multiplex bead arrays to determine cytokine levels (Table 4). In both control and infected subjects neither IL-17F nor IL-17A were produced above the limit of detection. Another cytokine examined, IL-17E, was able to be detected in six infected cases and one control case.[61]

Dry Eye

Ocular surface disease, such as dry eye, can predispose a patient to ocular infection. Eye irritation symptoms and blurred vision are the major symptoms that patients with dry eye suffer. As age increases, so does the prevalence of dry eye.[62] Of those aged forty years old, the prevalence of dry eye is around 6% and this increases between 2-3 times in populations of individuals over the age of sixty five.[63, 64] The De Paiva *et al*. (Table 5) study in humans and mice showed that in conjunctival tissues there was a mixed Th17 and Th1 response to dry eye. The desiccating stress experienced by the cornea produced CCL20 and IL-23 receptors which facilitate infiltration of IL-17 producing cells. The study highlighted IFN-γ and IL-17 as producing corneal epithelial damage, but described IL-17 as causing the main epithelial dysfunction in the acute setting. The number of $CD4^+$ T cells was found to be increased in conjunctival epithelium when desiccating stress was applied. The cornea, conjunctiva and tears were all found to have increased levels of IL-17, post desiccating stress. IL-17 neutralisation decreased levels of MMP-3 and MMP-9 and hence gelatinolytic activity in the corneal epithelium. The dysfunction seen in the corneal epithelium was reduced when treated with IL-17 neutralisation.[65]

Therapeutic agents

Clinical studies have focused on individuals with a number of different diseases, with underlying pathology caused by inflammation and autoimmunity. This has been used to evaluate the therapeutic efficacy of antibodies targeting the signalling pathway of IL-17. There are three main compounds that have been utilised in these studies which are Brodalumab (IL-17 receptor blocker, in particular the subunit IL-17RA), Secukinumab (IL-17 ligand inhibitor which is selective for neutralising IL-17A) and Ixekizumab (IL-17 ligand inhibitor). For Brodalumab, the IL-17 receptor subunit IL-17RA is thought to be shared by a number of IL-17 epitopes including IL-17A, IL-17C, IL-17E, IL-17F, viral IL-17, and the heterodimer ligands IL-17A/F. Thus when compared to Secukinumab and Ixekizumab,

Brodalumab has more targets, which means that it has been considered to have a potentially wider efficiency but due to this it also has an inherent risk of increased adverse effects.[66, 67]. The diseases that have been studied so far include rheumatoid arthritis, psoriasis, ankylosing spondylitis, asthma, Crohn's disease and uveitis.

There has been one clinical trial investigating IL-17 antibodies in ocular disease. A clinical trial of patients with uveitis treated with Secukinumab, used anterior chamber cell score, vitreous haze score, and visual acuity as outcome measures. A majority of the patients examined showed a decrease in ocular inflammation and improvement of visual acuity by eight weeks, with fifty percent of patients showing improvement (anterior chamber cell score of zero to trace and vitreous haze score of zero to trace) by two weeks. Of those patients with anterior uveitis, sixty percent had inactive disease without needing any form of steroid therapy. For those patients with posterior uveitis, seventy percent responded to the treatment with an improvement of visual acuity and vitreous haze, and over thirty percent were able to cease steroid treatment completely. The majority of side effects experienced by patients (ten of the sixteen patients in the study) were headaches, upper abdominal pain and conjunctival hyperemia. As the study period was short, two months, and there was no placebo or control group further studies need to be undertaken to know if these side effects are clinically significant.[68]

Of the diseases studied (rheumatoid arthritis, psoriasis, ankylosing spondylitis, asthma and Crohn's disease) in other clinical trials, it was found that IL-17 antibodies were an effective treatment for limiting rheumatoid arthritis symptoms[69] and in psoriasis, anti-IL-17 agents were also found to be more effective than placebo.[70] In ankylosing spondylitis, patients treated with Secukinumab showed a 2-fold improvement compared to the placebo,[71] and Crohn's disease patients treated with Secukinumab did not show an improvement in symptoms and resulted in adverse events at high rates compared to the placebo arm.[72] For patients with asthma who were treated with Brodalumab, there were no differences between the placebo and treatment groups for the overall study population.[73]

The majority of clinical trials investigating IL-17 antibodies have focused on Secukinumab and Brodalumab, individually. Therefore results could benefit from further analysing the difference between a number of anti-IL-17 agents versus placebo. A number of diseases only had one clinical trial conducted which means that these results warrant repeating in further

trials so results can be pooled for meta-analysis, and to measure effects in different populations.

Future directions

Future studies should investigate the role that IL-17 plays in other inflammatory eye diseases like Peripheral Ulcerative Keratitis, Mooren's Ulcer, Ocular Rosacea, and Granulomatosis with Polyangiitis in the cornea and also further studies in intraocular inflammatory conditions (uveitis). The administration of the anti-IL 17 agents was either subcutaneous or intravenous in all studies, so with respect to ocular surface disease it is of particular interest to observe if these agents could be formulated into a topical eye drop. That is, it would be important to determine whether topical agents could be produced that have the ability to inhibit IL-17 activity. As these agents have the potential to reduce inflammation, they would have potential for the treatment of corneal diseases. As this review has noted differences between the role of IL-17 in some ocular surface disease, it is important to assess the aetiology of the disease prior to commencing therapy. Once the aetiology of the ocular surface disease is identified, then IL-17 targeting therapeutics could be added to the treatment regimen to increase efficacy.

The underlying cause of dry eye needs to be assessed, as IL-17 targeted therapeutics have the potential to reduce inflammation. Topical IL-17 therapeutics could be utilised as an adjunct in reducing ocular surface symptoms in evaporative dry eye, Meibomian Gland dysfunction and ocular symptoms of some systemic diseases. The potential for therapeutics that target IL-17 remains untapped. If further studies of inflammatory eye disease identify IL-17 pathway as being pivotal for disease pathogenesis, the more vital IL-17 will become as a therapeutic target. From the author's perspective and from a review of the literature, these agents would be beneficial for the treatment of ocular surface disease.

Conclusion

The results of the studies show that IL-17 is important in the pathogenesis of infective keratitis and dry eye disease. The majority of the studies performed were on *in vitro* and murine models, which does not entirely reflect patient *in vivo* environments.[74] The majority of the studies to date have investigated viral and fungal keratitis therefore, keratitis caused by bacteria, Acanthamoeba and dry eye would benefit from further studies to test whether these results are able to be duplicated. From the outcomes of the studies identified here, IL-17 has

been shown to exacerbate HSV-1 and Pseudomonas keratitis lesion severity although was it found to be protective for Acanthamoeba. This worsening of disease is postulated to be increased through production of various chemokines and cytokines essential for migration and activation of neutrophils into the cornea. These studies highlight the need to identify the underlying cause of the keratitis before treatment commencement.

Work performed on the use of antibodies to neutralise IL-17 has shown some promise in reducing severity for some diseases. The use of anti-IL-17 antibodies are currently being investigated in clinical trials for a number of different diseases that include psoriasis, rheumatoid arthritis and ankyloses spondylitis.[71, 75, 76] This could underpin future work to scale-up experiments into patient trials for novel treatments for ocular surface disease.

Literature Search

Databases searched included Ovid and Medline. There was no restriction placed on years of publication. Search terms used included keratitis, ocular surface disease and bacterial or fungal or viral or acanthamoebal or dry eye. Non English articles were excluded from the review. Abstracts that fit the search criteria were read and if found to be clinically relevant were include in the review.

Declaration of interest

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Tables

Table 1: Results from studies of bacterial keratitis in relation to IL-17.

Author	Year	Model	Result	Ref
Heimer *et al.*	2010	Human corneal epithelial cells in vitro	• Noted highest secretion of inflammatory mediated was IL-6, IL-8, IL-17 and IFN-γ • IL-8 and IFN-γ expression not affected by strain • IL-17 increase expression in nontoxogenic strain • IL-6 decrease expression in nontoxogenic strain	(34)
Zaidi *et al.*	2012	Bacterial Pseudomonas Aeruginosa mice	• IL-17R knockout mice had decreased neutrophil infiltration • IL-17R knockout showed reduced corneal pathology and bacterial load • Anti-IL-17 antibodies reduced IL-17 levels and neutrophil infiltration	(35)

Table 2: Results from studies of fungal keratitis in relation to IL-17.

Author	Year	Model	Result	Ref
Zhang *et al.*	2013	Candida albicans in mouse cells	• Nude mice did not display significant candidiasis keratitis • IL-17 levels peaked acutely post inoculation • IL-23 neutralised and nude mice did not develop keratitis • Anti CD4 antibodies made cells more resistant to keratitis compared to with anti-CD25 and anti TCRγδ antibodies • Neutrophil depleted mice did not develop keratitis • Depletion of IL-17 and IL-23 reduced keratitis • chemokines (e.g. CXCL12, CXCL10, CXCL2, CXCL1, and CCL2 and also IL6 were upregulated post infection • CXCL2 restored neutrophil function in nude mice and worsened keratitis in immunocompetent mice	(46)
Taylor *et al.*	2014	Aspergillus and fusarium in mice	• IL-17 limited fungal progression over IFN-γ • Neutrophils were an early source of IL-17 • Immunisation increased IL-17 and IFN-γ but not neutrophil infiltration	(44)
Taylor *et al.*	2014	Aspergillus in mice and human cells	• Post IL-6 and IL-23 stimulations neutrophils production Il-17 and express IL-17R • Post IL-6 and IL-23 stimulations RORγt is seen to bind to the nuclear promoter region for IL-17 • IL-6 is seen as one of the key requirements of IL-17 production	(22)
Karthikeyan *et al.*	2015	Fusarium and A flavus in human cells	• Individual with keratitis or exposure to organisms that can cause the disease increased the number of IL-17-producing neutrophils	(47)
Taylor *et al.*	2016	Aspergillus in mice and human cells	• The capacity of peripheral neutrophils to clear fungal infection was impaired by the use of inhibitors tested • Cells treated with inhibitors produced less ROS, IL-17 and RORγt translocation • Neutrophils that have been activated by IL-6 and IL-23 produce increased secretion of the enzymes elastase and gelatinase	(45)

Table 3: Results from studies of viral keratitis in relation to IL-17.

Author	Year	Model	Result	Ref
Maertzdorf *et al.*	2002	HSV-1 in human cells	• Anti-IL-8 decreased neutrophil infiltration • IL-17 increased the activity of MMP-1 in combination with IFN-γ • Il-6 and IL-8 did not increase with IL-17 stimulation • IL-6 and 8 were increased by IL-1 and TNF-α • TNF-α in combination with IL-17 increased expression of IL-6 and IL-8 • Anti-IL-17 decreased the expression of IL-6 and IL-8 • Dexamethasone almost entirely decreased IL-6 and IL-8 expression	(52)
Molesworth-Kenyon *et al.*	2008	HSV-1 in mice	• IL-1 and IL-17 synergistically increase levels of IL-6 and CXCL2 • IFN- knockout mice had elevated levels of IL-17 • IL-17 receptor knock out mice and control had statistically similar levels of infiltrative neutrophils post-acute infection phase	(55)
Suryawanshi *et al.*	2011	HSV-1 in mice	• IL-17 expression was seen to be biphasic • γδ T cells secreted IL-17 in the early infection phase • CCL20 is expressed in the late stage of infection • IL-6 and TGF-β levels rise and fall over the duration of infection • Th1 prime the stroma for Th17 migration • Anti-IL17 antibodies reduced the severity of keratitis when used prior to disease progression and after lesions were established • IL-17 knock out mice had delayed development of keratitis and reduced severity of disease • Anti-IL-17 antibodies and IL-17 knockout mice produce less fibrosis and neutrophil infiltration histologically	(53)
Suryawanshi *et al.*	2012	HSV-1 in mice	• IL-17 stimulates VEGF-A • VEGF-A could be increased with IL-6 and IL-1a • IL-17 and IL-6 treated cells increased CXCL1/KC • Neutralising IL-17 decreased neutrophil infiltration • Anti-IL-17 antibodies inhibited the effects of IL-17 • Anti-IL-6 receptor antibodies were not seen to effect IL-17	(54)

Table 4: Results from study of acanthamoeba keratitis in relation to IL-17.

Author	Year	Model	Result	Ref
Suryawanshi *et al*.	2015	Acanthamoeba in mice	• Draining lymph nodes increased Th1, Th17 and Th2 populations • CD45 and neutrophils were raised in the acute phase of the infection • IL-17 neutralisation increased severity of keratitis • IL-17 knockout mice had increased disease severity	(60)
Carnt *et al*.	2017	Acanthamoeba in humans	• IL-17F and IL-17A cytokines were not detected by bead array • IL-17E was detected by bead array and ELISA in a small number of cases	(61)

Table 5: Results from a study of dry eye in relation to IL-17.

Author	Year	Model	Result	Ref
De Paiva *et al*.	2009	Desiccating stress in mice and human cells	• CD4 T cells were increased in conjunctival epithelium • IL-17 neutralisation decreased MMP-3 and -9 levels • Conjunctiva, cornea and tears had increased levels of IL-17 post stress • Desiccating stress increased CCL20 and IL-23 receptor levels • IL-17 produced the most epithelial dysfunction in the acute setting	(65)

Figure 1: Function and induction of IL-17. Adapted from Matsuzaki *et al*.(10)

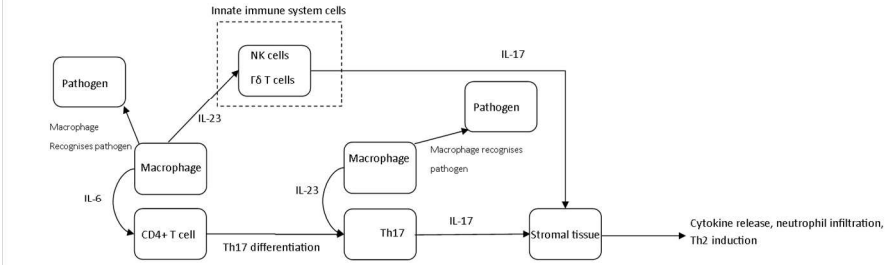

Figure 1: Function and induction of IL-17. Adapted from Matsuzaki et al.(10)

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