Aetiology of Late Age-Related Macular Disease

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Core Messages

- Choroidal neovascularization (CNV) grows in response to induced growth factors, including vascular endothelial growth factor (VEGF)
- Reasons for growth factor expression are not well elucidated at present
- Examination of identified causes of growth factor release with known physiologic information of the aging eye has led to several theories, some of which are more likely than others
- Oxidative damage can explain many aspects of late age-related macula disease
- A sequence of specific steps involved in formation of late age-related maculopathy can be constructed by integrating present knowledge
- The development of treatment and prevention strategies depends on knowledge of disease pathogenesis; understanding the pathogenesis is a basic step in creating a cure

7.1 Introduction

Late age-related macular disease is the largest cause of visual loss among older adults in industrialized countries. This disease entity comprises two main components involved in age-related macular degeneration. Patients may develop choroidal neovascularization, which is a growth of vessels, proliferation of a number of cell types including the retinal pigment epithelial cells, along with recruitment of inflammatory cells such as neutrophils and macrophages. The concept of choroidal neovascularization by its very name highlights the vascular aspects of the process, guided by the chief method of diagnosis, angiography, and the accompanying signs such as leakage and bleeding. However, the temporal and spatial sequence of cytokine expression, endothelial and inflammatory infiltration, endothelial cell proliferation, maturation, matrix remodelling, and apoptosis is quite similar to a wound healing response. The non-neovascular change that leads to significant loss of visual acuity is the development of geographic atrophy. Regions of retinal pigment epithelial cell death occur with atrophy of the overlying retina and underlying retinal pigment epithelium. The shared epidemiologic risk factors, the common occurrence of one of these disorders in one eye with the other being present in the fellow eye, and the common occurrence of both forms of AMD in one eye suggests they share some common aetiobiologic phenomena. While control of some aspects of the neovascular forms of AMD appears to be an attainable goal, the increasing prevalence and lack of any known treatment makes geographic atrophy an increasingly important public health problem.

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7.2 Epidemiologic Factors

The most significant risk factor for AMD is age, but additional important risk factors have been identified. A positive family history [89, 111, 200], cigarette smoking [89, 226, 203], and hypertension [1, 133, 226] are risk factors that have been fairly consistently found as risk factors for the development of exudative AMD. Additional risk factors found with varying degrees of consistency among studies [114] include increased C-reactive protein [188], increased white blood cell count [113], increased intake of vegetable fat, mono- and polyunsaturated fatty acids, increased intake of linoleic acid [33, 186], increased intake of fat [187], increased intake of baked goods [187], female gender [112, 201, 203], hyperopia [1, 12], and blue iris colour [89, 226]. Black race [35, 68], increased intake of docosahexaenoic acid (curiously the most polyunsaturated fatty acid) [33], higher intake of fish [186, 187, 202], nuts [187], and dark green leafy vegetables [185], and higher levels of serum carotenoids [226] have been associated with a lower risk. The Eye Disease Case Control Study only had a handful of women using oestrogen replacement, but these patients seemed to have a lower risk for neovascularization compared to women not using oestrogen [226].

7.3 Genetic Factors

There is a higher risk for the development of late age-related maculopathy in people with a positive family history [89, 111, 200]. This raises the possibility of finding a gene or genes that may be linked to macular degeneration. Genetic investigation into age-related macular degeneration is hindered because the disease occurs in older individuals who are unlikely to have parents or grandparents alive for comparative testing. Mutation of the Stargardt disease gene (ABCR) was found by Allikmets and associates [6] to be associated with AMD (in particular the non-neovascular subtype), but this same association was not found by other researchers [40, 237]. The APOE epsilon4 allele has been found to be associated with a decreased risk, and the epsilon2 allele was associated with a slight increase in risk for AMD [110, 204]. This association was not found by others, however [156, 183]. Macular degeneration is a complex disease, in that there are a number of possible genetic, epigenetic, dietary, and environmental factors all interacting to confer a risk for the development of disease in any given individual. Because there are probably a large number of polymorphisms of many different genes that potentially could be related to the development of AMD (in the context of various other genetic, epigenetic and environmental factors), it is likely that there is no single gene defect responsible for more than a minority of cases of AMD. It is also possible that with different genotypes there are different pathophysiologic mechanisms that produce a generic choroidal neovascular response.

7.4 Structurally Induced Changes Associated with Aging

Some cells in the body are capable of ongoing replication, while others like the RPE have very limited ability to divide before reaching replicative senescence [60]. Under most conditions individual RPE cells persist for the life of the individual. Located between the choroid and the retina, the RPE acts in the absorption of light passing