Age-related macular degeneration (AMD) is the world’s leading cause of the loss of central vision. It is usually classed as one of two forms: a dry form, characterized by the appearance of drusen (Fig. 1), which are proteinaceous collections at the level of the retinal pigment epithelium, and by atrophy of the retinal pigment epithelium; and a wet form, in which neovascularization complicates the retinal changes. Like several other chronic, progressive diseases associated with aging (e.g., Alzheimer’s disease and atherosclerosis), inflammation contributes to the pathogenesis of AMD. The role of inflammation is supported by the detection of products of the immune system in the drusen themselves and by the results of genomewide association studies, which have implicated several components of the complement cascade in the pathogenesis of this disease. Two recent publications, one by Doyle et al.3 and the other by Tarallo et al.,4 have shown that NLRP3, a component of the innate immune system that senses danger-associated molecular patterns, is implicated in macular degeneration. The two studies are remarkably similar and remarkably different.

Mutations in NLRP3 have been identified as the cause of uncommon autoinflammatory diseases known as cryopyrin-associated periodic syndromes.5 NLRP3 joins with two other cytoplasmic proteins, ASC and procaspase-1, to form a complex called the inflammasome. The inflammasome, in turn, activates the enzyme caspase 1, which goes on to activate several intracellular proteins, including interleukin-1β and interleukin-18. Insights gained from studies of the rare cryopyrin-associated periodic diseases have thus clarified the function of NLRP3 and have contributed to the appreciation that relatively common diseases such as gout and pseudogout are also mediated by the inflammasome.

Doyle et al. found that drusen themselves activate NLRP3 (Fig. 2). Activation is also induced by the complement component C1Q or enhanced by carboxyethylpyrrole, a protein modified by oxidative stress. Tarallo et al. also found that NLRP3 is activated in patients with AMD, but this group used an RNA motif known as an Alu repeat to activate the inflammasome in mouse and tissue-culture studies. They had previously reported evidence supporting a role for Alu repeats in the pathogenesis of AMD. Together, the two investigative teams have expanded the list of potential triggers of caspase 1 — a list that already includes such diverse chemicals as uric acid and aluminum hydroxide.

In most instances in which the inflammasome is activated, interleukin-1 becomes the major
"protagonist." For example, the inherited diseases caused by mutations in NLRP3 were nearly untreatable until recently, but they are now known to respond dramatically to interleukin-1 blockade. Surprisingly, therefore, both groups concluded that the major consequence of activation of the inflammasome in the retina is the production of interleukin-18. Doyle et al. believe that the source of this cytokine is probably myeloid cells. Although NLRP3 is usually expressed predominantly in bone marrow–derived cells, Tarallo et al. contend that the retinal pigment epithelium is primarily responsible for interleukin-18. (Interleukins, of which there are more than 36, are cytokines named for their role in communication among leukocytes, but their expression is not confined to leukocytes.)

The two groups arrived at opposite conclusions about the consequence of interleukin-18 in AMD. Tarallo and colleagues found that interleukin-18 promotes damage to the retinal pigment epithelium in a mouse model that mimics aspects of the dry form of AMD. Doyle and colleagues used a mouse model of choroidal neovascularization, the hallmark of wet AMD, and concluded that interleukin-18 inhibits new vessel formation; atrophy of the retinal pigment epithelium is not prominent in their model.

Thus, one group of authors concludes that inflammation in AMD is harmful and the other concludes that inflammation is beneficial. It is possible that both groups are right and that interleukin-18 has a dual role in AMD. If so, interleukin-18 as a therapeutic agent will present a Faustian dilemma, since delivering it might have both a favorable action (i.e., blocking neovascu-
larization) and an unfavorable action (i.e., destroying the retinal pigment epithelium) in the posterior portion of the eye. Inhibiting interleukin-18 might salvage the retinal pigment epithelium while promoting new vessel growth. As the biology is clarified, new targets downstream from interleukin-18 will likely emerge.

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