Age-Related Macular Degeneration

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Introduction to Age-Related Macular Degeneration

Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in the elderly population of industrialized countries [1]. Based on a meta-analysis, the prevalence of early-stage AMD is estimated to be 6.8 % and for the late stages 1.5 % [2]. Prevalence, incidence, and progression of all forms of AMD rise with increasing age. Thirty percent of all probands aged ≥75 years were found to have early AMD and 7.1 % suffered from late stages of the disease [3, 4].

Various cell layers are involved in the disease process: the choriocapillaris (i.e., the layer of capillaries adjacent to Bruch's membrane in the choroid), Bruch's membrane, the retinal pigment epithelium (RPE), and photoreceptors (see chapter "Overview" under part "Eye"). AMD typically affects the central retina (macula including the fovea) as the area with the highest resolution. Untreated, the disease results in severe loss of vision.

Different stages and phenotypic manifestations of the disease have been categorized [5]. The early and intermediate dry forms of the disease are characterized by the so-called drusen and pigmentary alterations. Drusen are extracellular deposits located within Bruch's membrane under the RPE. The late stages of AMD are subdivided into an exudative and a non-exudative form. The exudative form is characterized by the formation of choroidal neovascularizations (CNV) with concomitant extracellular fluid accumulation, RPE detachment, and/or hemorrhages. The non-exudative late stage, termed "geographic atrophy" (GA), is characterized by cell death of all affected cell layers. It has been speculated that GA is the natural end stage of AMD, if the disease does not convert into CNV [6]. The exudative and non-exudative forms are not mutually exclusive, as these may develop in the same eye.

Pathophysiology of Age-Related Macular Degeneration and Metabolic Alterations

The pathogenesis of AMD is incompletely understood. As a complex, multifactorial disease, it is thought to be affected by numerous systemic, genetic, and environmental factors, e.g., smoking.

Aging processes appear to play a major role in the pathogenesis of AMD, and it is presumed that everybody would develop AMD if only a high enough age would be reached.

During AMD, changes in Bruch's membrane are observed and accompanied by activation of the complement system. Deposition of molecules within Bruch's membrane leads to formation of drusen, a characteristic of early- and late-stage AMD. Accumulation of lipofuscin and reactive

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oxygen species (ROS) damage the RPE and likewise contribute to the progression of AMD.

Considerable structural changes in Bruch's membrane occur due to aging processes [7]. As a result of calcification, loss of its elastin layer, and formation of cross-links such as advanced glycation end products (AGEs), the membrane becomes more brittle. Furthermore, it increases in thickness due to the lifelong entrapment of molecules and cellular debris, particularly lipids. These accumulations of proteins and lipids are called drusen. Structural changes and accumulation of material within Bruch's membrane may reduce the free flow of molecules between the choroid and the photoreceptors and, eventually, in the most severe cases, lead to cellular atrophy.

Altered immune responses with complement system activation are thought to be further involved in AMD [8], as complement proteins are found within the drusen, and contain rise allows of complement jensen are associater with the disease. The complement system belongs to the innate immune system (see chapter "Overview" under part "Immune system") and can be activated via three different pathways, i.e., the classic, lectin, and alternative ones. Whereas the classical and lectin pathways are activated via antibodies and opsonins, respectively, which are bound to the surface of a pathogen, the alternative complement pathway is continuously active at a low level and becomes activated by the absence of complement regulatory proteins on the surface of most microbial pathogens. In each pathway, a proteolytic cascade is amplified, and effectors such as anaphylatoxins, the membrane attack complex, and opsonins may be activated. It has been suggested that aging causes an increased activation of the alternative complement system in the blood [9]. The role of the alternative complement pathway in AMD pathogenesis has been exemplified by the discovery of the gene for complement factor H (CFH) [10–12], an inhibitor of the alternative pathway, as well as other risk loci in this pathway [13–15]. Specific polymorphisms in these genes are thought to be associated with abnormal complement activation [16].

Furthermore, the retina provides an ideal environment for the generation of ROS due to its specific anatomical and metabolic characteristics [17], such as (1) high oxygen consumption by the retina and RPE compared to many other tissues, (2) high levels of cumulative irradiation, and (3) abundance of photosensitizers within the neurosensory retina and RPE. Furthermore, photoreceptor outer segment membranes are rich in polyunsaturated fatty acids, which are readily oxidized and thus can initiate a cytotoxic chain reaction.

Accumulation of lipofuscin granules in postmitotic RPE cells apparently due to incomplete lysosomal degradation of photoreceptor outer segments further contributes to AMD progression [7]. Lipofuscin is a photosensitizer generating a range of ROS. Furthermore, the photoreactivity of individual lipofuscin granules increases with age. Exposure of lipofuscin-containing RPE cells to blue light results in lipofuscin-dependent lipid peroxidation, protein oxidation, loss of lysosomal integrity, mitochondrial DNA damage, and retinal pigment epithelium (RPE) cell death (Fig. 1).

The interaction of these metabolic and structural alterations with genetic and environmental risk factors is thought to induce pathological changes promoting the development of phenotypic AMD changes and resulting in an earlier onset of the disease. They also form the basis for therapeutic rationales, e.g., targeting oxidative stress with prophylactic and interventional pharmacological measures (see below).

In exudative AMD, vascular endothelial growth factor-A (VEGF-A, or VEGF, in brief) has been identified as a major factor inducing ocular neovascularizations [18]. Further, VEGF plays a role in inflammatory processes, immunity, and wound healing; it acts as a survival factor for endothelial cells and as a neuroprotectant for neurons in the central nervous system and the retina. The angiogenic cascade and vascular permeability induced by VEGF [18] play an essential role in the therapeutic concept of VEGF inhibition (Fig. 2).

Treatment of Age-Related Macular Degeneration

So far, a number of different approaches have been tried to prevent the development of the late stages of AMD. However, with the exception of small effects of dietary supplements, efficacious

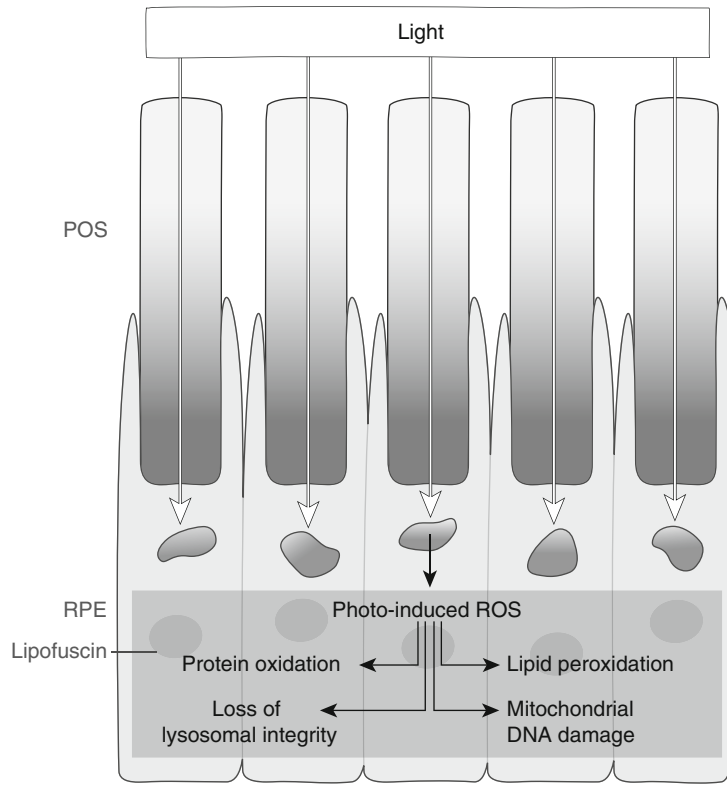

Fig. 1 Lipofuscin-dependent reactive oxygen species (*ROS*) generation – a metabolic pathway presumed to contribute to the age-related macular degeneration (*AMD*) disease process. *POS* photoreceptor outer segments, *RPE* retinal pigment epithelium

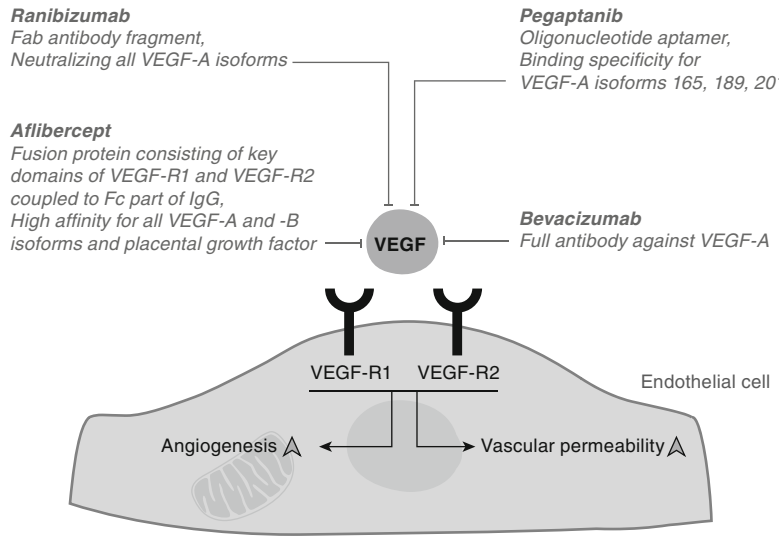

Fig. 2 Anti-vascular endothelial growth factor-A (*VEGF-A*) strategies currently used in the treatment of exudative age-related macular degeneration (AMD). The angiogenic cascade and vascular permeability [18] play an essential role in VEGF inhibition. *IgG* immunoglobulin G

measures are currently lacking. Only recently it has been achieved to treat exudative AMD successfully using anti-VEGF compounds injected into the vitreous at regular intervals. In clinical practice, this treatment strategy for exudative AMD has replaced angio-occlusive therapies such as laser photocoagulation and verteporfin photodynamic therapy.

For the non-exudative late stage of AMD, there is no treatment available yet to slow or to halt GA progression. A number of preclinical and clinical trials are currently carried out to find a treatment for this form of AMD manifestation.

Influence of Treatment on Metabolism

Nutritional Supplementation to Prevent Development of Late-Stage AMD

Alleviation of oxidative stress is thought to be a critical step to prevent the conversion from early to late AMD stages. Nutrients that may reduce oxidative damage include vitamins, carotenoids, and trace elements. The AREDS (Age-Related Eye Disease Study) trial demonstrated that a combination of vitamins C and E, β-carotene, and zinc oxide, reduces the risk of late-stage AMD in patients with intermediate risk of conversion [19]. A recent update suggested lutein and zeaxanthin as appropriate substitutes for β-carotene, which increased the incidence of lung cancer in former smokers [20]. Due to their high number of double bonds, these macular carotenoids/pigments can quench ROS, limiting oxidative stress, increasing membrane stability, and may also act as filters for blue light and thus limit retinal photo-stress [21].

Anti-VEGF Therapy in the Treatment of Exudative AMD

Pegaptanib, the first approved intravitreally injected anti-VEGF medication, is an oligonucleotide aptamer with a high binding specificity for the VEGF-A isoforms 165, 189, and 201. An important basis for the development of pegaptanib sodium was the results of studies showing that VEGF-A-165 plays an important role in the neovascularization process [22]. The complete blockage of all VEGF-A isoforms was thought to impair physiological functions [23]. Efficacy of pegaptanib in clinical studies was limited.

Ranibizumab is a Fab antibody fragment neutralizing all VEGF-A isoforms. It is well tolerated and shows a favorable safety profile. Monthly injected ranibizumab has been shown to stabilize or to improve vision in over 90 % of patients and significantly improve vision in over 30 % of patients [24–26].

Aflibercept is a fusion protein, consisting of the key domains of the human VEGF receptors 1 and 2, coupled to the Fc part of a human IgG molecule. It has a high affinity for all VEGF-A and VEGF-B isoforms as well as placental growth factor [27], and theoretical models as well as trials [28] indicate a longer duration of action compared with current treatments. In the studies with intravitreal aflibercept, no increase in ocular or systemic adverse events was noted, despite the increased affinity of aflibercept for all VEGF-A and VEGF-B isoforms [28].

Bevacizumab, a full antibody against VEGF-A, has originally been developed as a cancer therapeutic. It is also used for the intravitreal treatment of exudative AMD. However, the drug has not been approved for this indication and, therefore, represents an off-label therapy.

Intravenous administration of anti-VEGF compounds in the treatment of cancer has been associated with increased risks of stroke (see chapter "Stroke"), venous thromboembolism, congestive heart failure, and bleeding. However, results across studies with differing methodologies provide some reassurance that the widespread use of injections of VEGF inhibitors within the vitreous to treat exudative AMD has not resulted in significant increases of systemic adverse events [29].

Perspectives

The treatment of AMD will be one of the major challenges in health care during the next decades. In particular, primary prevention of AMD as well

as prevention of progression from early to late AMD stages represent an unmet need and are, therefore, in the focus of current research activities. While anti-VEGF therapy represents a breakthrough in the therapy of neovascular AMD, repeated, sometimes lifelong, administration of the drug is an enormous burden for the patients and health systems. Long-acting drug delivery systems would therefore be desirable.

As of yet, there is no treatment available to slow or to halt progression of the dry late form of AMD, i.e., GA. However, various preclinical and clinical trials are currently ongoing. Targets for this phenotype address various pathways including inflammation, complement system, trophic factors, oxidative stress, reduction of retinal toxins, and improvement of choroidal blood flow [30].

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