CRP in AMD Pathogenesis: Similarities with Atherosclerotic Process

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Age-related macular degeneration (AMD) is the most common cause of visual impairment in the individuals over 50 years of age. The molecular mechanism causing the AMD is still a huge enigma. The pathology of age-related macular degeneration is characterized by degenerative changes involving the outer portion of the retina, retinal pigment epithelium, Bruch's membrane, and choriocapillaris. There is mounting evidence from laboratory based studies that inflammation plays a key role in the pathogenesis of AMD [1].

C-reactive protein (CRP) is inflammatory marker known to be associated with cardiovascular disease, and a link between AMD and CRP has been suggested.

Previous studies showed that, elevated concentration of CRP has been associated with an increased risk for hypertension [2], and for type 1 and type 2 diabetes mellitus [3]. Because hypertension and diabetes are considered major risk factors for retinal vascular disorders, their association with inflammation and endothelial dysfunction has been suggested in humans with retinopathy and AMD [4].

Direct analysis by liquid chromatography and immunochemical analyses confirmed that drusen contain proteins associated with inflammation; among them fibrinogen, vitronectin, complement components and C-reactive protein (CRP) have been identified. Some of these proteins are locally produced by damaged RPE cells. Drusen components have been found in atherosclerotic plaques and deposits in Alzheimer disease and AMD [5].

Non-enzymatic oxidative modification mediated by reactive oxygen species transforms low density lipoprotein (LDL) to an atherogenic molecule (E-LDL) that activates complement and macrophages and is present in the early atherosclerotic lesions and drusen. It has been documented that the concept of AMD lesion formation started with a mechanism similar to atherosclerotic plaque formation, where the retention of LDL particles within the arterial wall initiates a cascade of pathologic events called the "response to retention hypothesis" [6]. In atherosclerosis, Apo B100 lipoproteins undergo a process called oxidative modification. This modification stimulates different biological processes including innate immune system-mediated inflammation which induce a cascade of pathological events than culminate in atherosclerotique plaques formation [7]. In AMD, the following evidence supports the "response to retention" hypothesis:

1. The accumulation of Apo B100-containing lipoproteins in Bruch's membrane occurs in the same location as basal deposits in drusen;

2. The oxidatively modified proteins and lipids are present in Bruch's membrane and RPE, inducing a pathologic phenotype to RPE cells [8]; and

3. The accumulation of inflammatory mediators with in drusen and basal deposits indicates a role for the innate immune response [9].

Oxidized lipoproteins can trigger complement activation [9]. CD36 is the major receptor implicated in up-taking the oxidized low density lipoproteins and is expressed also in RPE cells. It has been suggested that CD36 may have a role not only in the clearance of oxidized lipids from Bruch's membrane, but also in the subsequently inducing an immune response [10].

In addition to aforementioned facts, the presence of matrix metalloproteinases (MMPs) in higher concentration in the Bruch's membrane and RPE cells, especially MMP-2 and MMP-9 indicate to more similarity between atherosclerotic plaque and AMD lesion formation.

MMP-2 and MMP-9 are implicated in the degradation of extracellular matrix components leading to plaque destabilization and rupture and subsequent future cardiovascular events (i.e. AMI) [11].

Chronic inflammation seems to be a causative factor for the development of AMD and atherosclerosis. Macrophages have been documented, both morphologically and functionally in neovascular AMD, and in the area of geographic atrophy [12]. Activated macrophages and microglia may secrete chemokines and cytokines, causing further cellular damage, Bruch's membrane degradation and angiogenesis [13].

Recently, a strong association between the Y402H single-nucleotide polymorphism (SNP) of the complement factor H (*CFH*) gene and AMD was found. This SNP is located in the region that contains binding sites for heparin and CRP. The binding of CFH with CRP induces the CRP-dependent alternative complement pathway activation, initiated by damaged tissues [14]. It has been suggested that allele-specific changes in activities of the binding sites for CRP could modify the protective action of complement factor H, and inhibit this complement pathway [15]. It is also possible that persistent chronic inflammation that is a consequence of attenuated complement-inhibitory activity may occur in those individuals with the risk-conferring CFH SNP Y402H, and that this pro-inflammatory state, rather than impaired binding by CFH, leads to CRP accumulation in AMD retina. Without a doubt, further studies are necessary to elucidate the role, of the CFH Y402H SNP in AMD pathogenesis.

Several recent clinical studies suggest close association between serum CRP and ocular vascular disorders related to AMD [16-18]. Some of the recent clinical studies reported that patients with the highest quartile of CRP (over 6.5 µg/mL) are at high risk of AMD [19]. Hong., *et al*. [20] in his systematic review summarizing the currently available evidence from clinical-based and population-based studies showed that high serum levels (> 3 mg/L) of CRP are associated with a two-fold likelihood of late onset AMD, compared to low CRP levels (< 1 mg/L). Previous studies suggested that reduction of CRP levels might lower the risk for AMD.

According to recent studies, CRP is not only an inflammatory marker but also a mediator for development of the vascular disorders in the retinal and other organ's circulation. The results obtained from the present studies may help as to understand the pathogenesis of the retinal vascular disease associated with high levels of CRP.

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