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Choroidal neovascularisation in age-related macular disease

Age-related macular disease accounts for about 50% of blind registration in Europe and North America.[1-3] Despite the early expectations,[4-6] it is now evident that present techniques of laser treatment will not have a major impact on blindness due to macular degeneration in the elderly patient.[7-9] This requires that our knowledge of the behaviour and aetiology of the disorder be re-examined and alternative approaches to management be sought. Visual loss results from either subretinal neovascularisation, detachment of the retinal pigment epithelium from Bruch's membrane, or geographic atrophy.[10] It is widely believed that these lesions occur in response to progressive changes in Bruch's membrane that happen with age, including alteration of the collagen and interfibre matrix of Bruch's membrane,[11-15] and the accumulation of material derived from the retinal pigment epithelium.[16-18]

The causal relation between the changes in Bruch's membrane and the lesions causing visual loss is unknown. There is some evidence that the chemical composition of the drusen may determine the subsequent outcome of disease.[19-23] Drusen which are hypofluorescent and are believed to be hydrophobic due to high concentrations of neutral lipids give rise to detachment of the retinal pigment epithelium. It has been postulated that hydrophobicity of Bruch's membrane would cause a barrier to outward diffusion of fluid pumped from the neuroretina towards the choroid by the retinal pigment epithelium. A barrier to metabolic exchange between the choroid and the retinal pigment epithelium may also contribute to geographic atrophy.[24-25] By contrast those with hyperfluorescent drusen are more likely to sustain choroidal neovascularisation. However there are no well formulated concepts as to the mechanism by which neovascularisation is induced. This represents one of the most important challenges in ophthalmology since choroidal neovascularisation is the most common cause of visual loss in age-related macular disease.

For many years it was considered that Bruch's membrane represented a physical barrier to inward growth of choroidal blood vessels, and searches were made for spontaneous breaks in Bruch's membrane in the elderly. The realisation that angiogenesis plays an important role in the behaviour of many disorders, both ophthalmic and non-ophthalmic, prompted an extensive search for factors which govern blood vessel growth.[26-31] It was shown that tumours and activated macrophages can induce growth, while avascular tissues such as cartilage and vitreous may suppress it. As a consequence of this work it became apparent that choroidal neovascularisation was not simply due to physical changes in Bruch's membrane alone, but that alteration in the concentration of the various growth factors derived from the neighbouring tissues may be important. In particular it has been demonstrated that the retinal pigment epithelium may produce a factor which suppresses vessel growth.[32]

One clue as to a possible angiogenic influence arose as a result of the work by Sarks and others in which the presence of macrophages in Bruch's membrane of the elderly was documented some years ago.[33-36] The importance of this finding related to the potential of macrophages both to modify blood vessel behaviour and to alter Bruch's membrane. It was shown that macrophages were found in areas where Bruch's membrane was thin, and evidence was presented implying that the macrophages were responsible for removing collagen. It was suggested that the modification of Bruch's membrane may allow inward growth of choroidal blood vessels. Furthermore, activated macrophages induce vasoproliferation by production of growth factors.[37-39] Therefore, a rational therapeutic approach to the control of choroidal neovascularisation might be identified if the mechanism by which macrophages are induced to enter Bruch's membrane was defined. In this issue van der Schaft *et al* report an investigation of possible mechanisms which induce macrophage recruitment into Bruch's membrane; this group of workers has already made significant contributions to our knowledge of Bruch's membrane changes with age.[14-15] The presence of immune complexes in Bruch's membrane was sought by immunofluorescence microscopy. Although it was shown that macrophages were present and were associated with focal thinning of Bruch's membrane, accumulation of immunoglobulins was not found consistently. It is concluded that recruitment of macrophages is not preceded by deposition of immunoglobulins, and alternative mechanisms should be sought. Macrophages are found in a variety of situations such as infection and autoimmune disease in which immunoglobulins are present in high concentration, but these disease processes may have little in common with age-related macular disease in terms of pathogenetic processes. Macrophages are also found in atheromatous plaques which do not contain immunoglobulins,[40-42] and which may have closer homology with age-related macular disease.

As a result of recent clinical observation and laboratory research, new pathogenetic concepts have been formulated concerning the origin of the material in Bruch's membrane, its chemical composition, its influence upon retinal function, and the reactions it evokes. Recently there have been various attempts to identify treatment whereby the growth of choroidal new vessels may be modified.[43,44] These may prove to be beneficial to patients but have been devised on an empirical basis. It is to be hoped that identification of precise mechanisms governing blood vessel growth in age-related macular disease will give rise to a rational approach to therapy.

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