Medical Hypotheses 105 (2017) 17–21

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Hyperhomocysteinemia and Age-related Macular Degeneration: Role of Inflammatory Mediators and Pyroptosis; A Proposal

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ARTICLE INFO

Article history:
Received 1 November 2016
Accepted 22 June 2017

Keywords:
Age-related macular degeneration
Chemokines
Cytokines
Dry form
Inflammation
Pathogenesis
Risk factors
Vascular injury
Pyroptosis
Wet form

ABSTRACT

Age-related macular degeneration (AMD) and pyroptosis cause irreversible vascular changes in the eyes leading to central vision loss in patients. It is the most common eye disease affecting millions of people aged 50 years or older, and is slowly becoming a major health problem worldwide. The disease mainly affects *macula lutea*, an oval-shaped pigmented area surrounding fovea near the center of retina, a region responsible for visual acuity. It is fairly a complex disease as genetics of patients, environmental triggers as well as risk factors such as age, family history of CVDs, diabetes, gender, obesity, race, hyperopia, iris color, smoking, diabetes, exposure to sun light and pyroptosis have all been clubbed together as probable causes of macular degeneration. Among genes that are known to play a role include variant polymorphisms in the complement cascade components such as CFH, C2, C3, and CFB as potential genetic risk factors. So far, AMD disease hypothesized theories have not resulted into the anticipated impact towards the development of effective or preventive therapies in order to help alleviate patients' suffering because, as of today, it is still unclear what actually initiates or leads to this dreaded eye condition. Based upon our extensive work on the metabolism of homocysteine (Hcy) in various disease conditions we, therefore, are proposing a novel hypothesis for AMD pathogenesis as we strongly believe that Hcy and events such as pyroptosis make a greater contribution to the overall etiology of AMD disease in a target population of susceptible hosts by inciting and accelerating the inherent inflammatory changes in the retina of these patients (Fig. 2). In this context, we further state that Hcy and pyroptosis should be considered as legitimate and valuable markers of retinal dysfunction as they not only aid and abet in the development but also in the progression of AMD in older people as discussed in this paper. This discussion should open up new avenues in tackling inflammatory and pyroptosis centered pathways that are up-regulated or solely promoted by Hcy interaction within the ocular compartment of AMD susceptible hosts.

Introduction

Retinal pigment epithelium (RPE) forms a monolayer of cuboidal cells in the retina that is closely associated with the rod and cone photoreceptors, separating them from the capillary bed of the choroid [1]. RPE, apart from transporting nutrients to rod and cone photoreceptors, ensures overall ocular health by participating in the phagocytosis of photoreceptor outer segments, absorbing scattered light, and regenerating bleached visual pigments however it remains a prime target for a number of retinal diseases including AMD which is characterized by deterioration of the macula resulting into a loss of central vision. The macular degenerative changes occur due to alterations in RPE that can lead to drusen formation in the Bruch's membrane (BM) which is juxtaposed to the choroidal chorio-capillaries bed. Drusen are extracellular small nodule-shaped deposits, made up of phospholipids, collagen, and lipids [2]. Many theories exist today featuring potential predisposition for the development of AMD which occurs in two forms; dry AMD (dAMD) and wet AMD (wAMD). The late stage of dry AMD; also known as geographic atrophy (GA) proceeds through extensive RPE degeneration which can lead to the wAMD wherein uncontrolled vascular sprouting in the back of retina results to a debilitating vision loss in the affected patients.

We strongly believe that defining a new marker of AMD such as Hcy may provide further additional insights into the overall pathology of the disease process. Hcy elevates with age especially in older population and has been suggested as a powerful physiological stressor in the eyes where it generates lens oxidation,

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http://dx.doi.org/10.1016/j.mehy.2017.06.012
0306-9877/

proteolysis of lenticular proteins, and a subsequent decline in Nrf2-dependent antioxidant defense mechanisms during cataractogenesis. The European concerted action project declared hyperhomocysteinemia (HHcy) as an independent risk factor for vascular diseases as it leads to endothelial injury via free radicals, promoting lipid peroxidation, inhibiting glutathione peroxidase and nitric oxide, and interfering with clotting factors, all of them modify and damage the endothelium. Paraoxonase 1 (PON1) exhibits Hcy thiolactonase activity contributing towards the detoxification of Hcy and thus protects against atherosclerosis [3,4]. As we know patients with AMD tend to be older and have an increased prevalence of cardiovascular diseases (CVDs), and diabetes compared with people of similar age without AMD [5,6]. Meta-analyses of prospective studies confirmed an association between elevated plasma Hcy (Fig. 1) and CVDs [7] and other similar investigations also indicated the same [8,9]. Axer-Siegel and colleagues determined that HHcy is clearly involved in the pathogenesis of AMD because difference between HHcy and control subjects was significant [10]. Reactive carbonyl compounds generated via lipid peroxidation derived moieties from polyunsaturated fatty acids, among which malondialdehyde (MDA) is the most abundant, are unstable and decompose to form a series of compounds [11]. The higher Hcy levels correlates with higher serum MDA and lower PON1 activity and thus it can be argued that Hcy negatively regulates PON1 gene expression in AMD, which could contribute to lower serum PON1 activity because of enhanced oxidative stress [12]. Anatomically, the eyes are relatively isolated tissue compartments from the systemic circulation and our immune system has a limited access to them; therefore immune responses are less likely to occur [13] but this barrier is often disrupted in conditions that can lead to neovascular disorders such as AMD. For this reason, it is important to know that HHcy creates a toxic environment for the vascular endothelium and that it can modify the vessel wall by making it thickened, hypoxic and thereby stimulating the expression of vascular endothelial growth factor (VEGF) [9,14,15]. An animal study found that HHcy did increase VEGF immuno-reactivity in the retina of rats linking it to the AMD development [16,17].

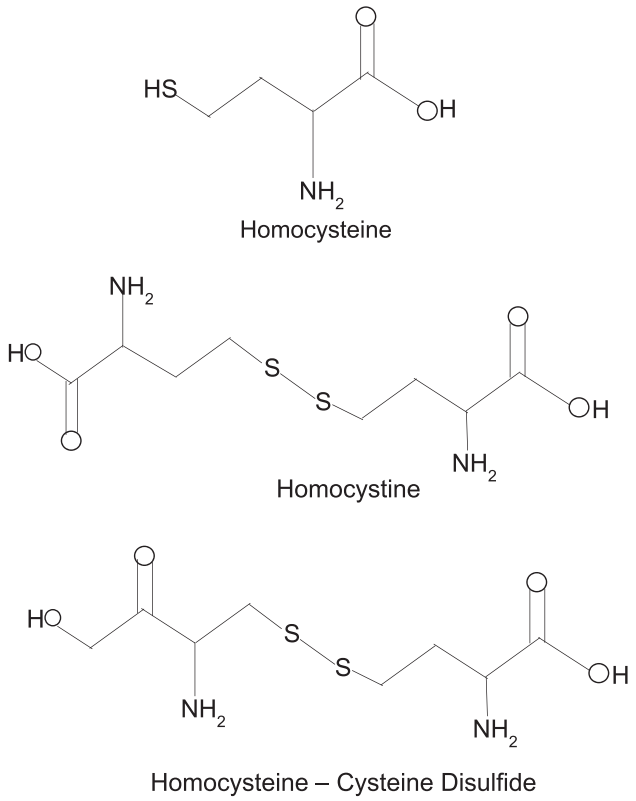

Fig. 1. Chemical structures of the total plasma homocysteine.

At present there are only two types of therapies available to improve the AMD outcome in the affected individuals. Antioxidant supplements and anti-VEGF biologics which are basically palliative in nature and do not serve well in all the patients [18]. Surprisingly, despite a significant progress in recent years the underlying mechanism(s) of RPE degeneration still remain elusive. Being a highly complex disease in its causation and progression, little is known about various inflammatory molecules that are regulated by Hcy in the retina specifically in the RPE cells. Overproduction of these molecule can potentially derail the ocular homeostasis in the susceptible patients thus setting the stage for the AMD disease initiation (Fig. 2). Thus, an in-depth knowledge of inflammatory pathway(s) upregulated by Hcy can help design newer class of treatment options because retinal inflammation remains one of the dominant determinants of AMD pathophysiology [19]. As reported by others, elevated c-reactive protein (CRP) and Hcy levels are clearly associated with AMD disease implicating the role of inflammation in the disease process [8]. Thus, interventions aimed at reducing inflammatory insults in the beginning of the disease can help reduce the incidence of AMD disease later in the life.

The hypothesis

Excess Hcy or HHcy has been reported in patients with AMD but its evidence as an inflammatory modulator and its direct role in the retinal pathogenesis is lacking. To make things complicated, genetic mutations in the methylmalonic aciduria and homocystinuria type C protein known as MMACHC can also lead to homocystinuria, a disorder of vitamin B12 resulting in symptoms, including neurological, thromboembolic events, maculopathy, pigmentary retinopathy, and optic atrophy [20,21]. We, therefore, are proposing a new hypothesis wherein HHcy acts as an initial trigger for the inflammatory process in the eyes of susceptible hosts that can lead to the beginning of subtle pathological changes sufficiently enough to start the degenerative process in the macula (Fig. 2). Our hypothesis is based upon critical observations stemming from our own work on retinal cells [22] and from other consistent indications where elevated level of Hcy were shown to induce chronic inflammation in the vascular bed, including glomerulus, and promoting glomerulosclerosis. Several laboratories, including our own, over the years have shown that HHcy induces glomerular injury [23,24], in part mediated through the induction of inflammatory molecules [25]. In glomerular injury, similar to other injuries, circulating monocytes through upregulated inflammatory molecules adhere to the vessel wall, roll and migrate to the site of injury. The migrated monocytes, through a sequence of events, modulate extracellular matrix, resulting in matrix deposition and glomerulosclerosis. This ultimately causes chronic kidney disease (CKD) [26]. Studies have shown that cytokine and chemokine mediated inflammation is a major factor in the development and progression of CKD corroborating clinical evidence that HHcy levels are linked to the inflammatory state associated with CKD [27,28]. Specifically, Hcy can induce the expression of cytokines, such as monocyte chemoattractant protein-1 (MCP-1) and chemokines, such as macrophage inflammatory protein-2 (MIP-2), in cultured mesangial cells [19,26,29–31]. Also, findings from the pre-clinical mouse model of HHcy, in which cystathionine-β-synthase was deficient, revealed abnormal RPE morphology with features similar to that of human AMD upon optical coherence tomography, fluorescein angiography, histology, and electron microscopy. These features included atrophy, vacuolization, hypopigmentation, thickened basal lamina, hyporeflective lucency, choroidal neovascularization (CNV), and disturbed