Chronic, Systemic Interleukin-18 Does Not Promote Macular Degeneration or Choroidal Neovascularization

Age-related macular degeneration (AMD) and its complications remain major causes of ocular disability. We have followed with interest the debate regarding whether IL-18 contributes to, or protects from, AMD and subsequent choroidal neovascularization (CNV). Two articles published in 2012 approached the role of this inflammasome-activated cytokine with conflicting conclusions. Tarallo et al.[1] observed damage in the eyes of DICER1-deficient mice. Such mice are unable to degrade, and thereby accumulate, Alu-RNA retroelements. This caused ocular damage resembling geographical atrophy and was attributed to Nlrp3 inflammasome activation and IL-18 signaling in RPE cells. By contrast, Doyle et al.[2] reported that drusen-derived inflammasome activators drove IL-18 that was protective against CNV in mice. The debate continued in 2014 with a focus on the effects IL-18 on laser-induced CNV in mice and again no agreement was reached.[3,4] Meanwhile, Doyle and colleagues[5,6] tested the effects of human IL-18 by intravitreal injection in primates and noted no detriment, and even a moderate improvement, in laser-induced CNV in these animals.

Of relevance to this controversy are patients with certain autoinflammatory diseases, particularly systemic juvenile idiopathic arthritis and adult-onset Still's disease (AOSD), who have extraordinary elevation of serum IL-18. Such patients suffer from fevers, skin rashes, arthritis, adenopathy, and organomegaly and can develop a life-threatening hyperinflammatory state called macrophage activation syndrome (MAS). To our knowledge, AMD is not a prominent feature of these diseases, and these patients do not routinely receive retinal screening. Notably, rates of AMD may be lower among patients with rheumatic diseases and, notably, patients with uveitis.[7,8]

As part of a study of the natural history of autoinflammatory diseases (all patients seen under an institutional review board–approved clinical research protocol [NCT00059748], and the research adhered to the tenets of the Declaration of Helsinki), we have measured serum IL-18 levels longitudinally in our cohort and identified a small group of patients with chronic, massive elevation of serum IL-18. Nine such patients underwent dilated ophthalmic evaluation to screen for subclinical pathology, and none were found to have retinal abnormalities or drusen. This group includes patients with MAS (Fig., black, light blue, dark blue, purple, green), AOSD (orange), and gain-of-function mutations in *NLRC4*[9,10] (pink, red). All ophthalmic examinations, with one exception, were performed at the National Institutes of Health and documented to be normal. One patient (Fig., pink) was evaluated as an inpatient at an outside institution multiple times for self-resolving papilledema thought to be steroid-induced.[10] Macular and vessel evaluations were normal, even after steroid weaning and resolution of papilledema. Three of the eight patients seen at the National Eye Institute had normal optical coherence tomography and fundoscopic pictures. Concurrent serum analysis demonstrated serum IL-18 levels several orders of magnitude above normal in all samples, demonstrating the likelihood of chronic exposure.

The lack of correlation between chronic, systemic IL-18 exposure and development of AMD or drusen has some caveats: first, levels of IL-18 in the serum may not reflect the exposure of RPE cells or intraocular levels of IL-18; and second, most patients were children (except the patient in orange, who presented at 27 years) and may not have had a retinal insult whose resolution would be exacerbated by high IL-18 levels. Furthermore, all patients had received immunomodulating therapies, often including corticosteroids, IL-1 inhibitors, cyclosporine, and others. Nonetheless, we find it compelling that these patients appear to be systemically exposed to very high levels of IL-18 for multiple years and none have evidence of retinal pathology or toxicity. Although this observation is not instructive as to whether IL-18 is beneficial, it suggests that chronic IL-18 exposure in the context of systemic inflammation is not a potent inducer of RPE toxicity or aberrant choroidal vascular homeostasis. It further suggests that the use of exogenous IL-18 to treat ophthalmologic conditions may be well-tolerated. While we await results from ongoing prospective human studies, these patients' healthy-appearing retinas

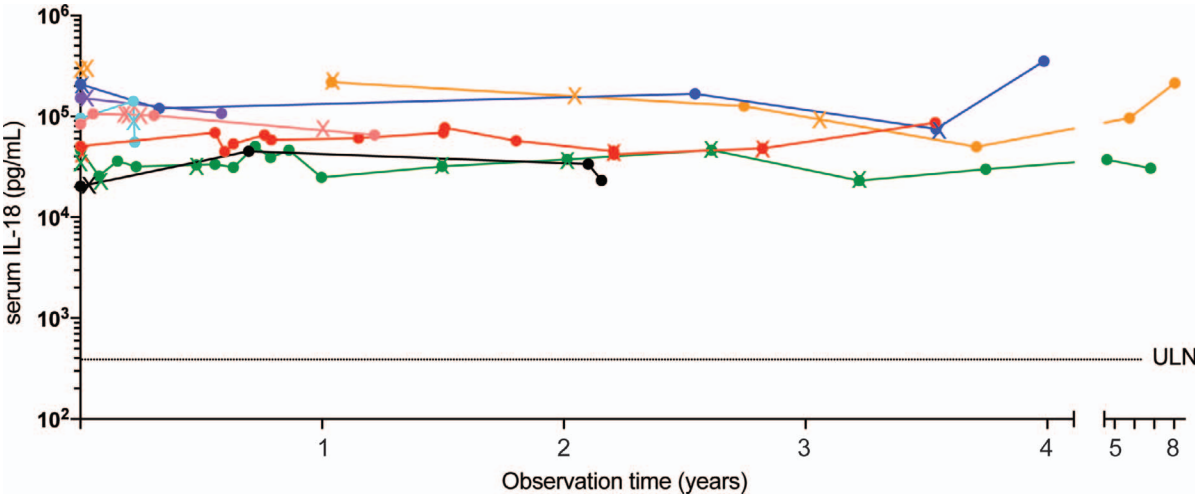

Figure. Timeline of serum IL-18 measurements and fundoscopic examinations. The *x*-axis represents time since initial National Institutes of Health evaluation, often years after symptom onset. Serial measurement of serum IL-18 (*closed circles*) was compared with instances of ophthalmologist's fundoscopic examination (X). Patients are represented by different colors. All fundoscopic examinations were documented to be normal, save one patient with self-resolving steroid-induced papilledema (*pink*, see text). ULN, upper limit of normal.

may provide reassurance against the potentially toxic effects of IL-18.

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