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Editorial

Gene-Diet Interaction in Age-Related Macular Degeneration: New Insights and Perspectives

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Age-related macular degeneration (AMD), the most common cause of visual loss in the developed world, is a chronic and degenerative disease of the central part of the retina which can significantly reduce quality of life. Prevalence of AMD is expected to increase as the elderly population grows, with an estimated 50% increase by 2020. The asymptomatic early and intermediate stages, characterized by the deposition of retinal cellular debris in clusters termed "drusen", can progress to advanced forms of the disease, including neovascular disease and geographic atrophy.

In the last decade, several genome-wide association studies have identified many genetic variants that account for an increased risk of disease; among these, the most common associations were reported for the Y402H variant, within the complement factor H gene (CFH), and the A69S (rs10490924) variant, within the age-related maculopathy susceptibility 2 (ARMS2) gene.

Although the mechanisms are not completely clarified, genetic, environmental and other unknown factors can influence the pathogenesis of the disease, modifying the individual risk of developing AMD. Due to the coexistence of genetic and environmental risk factors, the etiology of AMD is multifactorial, with a typical gene–environment interaction in which environmental effects may be under genetic control, as well as environmental risk factors may trigger the disease in genetically susceptible subjects.

In this framework, the role of diet cannot be overlooked, considering its significant impact on the incidence and treatment of AMD. It has been well established that individuals consuming the lowest amount of ω-3 fatty acids and carotenoids are at increased risk for AMD. Accordingly, the National Eye Institute promotes the consumption of ω-3 fatty acids and carotenoids rich foods such as fish and green leafy vegetables. Particularly, an adequate intake or supplementation of natural antioxidants, such as lutein and zeaxanthin, may prevent oxidative retinal damage.

However, foods and nutrients are consumed in combination and they may have synergistic effects. Hence, the need to identify the relationships between dietary patterns and the risk of developing AMD. Current evidences show that individuals, consuming higher glycemic index diet, are at increased risk for AMD compared to those consuming lower glycemic index diet. Further, the adherence to a Western dietary pattern, characterized by a high intake of red meats, high-fat dairy products, processed meats and refined grains, increases the AMD risk compared to an healthy diet rich in fruits, vegetables, legumes, seafood, and whole grains. More recently, it has also been demonstrated that the adherence to the traditional Mediterranean diet is associated with a lower prevalence of both early and late AMD.

To date, the treatment of neovascular AMD consist in antivascular endothelial growth factor therapies injected into the vitreous cavity of the eye. Conversely, atrophic AMD causes a more gradual visual decline, for which treatment can only delay disease progression, without the possible reversal of vision loss. The pivotal therapy for atrophic AMD has been investigated in two randomized control trials, known as Age-Related Eye Disease Study (AREDS) and the follow-up Age-Related Eye Disease Study 2 (AREDS2). The treatment consist

of oral supplementation of the AREDS antioxidant formulation (beta-carotene, vitamin C, vitamin E, copper, and zinc) which showed to be able to slow disease progression.

Recent researches have been conducted to study the interaction between genetic variants and antioxidant treatment in atrophic AMD. For example, it seems reasonable a lower risk of early AMD for patients with either Y402H CFH or A69S ARMS2 variants who consumed diets high in fish and/or lutein/zeaxanthin. Conversely, there are also some suggestions that patients having the at-risk Y402H CFH variant, who consumed zinc-containing supplements, show less reduction in AMD progression.

It has been demonstrated that retinal pigmented epithelium and retina cells show altered gene expression in response to external environmental factors, including nutrient intake, light, and oxidative stress, as well as internal cellular signals such as reactive oxygen species, calcium concentration, and DNA damage.

Epigenetics, representing a bridge between the individual genetic type and the environmental exposure, could partially explain the modulation of gene expression by external environmental signal. Epigenetic mechanisms encompass a range of attributes including DNA methylation, histone modifications, chromatin remodeling, and deployment of non-coding RNAs. DNA methylation at gene promoter regions modifies DNA accessibility to transcription factors or helps the recruitment of silencing-associated proteins, resulting in gene silencing, whereas global DNA methylation is strictly related to genome and chromosome stability. Histones are subjected to various post-translational modifications, including acetylation, methylation, ubiquitination, phosphorylation, and sumoylation. These modifications occur primarily within the N-terminal tails of histones protruding from the surface of the nucleosome, as well as on its core region. Chromatin remodelling is the dynamic modification of chromatin architecture to allow the access of condensed genomic DNA to the transcription machinery proteins, and thereby controls gene expression. Non-coding RNAs include the infrastructural RNAs (small nuclear and nucleolar RNAs, and ribosomal RNAs) and the regulatory RNAs (microRNAs, long non-coding RNAs, Piwi interacting RNAs, and small-interfering RNAs).

The set of these aberrant epigenetic patterns have been described in the regulation of various cellular and tissue processes, such as aging, inflammation, immunomodulation and angiogenesis, and, hence, they have been investigated in the etiopathogenesis of AMD. Several studies have assessed the interaction between dietary compounds and epigenetic mechanism. Nutrients as folate, methionine, choline, vitamin B-12, and vitamin B-6 are involved in one-carbon metabolism and play a critical role in maintaining DNA methylation. Recently, dietary patterns deficient in methionine, choline, vitamin B-12, or folate were associated with global hypomethylation and site-specific hypermethylation. Moreover, some natural compounds have been also proven to inhibit histone de-acetylation; one example is L-sulforaphane, an extract derived from cruciferous vegetables, that protects the retina by exerting ant oxidative and anti-inflammatory effects.

In this context, epigenetics research could provide new prospects to examine the molecular mechanisms of non-inherited risk and the environmental basis of retinal degeneration. However, given the highly preliminary nature of these evidence, further researches are required to better investigate any potential gene–diet interactions in the development, progression and treatment of AMD.

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