Expert Review of Clinical Immunology

ISSN: 1744-666X (Print) 1744-8409 (Online) Journal homepage: informahealthcare.com/journals/ierm20

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Matthew Campbell, Sarah Doyle & Peter Humphries

To cite this article: Matthew Campbell, Sarah Doyle & Peter Humphries (2014) IL-18: a new player in immunotherapy for age-related macular degeneration?, Expert Review of Clinical Immunology, 10:10, 1273-1275, DOI: 10.1586/1744666X.2014.950231

To link to this article: https://doi.org/10.1586/1744666X.2014.950231

Published online: 21 Aug 2014.

IL-18: a new player in immunotherapy for age-related macular degeneration?

Expert Rev. Clin. Immunol. 10(10), 1273–1275 (2014)

Matthew Campbell

The Ocular Genetics Unit, Department of Genetics, Trinity College Dublin, Dublin 2, Ireland

Sarah Doyle

Department of Clinical Medicine, National Children's Research Centre, School of Medicine, Our Lady's Hospital for Sick Children, Trinity College Dublin, Dublin 2, Ireland

Peter Humphries

Author for correspondence: The Ocular Genetics Unit, Department of Genetics, Trinity College Dublin, Dublin 2, Ireland
pete.humphries@tcd.ie

Recent evidence suggests that the pro-inflammatory cytokine IL-18 may have utility as an anti-angiogenic agent in the eye. Numerous laboratories, including our own have demonstrated the ability of murine IL-18 to prevent neovascularization in the retina, choroid and cornea in pathological scenarios. Here, we summarize the potential use of IL-18 as an immunotherapy for wet age-related macular degeneration treatment, describing past and recent findings pertaining to its biological function in the eye.

Recent evidence from this laboratory has indicated that in the context of age-related macular degeneration (AMD), the NACHT, LRR and PYD domains-containing protein 3 (NLRP3) inflammasome in macrophages resident in and infiltrating into Bruch's membrane can allow for the secretion of IL-18, a pro-inflammatory cytokine whose role in angiogenesis in various vascular beds has been examined previously [1,2]. Why the excitement? The reason is that it has previously been established that IL-18 has the potential to suppresses angiogenesis in the eye; hence IL-18 could potentially play a protective role in suppressing choroidal neovascularization (CNV), the hallmark pathology of the neovascular form of AMD, representing the most vision-threatening sequelae to advancing disease. IL-18 was initially described in 1995 as an inducer of IFNγ [3] and was subsequently shown to potently inhibit the proliferation of FGF-2-stimulated bovine capillary endothelial cells in culture. In 1999, it was demonstrated that FGF-2-induced corneal neovascularization could be potently suppressed by systemic administration of IL-18 (50 μg/kg) for 6 days in mice [4]. IL-18 has also previously been reported to regulate pathological retinal neovascularization developmentally in the murine model of oxygen-induced retinopathy [5,6].

There is now an unmet clinical need for better management of wet AMD, current anti-VEGF treatments involving periodic intravitreal inoculation of anti-VEGF monoclonal antibodies (e.g., Lucentis) being invasive, extremely expensive and targeting established disease. In addition, there is a low, but significant risk of endophthalmitis, retinal hemhorrage or detachment with each injection, and no endpoints for therapy have been established. We have now shown in rodents (Doyle *et al.* 2014) that intravitreal or indeed systemic inoculation of murine IL-18 (SB-528775) can prevent experimentally induced CNV. Therefore, working alone, or in combination with other anti-neovascular agents, a reduction in the frequency with which intraocular injections are required may well be achievable. In addition, we determined that both murine and human recombinant IL-18 have an excellent safety profile as it pertains to the retinal pigment epithelium (RPE) cells, the key cell type that becomes dysfunctional in AMD.

In February 2014, a clinical trial study from the group of Peter Campochiaro at Johns Hopkins University reported that high levels of IL-18 in the aqueous of patients receiving Lucentis injections for macular edema secondary to retinal vein occlusion correlated with a significantly improved visual outcome. The same group also showed that IL-18 was regulated by VEGF in a reciprocal fashion and utilized numerous models of

Keywords: AMD • choroidal neovascularization • geographic atrophy • IL-18 • immunotherapy • inflammasome • NLRP3 • retina • retinal pigment epithelium • VEGF

EXPERT REVIEWS

 10.1586/1744666X.2014.950231 ISSN 1744-666X

retinal/CNV to show that recombinant IL-18 could regulate permeability in the eye in pathological scenarios, and in a similar conclusion to ourselves, they suggested that IL-18 could represent a novel means of regulating pathological neovascularization in the eye [7].

Recombinant human IL-18, also called Iboktadekin, is a clinically enabled asset that has been in development as a cancer therapy by the pharmaceutical company GlaxoSmithKline. There are now numerous published articles detailing the safety profile of IL-18 in human subjects, and adverse events relating to ophthalmological anomalies in clinical trial participants have not been reported. In addition, it has previously been shown in rodents that systemic dosing with IL-18 allows for its detection in high levels in the retina [5], suggesting that it is likely bioavailable within the retinas of clinical trial participants [8–10]. Dosing of patients with IL-18 can result in grade 1–2 transient fevers; however, these were previously reported to be manageable and rapidly resolve. Doses as high as 2000 μg/kg have also been used in patients with no apparent ocular side effects.

In apparent contradistinction to our own data, Tarallo *et al.* [11] showed that *Alu*RNA treatment of RPE cells resulted in the induction of reactive oxygen species, which induce oligomerization of the NLRP3 inflammasome. IL-18 was then proposed to interact in an autoregulatory manner with its receptor on RPE cells and to cause RPE-specific degeneration via apoptosis. In support of this, Tarallo *et al.* showed (Figure 5C of their paper) that recombinant IL-18 induces RPE-specific apoptosis when injected intravitreally. However, the paper did not state how much IL-18 was used. In a follow-up to this work, presented as a paper at the recent meeting of the Association for Research in Vision and Ophthalmology, May 2014, entitled, *IL-18 is not Therapeutic for Neovascular Age-related Macular Degeneration*, Gelfand *et al.* from the same laboratory, and collaborators at five independent laboratories, studied the effects of intravitreal inoculation of IL-18 on laser-induced CNV in mice and conclude 'this study confirms that IL-18 induces RPE degeneration, argues against pursuing IL-18 as a therapeutic agent for neovascular AMD' [12].

Why are these data so contradictory? We suggest that there are two very simple reasons. Gelfand *et al.* report testing IL-18 over a range of three orders of magnitude, starting with 1 ng intravitreally in mice. As we know, IL-18 is a highly potent pro-inflammatory cytokine and will certainly impact on generic cell viability if used in non-physiological amounts. In our own recent study, murine IL-18 was indeed shown to affect both RPE and retinal cell viability at doses above 3 ng per injection, where dying cells within the RPE and other retinal layers, together with a probable immune cell infiltrate, were observed within the vitreous. However, at physiological doses of 0.15 and 0.3 ng per injection, no negative effects whatever were observed on RPE or retinal function or viability in a variety of assays. Furthermore, we were able to demonstrate that an injection of 0.15 ng IL-18 potently suppresses laser-induced CNV in mice. In our recent study [1], we made a direct comparison of commercially available murine IL-18 and that provided by our collaborators at GlaxoSmithKline (termed SB-528775). There were vast differences in the bioactivity of IL-18 from these two different sources, with SB-528775 inducing almost four fold more activated natural killer (NK) cells when compared to IL-18 purchased from RnD Systems (MBL). In addition, SB-528775 could induce almost two fold more IFNγ, a cytokine previously shown to very potently regulate the development of CNV in the laser-induced murine model [13].

Taken together, our observations and those of other completely independent international laboratories on the anti-angiogenic potential of recombinant IL-18 as it pertains to the eye suggest that there may be a role for its use in regulating pathological neovascularization in eye diseases. Given its proven safety in clinical trials to date, it is tempting to suggest that IL-18 has utility as an additive therapy for CNV secondary to wet AMD; however, only time will tell if it can be deployed in such a manner. These studies have, however, highlighted the growing need for a better understanding of the pathobiology of AMD and the critical need for improvements on the current standard of care.

Financial & competing interests disclosure

M Campbell was supported by Science Foundation Ireland, Enterprise Ireland, GlaxoSmithKline. P Humphries was supported by Science Foundation Ireland, European Research Council, and the Health Research Board. S Doyle was supported by the Health Research Board, Bright Focus Foundation, National Children's Research Centre. Trinity College Dublin owns a patent pertaining to the use of IL-18 for the treatment of wet AMD. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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