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Association Between C-Reactive Protein and Age-Related Macular Degeneration:

Les Liaisons Dangereuses

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Triangular relationships might make life interesting, but they can be hard to untangle. In this issue of *JAMA Ophthalmology*, Cipriani et al[1] have conducted an elegant study examining the triangular association between circulating concentrations of C-reactive protein (CRP), *CRP* (OMIM 123260) genetic variants, and risk of late age-related macular degeneration (AMD) (choroidal neovascularization or central geographic atrophy). Their findings have important implications for our understanding of the pathophysiology of AMD, particularly the distinction between systemic and local inflammation.

The authors pooled data from 3 European studies to test potential associations in this triangular affair. Two *CRP* genetic variants did share some association with circulating CRP concentrations (in control participants). However, no genetic variant was significantly associated with the risk of AMD; previous observers[2] have also searched for this association in vain. In any case, as the authors helpfully pointed out by analogy with cardiovascular research, there is a big difference between association and causation.

In the study by Cipriani et al,[1] circulating CRP concentrations were weakly associated with geographic atrophy, along partly similar lines to those of findings for late AMD in some previous studies. It is important to remember, however, that circulating CRP concentrations can be strongly affected by other factors; for example, *C3* risk variants and cigarette smoking are both strongly linked to increased serum complement activation.[3] Indeed, the confidence of the association between serum CRP concentrations and geographic atrophy in the study by Cipriani et al[1] was notice-ably less striking ($P = .03$ vs $P = .006$) after adjustment for potential confounders, including smoking.

So much for the crowded and promiscuous atmosphere of serum. What about the more intimate environment of human macular tissue, specifically the retinal pigment epithelium, Bruch membrane, and choriocapillaris complex, the principal site of AMD pathologic conditions? Here the role of the complement factor H (*CFH* [OMIM 134370]) genotype becomes vital. It is also worth distinguishing between 2 close relatives: pentameric CRP prefers life in serum, where its role is broadly anti-inflammatory; monomeric CRP, the

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smaller cousin, is more at home in tissues, where it tends to promote inflammation.[4] In fact, pentameric CRP seems to search out toxic associations with pathogenic cell membranes and other damage in tissues, where it disassociates irreversibly into monomeric CRP to carry out its inflammatory and dangerous liaisons.

One early study demonstrated that macular Bruch membrane and choriocapillaris concentrations of CRP were significantly elevated in human tissue from donors with *CFH* risk.[5] Keenan et al[6] replicated this finding in human macular tissue from genetically "pure" donors (ie, in the absence of *ARMS2* [OMIM 611313] or *HTRA1* [OMIM 602194] risk alleles) but further demonstrated a significant interaction between *CFH* genotype and smoking status. Macular CRP concentrations were significantly higher in donors with homozygous risk vs nonrisk at *CFH*, and were significantly elevated in smokers vs non-smokers; however, concentrations were highest by far in donors with *CFH* risk who continued smoking until death. Similar findings for *CFH* genotype were also observed in a recent study[4]; the authors further showed that monomeric CRP is the predominant form of CRP found in choroidal tissue and that it substantially affects endothelial cell phenotypes, perhaps contributing to choriocapillaris dysfunction in AMD.

Complement activation and inflammation are closely related. The distinction between circulating and local CRP concentrations mirrors similar ideas about circulating and local complement activation. We know that *CFH* risk haplotypes are associated with increased complement activation in human macular tissue[6] but not in the circulation[3,7]; by contrast, *C3* and *C2/CFB* risk genotypes are linked to elevated circulating complement activation concentrations.[3,7] This finding suggests that AMD pathogenic mechanisms might differ by genotype. Some variants may predispose to AMD by increasing systemic complement activation concentrations, while the consequence of the *CFH* genotype may be limited to local effects at the retinal pigment epithelium, Bruch membrane, and choriocapillaris interface. Cigarette smoking, meanwhile, is known to increase complement activation both systemically[3] and in human macular tissue.[6]

In summary, this thorough study by Cipriani et al[1] did not support a direct link or causal role between genetic variants in *CRP* and AMD risk, at least not in the 4 single-nucleotide polymorphisms that they tested. However, when a triangular relationship does not work out, it may be worth suspecting other partners. Indeed, other factors (particularly *C3* genotype and smoking status) strongly affect serum CRP concentrations and do appear to be directly linked to AMD pathophysiology and risk through complement activation and chronic inflammation. Hence, serum CRP concentrations might still be useful as an AMD biomarker, despite the results of this study. In addition, important differences exist between the systemic circulation and the local environment of macular tissue. In particular, *CFH* genotype is strongly linked to elevated macular but not serum concentrations of CRP and, again, is linked directly to AMD pathophysiology and risk. The combination of *CFH* risk and smoking seems particularly potent in increasing macular concentrations of complement activation and inflammation.

All of this information helps make the more general point that we might need to distinguish in future research studies between AMD associated with different genotypes and

environmental factors. In disease mechanism discovery, bio-marker evaluation, and clinical trial research, inclusion of genotype and smoking status may reveal important differences within the broader umbrella of AMD.

Conflict of Interest Disclosures:

Both authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Keenan reported receiving grant funding from Bayer. No other disclosures were reported.

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