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Review Article

Ophthalmology Section

Interleukin-18 an Emerging Player in the Age-related Macular Degeneration Treatment: A Narrative Review

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ABSTRACT

The goal of this review was to investigate the role of chronic inflammation in age-related disorders, with a particular focus on the possible use of Interleukin-18 (IL-18) as an immunotherapy for Age-related Macular Degeneration (AMD). The literature has been extracted from numerous scientific databases, comprising PubMed, Scopus, WoS, Springer Nature, and Google Scholar, with an emphasis on English-language papers about IL-18 and AMD. Evidence shows that age-dependent modulation of proinflammatory cytokines like IL-1 and IL-18 connects the ageing process to inflammasome-mediated caspase-1 activation. IL-18, in particular, shows antiangiogenic characteristics in the retina, choroid, and cornea, indicating that it might be used as therapeutic role in preventing pathological neovascularisation in AMD. The review emphasises that, while IL-18 may be a potential immunotherapeutic drug, successful AMD care necessitates a multidisciplinary strategy that includes sophisticated diagnostic technologies and clinical skills.

Keywords: Diagnosis, Immunotherapy, Neovascularisation, Ocular disease, Proinflammatory cytokines

INTRODUCTION

AMD is a progressive, long-term degenerative eye condition that causes permanent obscured or reduced vision by gradually destroying the macula [1,2]. It is the leading cause of vision loss among the elderly, and, if untreated, its incidence is projected to rise by 40% by 2040 [3]. Although its pathophysiology remains incompletely understood, AMD is a complicated disease that is closely linked to inflammation and chronic oxidative stress [4].

The two primary forms: wet AMD (neovascular or exudative) and dry AMD (non neovascular, non exudative, or atrophic AMD). Dry AMD is the most prevalent kind and is characterised by the accumulation of extracellular deposits known as drusen. In its advanced stage, Geographic Atrophy (GA) is characterised by a decrease in photoreceptors, choroidal capillaries, and Retinal Pigment Epithelium (RPE) cells. Clinically, AMD can be categorised as early, moderate, or late stage, based on pigmentary abnormalities and drusen size [2,5]. The late stage includes GA or neovascular AMD [6]. Neovascular AMD is characterised by abnormal blood vessel growth that pierce Bruch's membrane from the choroid, causing progressive damage to the RPE layer as well as nearby photoreceptors, is linked to neovascularisation of the retina.

Genetic, metabolic, functional, and environmental variables are all involved in the intricate multifactorial pathogenesis of AMD [7,8]. Accumulation of oxygen radicals and oxidative stress in RPE can cause RPE dysfunction, impairing photoreceptor nutrition and promoting angiogenesis and Choroidal Neovascularisation (CNV). These factors contribute to an excess of Reactive Oxygen Species (ROS) [9].

When germs or poisons are recognised by pattern-recognition receptors, the mammalian inflammatory response is set off [10]. This can result in the development of multiprotein platforms called inflammasomes, or the induction of proinflammatory gene expression [11]. Inflammasomes regulate the maturation of key proinflammatory cytokines, including IL-1 and IL-18, by permitting their cleavage from inactive precursors. Inflammation that does not involve infection arises when host-derived components change and/or build up to create deposits that are difficult to remove [3].

By blocking Vascular Endothelial Growth Factor (VEGF) activity, current antibody-based treatments for AMD target the disease's advanced terminal stages [12]. Since monoclonal antibodies (such as Lucentis and Avastin) and fusion proteins (such as Eylea) must be directly and consistently injected into the eye, there is a risk including retinal detachment, bleeding, and infection [13,14].

Clinical studies exploring the therapeutic applications of human recombinant IL-18 have already been initiated for the treatment of solid tumours, metastatic melanoma, peritoneal carcinoma, non Hodgkin's lymphoma, and several other malignancies [15]. Although IL-18 has been given intravenously as well as subcutaneously, and substantial body of data about patients' systemic tolerance to recombinant human IL-1 8 is already available, its application in AMD remains uncommon [16]. IL-18 demonstrated antiangiogenic factor in the eye and its shown safety as a systemic agent in human subjects, its application in the treatment of IL-18 has the potential for enormous therapeutic benefit for AMD patients.

Therefore, the aim of this review was to evaluate the biological role of IL-18 in ocular inflammation and angiogenesis, as well as to critically assess its potential as a novel immunotherapeutic agent for the treatment of AMD, using evidence from both preclinical and clinical evidence.

Literature Search

A thorough literature search was conducted to find relevant publications on the function of IL-18 in AMD. Databases searched included PubMed, Scopus, Web of Science, Springer Nature, and Google Scholar. The article selection procedure begins with the elimination of duplicate records. The abstracts of the remaining papers were then assessed for relevance, and the full texts of possibly qualifying research were carefully reviewed. The final evaluation only included papers focused on IL-18's biological function, association with inflammatory pathways, and its therapeutic potential in AMD were included in the final review. The search method included certain terms and Boolean operators, such as: (IL-18) AND (AMD) AND ("inflammation" OR "angiogenesis" OR "therapy" OR "immunotherapy").

Inclusion criteria: Peer-reviewed English-language studies that discussed IL-18 and its function in inflammation, angiogenesis, or AMD. Experimental (in vitro and in vivo), clinical, and translational research that directly examined IL-18 pathways in ocular disorders, as well as relevant systematic reviews and meta-analyses were included in the study.

Exclusion criteria: Non English publications, papers unrelated to AMD or IL-18, case reports, conference abstracts, editorials and comments original data, and studies with insufficient methodological or outcome details were excluded from the study.

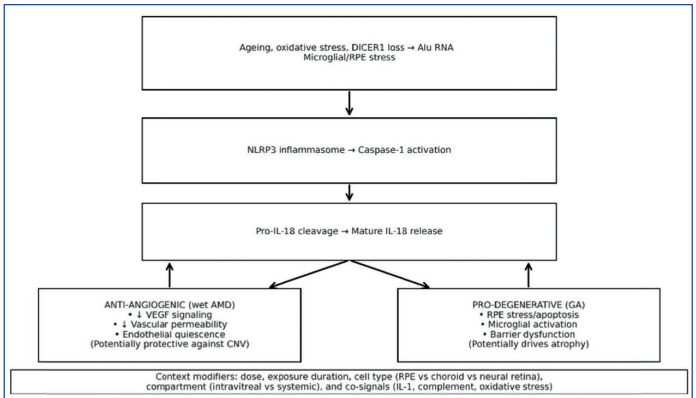
Pathophysiological Role of IL-18 in AMD

Ageing retinal and RPE cells are exposed to oxidative stress, lipid by-products, and—less commonly—DICER1 loss due to the buildup of toxic Alu RNAs. These stimuli can prime or activate the NLRP3 inflammasome in RPE and myeloid cells, causing caspase-1 to convert pro-IL-18 into mature IL-18, which is then released locally. Alu RNA–NLRP3–IL-18–MyD88 signalling axis has been demonstrated to induce cellular stress and death in GA mice, and inhibition of IL-18 or upstream inflammasome components can prevent RPE degeneration in those conditions. This positions IL-18 at the intersection of age-related stress pathways and inflammasome biology in the presence of dry AMD [4].

In neovascular ("wet") AMD models, mature recombinant IL-18 exhibits strong antiangiogenic and antipermeability activity: It inhibits VEGF-induced vascular leakage, enhances endothelial tight-junction integrity (e.g., Claudin-5), boosts antiangiogenic cues (e.g., thrombospondin-1), and inhibits retinal/CNV [16]. These affects have been observed in OIR and laser-induced CNV models. IL-18 was additive to anti-VEGF treatment, indicating a possible function as an adjuvant or alternative to VEGF inhibition in specific situations [17,18].

Critically, IL-18 ocular effects of IL-18 are highly context-dependent. Dose, compartment (intravitreal vs systemic), duration of exposure, and target cell type (RPE vs choroid vs neural retina) all influence results towards endothelial quiescence or RPE stress and atrophy [19]. This duality underpins the literature debate: although some researchers claim that IL-18 inhibits CNV and vascular leakage, others have detected RPE toxicity and question its applicability to human nAMD, triggering a nature medicine conversation regarding IL-18's therapeutic potential.

Downstream pathway subtleties (for example, caspase-8-linked death signalling following inflammasome activation) are likely contribute to these disparate phenotypes and should be addressed in any translational effort by dose optimisation, compartment-specific delivery strategies, and careful patient selection [Table/Fig-1] [20].



[Table/Fig-1]: IL-18 in AMD- upstream triggers, inflammasome activation and divergent effects.

Preclinal Evidence of IL-18's Effects in Different AMD Models

Several experimental investigations have emphasised the dual nature of IL-18 in AMD models, suggesting both therapeutic promise and potential safety issues. Doyle SL et al., found that recombinant IL-18 dramatically decreased CNV area in laser-induced CNV mice and exhibited additive effectiveness when paired with anti-VEGF treatment, indicating its potential use as an adjunct or alternative method for neovascular AMD (nAMD) [4]. Similarly, Shen J et al., found that IL-18 showed potent antipermeability and antiangiogenic effects in ocular models, working in tandem with VEGF to maintain endothelial barrier integrity [18]. Previously, Qiao H et al., demonstrated that IL-18 controlled pathological neovascularisation in an oxygen-induced retinopathy model, giving early in vivo evidence of its antiangiogenic activity [17].

However, some organisations have expressed concerns regarding the safety of the RPE. Ijima R et al., discovered that intravitreal IL-18 at tested dosages caused RPE degeneration and visual impairment in mice [21], whereas Hirano Y et al., claimed that IL-18 was not effective for nAMD, emphasising its dose-dependent toxicity [19]. Tarallo V et al., linked DICER1 loss and Alu RNA accumulation in GA models to NLRP3 inflammasome activation and IL-18–driven RPE mortality, indicating that IL-18 plays a role in the pathophysiology of dry AMD [16]. Together, these findings show that IL-18 has significant antiangiogenic effects but also poses a risk of RPE harm, emphasising the relevance of delivery mechanism, dosage, and disease context in its use to AMD treatment.

Clinical Evidence IL-18's Effects in Different AMD Models

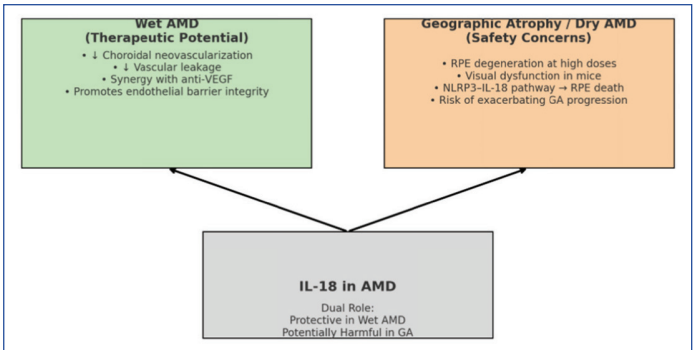
Although IL-18 has not yet been routinely used in AMD patients, studies of recombinant human IL-18 (rhIL-18) in cancer provide useful insights. In a Phase I dose-escalation study on patients with advanced solid tumours, Robertson MJ et al., found that systemic administration of rhIL-18 (intravenous or subcutaneous) was biologically active and well tolerated, showing dose-dependent induction of interferon-γ and other immune mediators [22]. Similarly, in post-transplant settings for chronic lymphocytic leukaemia, rhIL-18 combined with ofatumumab demonstrated adequate tolerability and immune activation.

These clinical findings imply that rhIL-18 has a favourable systemic safety profile, which is particularly important when considering its ocular use. However, because no AMD-specific clinical studies have been conducted, its effectiveness and safety in the particular microenvironment of the retina and RPE remain unknown. Translating systemic safety data to eye requires caution, given preclinical reports of RPE toxicity at certain doses. Thus, whereas clinical cancer trials provide a reliable baseline understanding of systemic tolerance, well-designed ocular trials are required to assess IL-18's context-specific effects in AMD [23].

Therapeutic Implications, Safety Concerns, and Clinical Translations

IL-18 has emerged as a potential immunomodulator with strong antiangiogenic properties, making it particularly important for neovascular ("wet") AMD. Exogenous IL-18 has regularly been proven in preclinical models, exogenous IL-18 has to diminish CNV, inhibit vascular leakage, and even synergise with known anti-VEGF therapy [Table/Fig-2]. Doyle SL et al., found that intravitreal or systemic recombinant IL-18 decreased the extent of CNV lesions, whereas Shen J et al., discovered that VEGF signalling was suppressed and the endothelial barrier [4,18]. Such data imply that IL-18 might be used as an adjunct or alternative treatment in individuals who do not respond well to anti-VEGF monotherapy alone. Furthermore, IL-18's capacity to reinforce endothelial tight junctions and lower vascular permeability demonstrates its potential to regulate angiogenesis while maintaining tissue homeostasis [17,18].

Despite promising antiangiogenic results, questions concerning IL-18's safety profile persist. Ijima R et al., found that intravitreal IL-18 caused RPE degeneration and visual impairment in rats, highlighting the potential of dose- or compartment-dependent



[Table/Fig-2]: Therapeutic vs safety outcomes of IL-18 in AMD.

toxicity [21]. Similarly, Hirano Y et al., suggested that IL-18 is not a viable treatment for AMD, citing experimental evidence of RPE damage following intravitreal injection [19]. Tarallo V et al., established in dry AMD (GA) models that inflammasome-mediated IL-18 signalling leads to RPE mortality after DICER1 deletion and Alu RNA accumulation [16].

These data show that IL-18 plays a dual role: it is beneficial in the event of pathological angiogenesis but may be damaging in contexts of chronic RPE stress. Therapeutic translation will thus need rigorous dosage optimisation, tailored administration techniques, and illness stage-specific assessment in order to maximise benefits while minimising hazards.

Clinical cancer trials using recombinant human IL-18 give important systemic safety information. In Phase I studies involving patients with advanced cancers, systemic IL-18 was biologically active, induced interferon-γ production, and was typically well tolerated whether administered intravenously or subcutaneously [23,24]. These findings provide a reassuring safety baseline for human usage. However, ocular administration presents distinct complications due to the vulnerability of RPE and retinal neurons to cytokine-induced stress. Before IL-18 can be practically used for AMD, carefully controlled ophthalmic studies will be needed to stratify individuals by AMD subtype, employ precise administration modalities, and monitor both angiogenic and atrophic results. While IL-18 shows promise as a new immunotherapy, its therapeutic window must be well defined to enable safe and successful translation into AMD treatment [4].

Future Implications of IL-18 on AMD

The dual function of IL-18 in AMD underscores the need for precision-based therapeutic advantages while minimising harm. Preclinical investigations have repeatedly indicated that IL-18 inhibits choroidal neovascularisation and reduces vascular leakage, making it a viable complement or alternative to existing anti-VEGF therapy in neovascular AMD. As many patients eventually show suboptimal or diminishing responses to anti-VEGF medicines, IL-18-based immunotherapy could represent a new strategy targeting both the inflammatory and angiogenic axes.

Future medication research might concentrate on optimised dose regimens, tailored ocular delivery methods, or gene-based therapeutics to boost local IL-18 activity in the retina while avoiding systemic or off-target effects.

At the same time, concerns about IL-18-mediated RPE degeneration, particularly in GA models, emphasise the significance of disease context. Moving ahead, stratifying individuals based on AMD subtype, disease stage, and genetic risk factors might help evaluate whether IL-18 acts predominantly as a protective or pathogenic mediator. Furthermore, longitudinal investigations and well-designed early-phase clinical trials are necessary to evaluate the safety, effectiveness, and durability of IL-18 therapy in AMD populations. Such attempts will clarify whether IL-18 evolves into a safe supplementary therapy for wet AMD or if its utility is still limited by safety concerns in dry AMD.

CONCLUSION(S)

IL-18 has emerged as an important immunomodulatory cytokine with promising therapeutic applications in AMD. Preclinical investigations have demonstrated its antiangiogenic and antipermeability effects, particularly its ability to inhibit choroidal neovascularisation and lowering vascular leakage in wet AMD. These data suggest that IL-18 might be a potential supplementary or alternative strategy to anti-VEGF treatments, particularly in individuals with unsatisfactory responses. Furthermore, the known systemic safety profile in early cancer studies reinforces the case for IL-18 as a potential ocular therapeutic agent.

However, the dualistic character of IL-18 cannot be ignored. The evidence relating IL-18 to RPE degeneration and worsening of GA in animal models highlights the importance of disease-specific, properly stratified methods to its therapeutic usage. Moving ahead, advancements in delivery technologies, dose optimisation, and patient selection will be crucial in evaluating if IL-18 can safely enter clinical trials for AMD. Thus, whereas IL-18 represents a promising emerging candidate in AMD therapy, its ultimate role will depend on addressing safety issues and establishing its therapeutic niche through strong clinical studies.

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