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Review

Age-related macular degeneration (AMD): pathogenesis and therapy

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Abstract:
Age-related macular degeneration (AMD) is a disease leading to severe visual loss and legal blindness in the elderly population. Its pathogenesis, likely multifactorial, involving a complex interaction of metabolic, functional, genetic and environmental factors, remains poorly understood. For these reasons currently used therapeutic approaches are insuffiently effective. Although major abnormalities are seen in four functionally interrelated tissues, i.e., photoreceptors, retinal pigment epithelium (RPE), Bruch's membrane and choriocapillaries, the impairment of RPE cell functions is an early and crucial event in the molecular pathways leading to clinically relevant AMD changes. RPE progressively degenerate, which results in a progressive irreversible degeneration of photoreceptors. Four processes: lipofuscinogenesis, drusogenesis, inflammation and neovascularization, specifically contribute to the development of two forms of AMD, the dry form (non-exudative; geographic atrophy) and the wet form (exudative, neovascular). This paper briefly describes major molecular and cellular events leading to AMD, and presents currently used and new experimental, forthcoming therapeutic strategies.

Key words:
age-related macular degeneration, AMD, pathogenesis, lipofuscin, drusen, inflammation, therapeutic strategies

Introduction

Age-related macular degeneration (AMD) is one of the most common irreversible causes of severe loss of vision, including legal blindness, in the elderly population (usually over 60) [14, 28, 30]. Despite intensive basic and clinical research, its pathogenesis remains unclear, likely due to the multifactorial character [14, 33, 40, 41]. In addition to strong age-dependence of the disease, a complex interaction of metabolic, functional, genetic and environmental factors seems to create a stage for chronically developing changes in ocular structures of the macular region (choriocapillaries, Bruch's membrane, retinal pigment epithelium-RPE, photoreceptors) which may contribute to varying degrees to the onset and final picture of AMD. Taking into account clinical and pathological features, two subgroups of AMD are classically distinguished: atrophic (dry form) and exudative (wet form). The dry form (also known as geographic atrophy, both central and/or non-central) is typically characterized by a progressing course leading to degeneration of RPE and photoreceptors. The exudative form is linked to choroidal neovascularization directed to the subretinal macular region, with subsequent bleeding and/or fluid leakage, which may result in a sudden loss of central vision; it is the most rapidly progressing form of AMD. Clinical features common for the two types of AMD include the presence of drusen, as well as hypo- and/or hyperpigmentation of the RPE.

More than 80% of all people with intermediate and advanced AMD have the dry form, yet this form may progress to the wet form which leads to significantly more vision loss [14, 28, 30].

The pathophysiology of AMD is complex and, in addition to genetic predispositions, at least four processes contribute to the disease, i.e. lipofuscinogenesis (with its linkage to oxidative stress), drusogenesis, local inflammation and neovascularization (in the case of wet form) [2, 10, 14, 25, 28, 33, 40, 41, 51, 58]. Figure 1 schematically depicts major processes involved in the development of AMD, and Figure 2 shows functional – physiological and pathological – aspects of the RPE cells, and their interactions with photoreceptors, in the course of ageing and the development of AMD.

Genetics

Genetic predispositions seem likely to occur, as much evidence points to a familial component of AMD. Concerning the genetic aspect, in the past several genes were identified that cause diseases with clinical features that overlap with AMD (e.g., *ABCA4*, *ELOVL4*, *FIBL-6*, *APOE*, *SOD2*) [53, 54]. Although mutations in the mentioned genes may to some extent contribute to the development of particular features of AMD, they obviously are not responsible for the advanced and complex AMD pathology. Very recently, several independent research groups have identified a common variant (Y402H) of the complement factor H (CFH) gene that may explain about 50% of AMD cases [6, 30]. This observation is the first that shows a strong association of a single gene anomaly with the pathogenesis of AMD (see paragraph "Drusen and drusogenesis").

Lipofuscin and lipofuscinogenesis

It is generally accepted that the impairment of RPE cell function is an early and crucial event in the molecular pathways leading to clinically relevant AMD [40, 51, 55]. Such a view has its rationale in the fact that RPE serves a variety of metabolic and supportive functions that are of vital importance for retinal photoreceptors, including maintenance of the blood-retina barrier, participation in the visual cycle (uptake, processing, transport and release of vitamin A derivatives), and phagocytic uptake and degradation of constantly shed apical photoreceptor outer segments (POS) (Fig. 2) [52]. One of driving forces of the RPE dysfunction is an age-dependent phagocytic and metabolic insufficiency of postmitotic RPE cells. This leads to a progressive accumulation of lipofuscin (or "age pigment") granules composed mostly of lipids (≈ 50%) and proteins (≈ 44%) of phagosomal, lysosomal, and photoreceptor origin (including also retinoid transporter – the cellular retinoid binding protein, CRALBP), modified to varying degree by oxidative processes as a result of both exposure to visible and UVA light and high oxygen levels in the eye (Fig. 2) [51, 55, 58]. A well-established cytotoxic constituent of lipofuscin is bisretinoid fluorophore consisting of two retinoid-derived side chains extending from a pyridinium ring (A2E), which, together with other photoreactive molecule/s (still requiring identification) – is a potent photoinducible generator of reactive oxygen species with a potential to damage proteins, lipids and DNA [40, 51]. Although lipid peroxidation products are considered to be a major substrate for the genesis of lipofuscin and its cytotoxic constituents [51], many identified "lipofuscin" proteins may also play a significant role in its overall toxicity [55]. Figure 3 schematically depicts major processes involved in visual excitation and retinoid cycle in a functionally interrelated complex of photoreceptors and RPE cells, with indicated reactions leading to lipofuscin formation. Molecular and cellular aspects of the lipofuscinogenesis, with its impact on AMD development, were discussed in detail earlier [40].

Drusen and drusogenesis

Another pathogenic component of AMD are drusen that are amorphous deposits accumulating extracellularly in the area between RPE and the inner collagenous zone of Bruch's membrane (Fig. 2) [1, 7, 14, 33, 41]. Drusen are considered the hallmark of AMD. Clinically, they are divided into two main phenotypes, "hard" and "soft", depending on their relative size and shape [1, 7]. Although a few small (< 63 μm) hard drusen can be found in at least 95% of the aged popula-

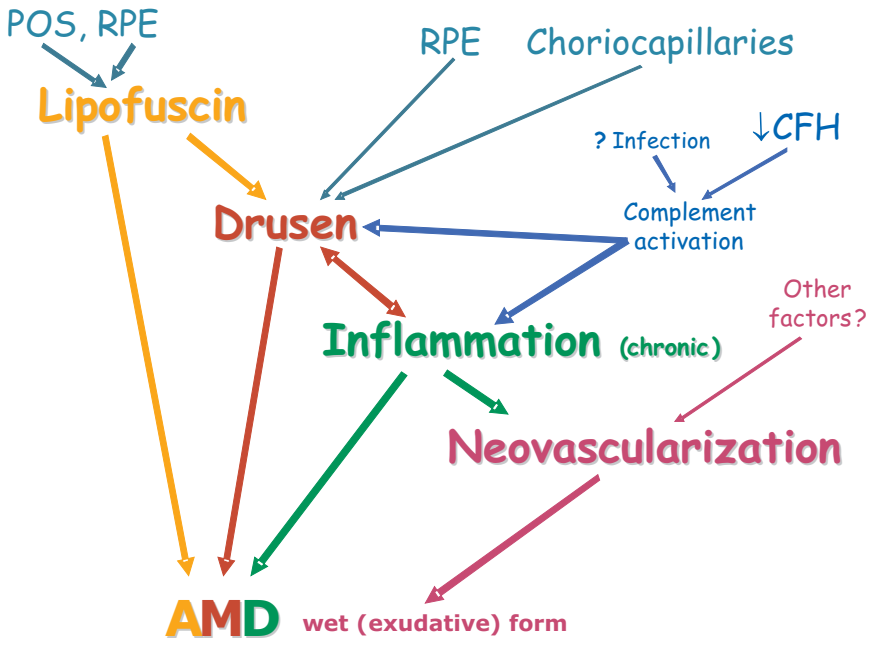

Fig. 1. Four main processes: lipofuscin formation, drusen formation, local inflammation, and neovascularization, contribute to the pathogenesis of age-related macular degeneration (AMD). Explanations in the text. Abbreviations: POS – photoreceptor outer segment; RPE – retinal pigment epithelium; CFH – complement factor H

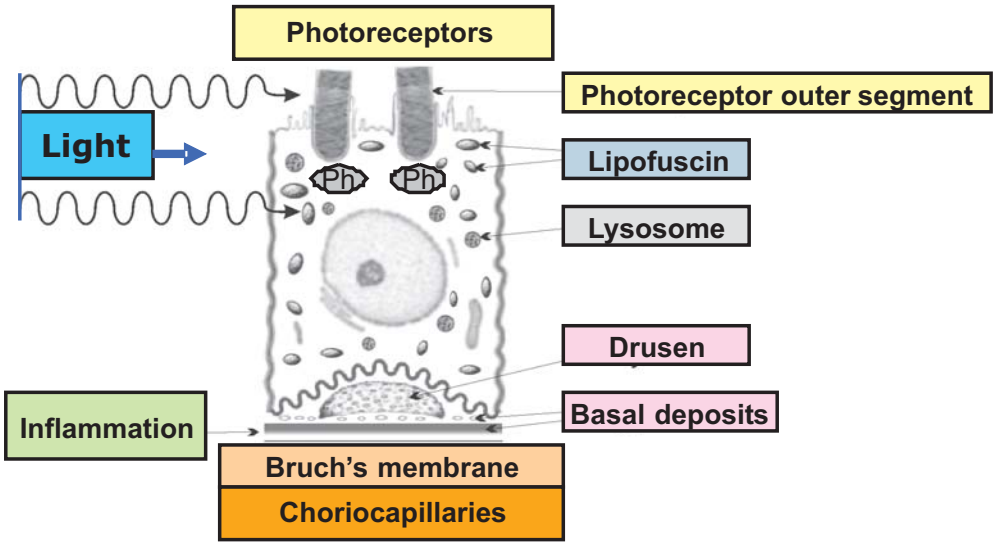

Fig. 2. Morphological and functional aspects of the retinal pigment epithelial (RPE) cells in the course of ageing and the development of age-related macular degeneration. The indicated structures/organelles are: *phagosomes* (Ph; containing apical parts of photoreceptor outer segments that will undergo enzymatic digestion within phagolysosomes); *lysosomes* (containing an array of lytic enzymes, including catepsines); *lipofuscin* granules (which represent incompletely degraded membrane material and waste products; lipofuscin is a hallmark of ageing, accumulating in various postmitotic cells, including RPE); *basal deposits* (they occur in two forms as basal laminar deposits and basal linear deposits; they represent mostly non-degraded material extruded from the RPE cells, located between the RPE plasma membrane and the basal lamina, as well as in the inner collagenous layer of Bruch's membrane; their presence, together with progressive accumulation of lipidic deposits may decrease bidirectional conductivity of different nutrients between choriocapillaries and RPE); *drusen* (are considered the hallmark of AMD and represent aggregates resulting from accumulation of debris or waste products in the extracellular matrix between RPE and Bruch's membrane). Drusen may occur in healthy eyes, however, over years, becoming larger in size and more complex in composition, they may be a target of immune reactions with resulting *inflammation*. Light causes the isomerization of the rodopsin's chromophore 11-*cis*-retinal to all-*trans*-retinal and triggers the visual cascade (phototransduction) in photoreceptors; light (especially in blue or near-ultraviolet range) also affects the photosensitive lipofuscin constituents (e.g., A2E) in RPE thus upon photoexcitation stimulating the generation of cytotoxic free radical species which is the process being of importance in the pathogenesis of AMD

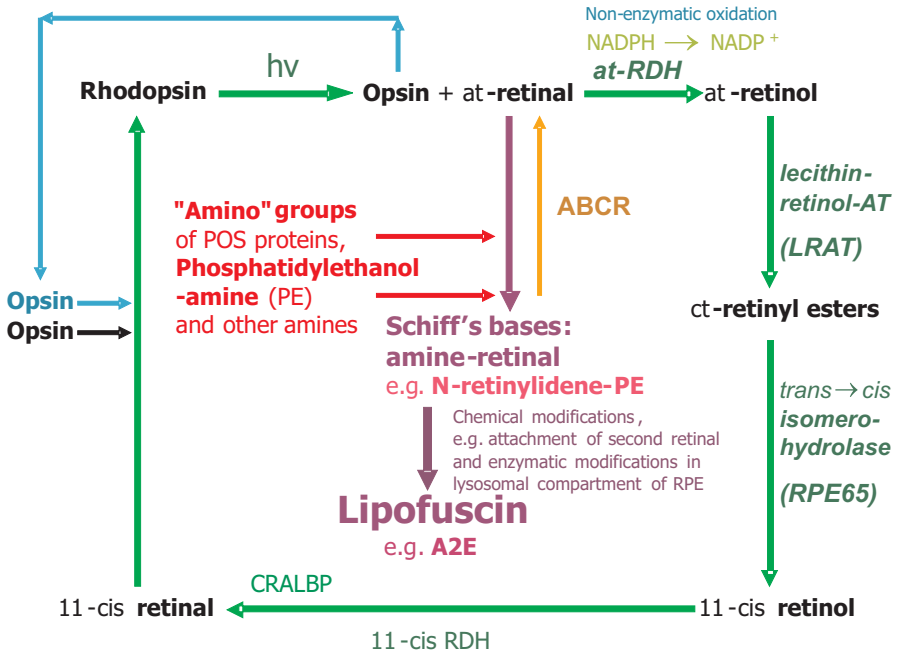

Fig. 3. Molecular events underlying lipofuscin formation in the retinal pigment epithelial (RPE) cells. At least some of highly photocytotoxic components of lipofuscin (e.g., A2E; N-retinylidene-N-retinyl-ethanolamine) are formed from all-*trans*-retinal – *via* a Schiff's base reaction product (e.g., N-retinylidene-phosphatidylethanolamine) – as by-products of the visual cycle. Removal of all-*trans*-retinal from the lipofuscin-directed pathway may be facilitated by an ATP-binding cassette transporter (ABCR), mutations of which can result in faster accumulation of lipofuscin granules within the lysosomal compartment of the RPE, thereby increasing the risk of AMD development

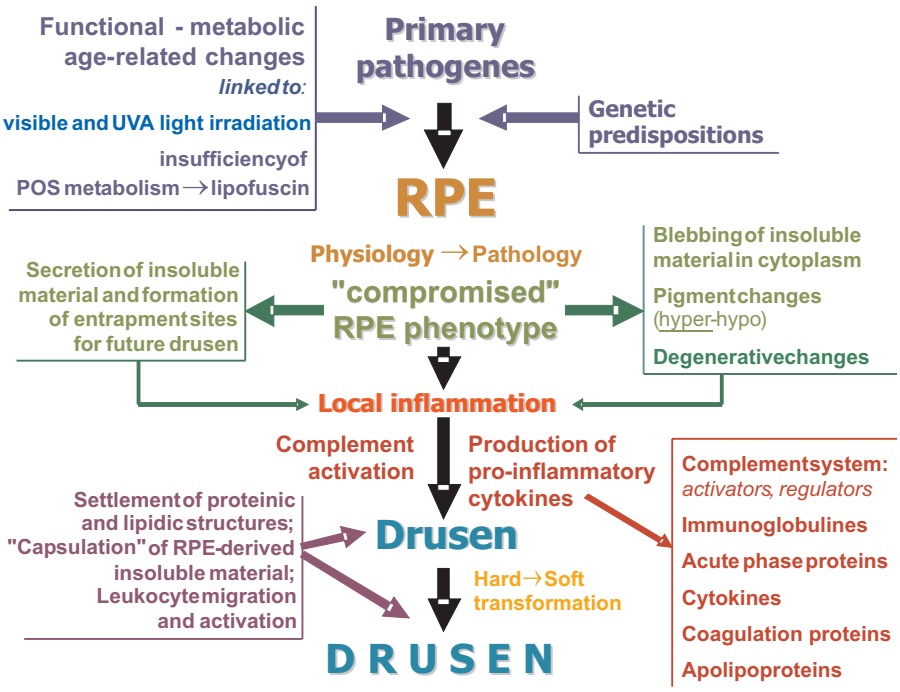

Fig. 4. Schematic representation of drusogenesis. Note that drusogenesis is a complex and multifactorial process, with genetic predispositions, environmental and dietary influences, and age-related metabolic malfunctions affecting primarily RPE. The resulting "compromised" phenotype of RPE can be considered a crucial initiatory factor driving slowly – from the very beginning over years – a series of processes, including immune reactions, leading to the formation of drusen, first small in size "subclinical" structures, and then larger in size (both "hard" and "soft" drusen) with resulting overt pathology. It is thought that drusen-related inflammatory process creates a molecular milieu for choroidal neovascularization (see Fig. 5)

tions [14], the presence of numerous larger (≥ 125 μm) hard drusen, and especially soft drusen (≥ 125–250 μm) in the macula is considered – particularly when accompanied by pigment irregularities or depigmentation – a major risk factor for developing the advanced forms of AMD, including the exudative-neovascular form and the loss of central vision. In fact, it was shown that degenerative changes, with either impending or executed photoreceptor cell death, occur in populations of photoreceptors overlying drusen (with a tendency to extend laterally to drusen) of all sizes, including small subclinical structures (< 63 μm) [1, 7, 14]. Drusogenesis is a complex and multifactorial process (see Fig. 4) taking place slowly over many years, and the idea is that the negative impact of the forming drusen on overlying (and neighbouring) RPE/photoreceptor cells relies not only on the physical displacement of the RPE monolayer and photoreceptors by them, but also on their indirect influence, most probably *via* the activation of the immune system and local inflammation [2, 41, 42]. Proteomic and immunohistochemical analysis of drusen has revealed many protein constituents, including – in addition to RPE remnants – a number of immune-associated elements/molecules, such as dendritic cell processes, immunoglobulins, class II antigens, and components of the complement cascade, e.g. activators, inhibitors (notably complement factor H, CFH), activation-specific complement fragments, and terminal pathway components, including the membrane attack complex (MAC; C5b-9), the latter being lethal not only to foreign pathogens but also to local host cells and tissues (such as RPE, photoreceptors, and other ocular structures) [2, 12, 25, 41]. The complement system is the key element of the innate immune system in host defense [17, 59]. It seems likely that local inflammation and activation of the complement cascade, with uncontrolled generation of MAC, may actively contribute to drusogenesis, RPE/photoreceptor degeneration, and Bruch's membrane disruption (associated with a late-stage neovascular AMD) (Fig. 4) [2, 25, 41]. Recent genetic studies, first published in 2005, proved that a tyrosine → histidine exchange at amino acid 402 (Y402H) of the CFH gene localized to chromosome 1 (1q31) markedly increases the risk of developing AMD [6, 30]. This would be in line with what is known about CFH physiological role [17, 59]. As CFH prevents uncontrolled complement activation and inflammation, its mutation is thought to increase inflammation and its consequences. Although our knowledge of AMD-promoting factors becomes broader and deeper, many important details at molecular and cellular level still remain unexplained. An extensive discussion of the process of drusogenesis, emphasizing the role of inflammation and immune reactions, was presented previously [41, 42].

Choroidal neovascularization

The adult retina is a neural tissue with high metabolism and the highest oxygen consumption per unit weight of all human tissues; it is vascularized by two independent circulatory systems: the choroid and the retinal vessels. The retinal system, whose vessels penetrate as far as the outer plexiform layer (and thus are visible through the pupil), supplies oxygen and nutrients to the inner two-thirds of the retina. The outer third part of the retina physiologically remains completely avascular – yet it receives necessary nutrients and oxygen *via* the choroidal system (which is more difficult to visualize because it is partially obscured by the pigment of the RPE). Eyes with the choroidal (or subretinal) neovascularization (CNV) in the macular region can have widely varying degrees of distortion and scotomata. New vessels usually bleed and form dense macular scars. Due to weak, curled, and leaky vessels, the CNV is a major cause of visual loss in AMD [10, 13, 14].

Under normal conditions, endothelial cells lining blood vessels are resistant to neovascular stimuli, and negligible endothelial cell proliferation takes place in the retinal vessels. Such cells are relatively "silent", due to a balance between pro-angiogenic (e.g. vascular endothelial growth factor, VEGF) and anti-angiogenic (e.g. pigment epithelium derived factor, PEDF) factors. In order to stimulate the process of angiogenesis in any case, including CNV, the angiogenesis-linked molecular machinery must be disbalanced in a way promoting functional overactivity of pro-angiogenic signaling (e.g. VEGF > PEDF). This may result from either an unbalanced increase in pro-angiogenic (e.g. VEGF) activity or an unbalanced decrease in anti-angiogenic (e.g. PEDF) activity [8, 13, 37, 39, 43]. In reality, the process of neovascularization is a complex interplay between numerous stimulators and inhibitors, usually being under speci-

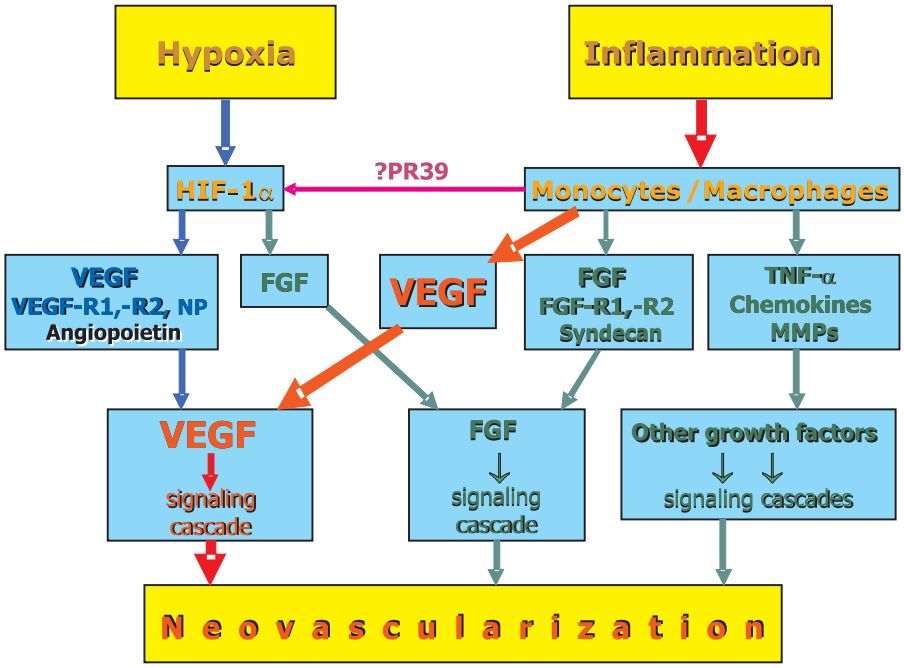

Fig. 5. Established and possible mechanisms leading to the choroidal neovascularization (CNV). A still unanswered question concerns the trigger factor (hypoxia or inflammation, or both) of the process of CNV. Although the role of a local hypoxia cannot be decisively excluded, recent evidence suggests that immune reactions and inflammation may play a predominant role in the development of the wet (exudative) form of age-related macular degeneration (AMD), by creating cellular and molecular milieu promoting the proangiogenic mechanisms. The main stream of molecular events seems to be as follows: local inflammation → monocytes/macrophages/neutrophils → VEGF → VEGF-R2 (and related signaling) → neovascularization. A proangiogenic role of other growth factors (e.g., FGF, TNF-α, PlGF, PDGF) or angiopoietin, may also contribute to the development of CNV. Possible, although not proven in ocular angiogenesis, is a role of a peptide PR39 which, being synthesized by e.g. monocytes, is capable of inducing the VEGF expression in a HIF-1α-dependent manner; such a mechanism could additionally stimulate VEGF expression *via* the "hypoxic" pathway. Abbreviations: HIF-1α – hypoxia-inducible factor-1α; VEGF – vascular endothelial growth factor; VEGF-R1, -R2 – receptors of VEGF; NP – neuropilin; FGF – fibroblast growth factor; FGF-R1, -R2 – receptors for FGF; TNF-α – tumor necrosis factor; MMPs – matrix metalloproteinases; PlGF – placenta growth factor; PDGF – platelet-derived growth factor; R39 – a proline- and arginine-rich peptide with 39 amino acids

fied control systems [10, 13, 43]. As for retinal neovascularization, hypoxia or ischemia (which is an effective initial stimulus leading to the up-regulation of growth factors, e.g. VEGF, integrins and proteinases), may play a role in the development of CNV as well (Fig. 5) [10, 13, 21]. However, despite many similarities in the pathways leading to the retinal and choroidal neovascularization, there are some major differences between these two types of angiogenesis. Current view suggests that in the initiation and development of CNV, there may be a role for local inflammation together with immune reactions as a process creating cellular and molecular milieu promoting the prevalence of pro-angiogenic mechanisms (Fig. 5); in fact, neutrophils, macrophages, mast cells, activated microglia, all are capable of producing and releasing an array of pro-angiogenic factors, including VEGF [2, 13, 25]. Figure 5 schematically depicts major established and possible factors/events initiating and leading to neovascularization (CNV). Whichever mechanism underlies the development of CNV [8–10, 13, 39], recent findings confirm the role of VEGF and PEDF as important regulators engaged in CNV, and this fact has already its impact on establishing therapeutic strategies to combat the existing or to prevent the development of newly formed unwanted blood vessels.

Therapy

Although the symptomatology of AMD is relatively straightforward, there are evidently many various pathogenetic factors underlying the disease. Therefore, it cannot be excluded that this clinical entity embraces in fact a constellation of diseases with different, mostly undefined causes. For this reason, available therapies are not causal treatments but generally,

they help to avoid further vision loss rather than to improve vision. None of up-to-now used treatments can "cure" the disease or reverse its course. Taking into account the extensive research that is under way to define environmental influences as potential risk factors, as well as to define the disease process at a molecular, genetic and cellular level, there is a hope that future treatments will offer more promise.

Currently, there is no established effective treatment for the dry-form AMD, and most current therapies and new investigational treatments are directed at CNV. There are the following established medical treatments, including anti-angiogenesis approaches:

– Photodynamic therapy (PDT; another abbreviation used by ophthalmologists for this kind of therapy is TAP – the Treatment of AMD with PDT) using an intravascular photosensitizer verteporfin (a benzoporphyrin derivative monoacid, BPD; Visudyne) and low energy visible red laser (689 nm) applied locally in order to activate verteporfin with a subsequent transfer of its energy to molecular oxygen, resulting in the formation of highly reactive singlet oxygen capable of producing direct damage of endothelial cells. Currently, PDT is a widely used treatment with generally good therapeutic output [21, 35]. Despite its acceptance by physicians (who consider it an important treatment choice), verteporfin-based PDT represents only a palliative therapy, as it temporarily stabilizes the existing leaky blood vessels, but does not prevent the formation of new abnormal vessels that will eventually leak and cause disease progression. According to the latest findings, PDT (with verteporfin) may stimulate in at least some situations the expression of VEGF, an unpredictable effect which validates the usefulness of a combination therapy involving PDT and some newer agents, for example an additional anti-VEGF co-treatment [26, 49].

– **Thermal laser photocoagulation** (TLP) uses an argon laser (or other laser in the visible light spectrum). Before the advent of PDT, it was the only well-established and widely accepted treatment for classic CNV secondary to AMD. TLP is simple and relatively inexpensive, being suitable for elimination of extrafoveal vessels/lesions [21].

– Transpupillary thermotherapy (TTT) uses a long-pulse 810 nm near-infrared diode laser which closes CNV *via* still unknown mechanism (the procedure is expected to locally rise temperature by 10°C on target tissue) [21]. It is an inexpensive and one of the few treatments available for occult CNV.

– **Anti-angiogenic agents** that attempt to block various steps in the pathway of angiogenesis in CNV; they include:

• **Pegaptanib sodium** (Macugen) – an aptamer; a pegylated modified RNA oligonucleotide of 28 bases in length that binds with a high affinity (in the picomolar range) to the major VEGF isoform, $VEGF_{165}$. A number of randomized, double-blind trials have recently been published, showing Macugen (tested in various doses up to 3 mg/eye) to be capable of producing a statistically significant and clinically meaningful benefit in the treatment of neovascular AMD. Interestingly, dosages above 0.3 mg were not found to confer any additional benefit. In December 2004, the FDA approved Macugen to slow vision loss in eyes affected by all subtypes of neovascular AMD, with a recommended dose of 0.3 mg administered intravitreally once every 6 weeks [16, 29, 37].

• **Bevacizumab** (Avastin) – a 149 kDa full-length anti-VEGF-specific recombinant humanized murine monoclonal antibody (rhumAb-anti-VEGF antibody) binds to all isoforms of VEGF-A. It is the first approved by the FDA antiangiogenesis-specific agent for cancer patients, originally recommended as a first-line treatment for patients with advanced, metastatic, colorectal cancer, preferably in a conjunction with standard chemotherapy (FDA, February 2004) [22, 24]. The recommended dose of Avastin (bevacizumab) is 5 mg/kg given once daily every 2 weeks as an intravenous infusion (*iv*). Bevacizumab, 5 mg/kg *iv*, has also been tested in neovascular AMD and in CNV secondary to pathological myopia, with a generally positive therapeutic outcomes (improved visual acuity and reduced, or even blocked leakage from CNV) [36, 38]. The first clinical trials of intravitreally applied bevacizumab (Avastin) at a dose of 1 mg or 1.25 mg (on a monthly basis) in neovascular AMD patients have already been conducted, and the results, although preliminary, are promising (an improvement in visual acuity, decreased macular thickness, reduction in angiographic leakage in most patients) [4, 45]. Although bevacizumab was not approved for ophthalmological neovascular diseases, it is available on the market, and thus can be used on an off-label basis. A commercially available bevacizumab (25 mg/ml sterile solution) can be utilized for neovascular AMD as a ready-for-use solution in a volume of 50 µl/eye which is equivalent to 1.25 mg dose [4, 45].

• **Ranibizumab** (rhuFab V2; Lucentis) is a 48 kDa fragment of a humanized murine anti-VEGF antibody

active against all isomers of VEGF; the drug is prepared for intravitreal infusion [18, 29, 37]. In fact, ranibizumab is one-third in size of the full-length antibody, i.e. bevacizumab, which as tested in rhesus monkey's eyes following its intravitreal administration, readily penetrates all layers of the retina [19]. Of the tested doses (0.05–2 mg/eye) the maximum tolerated single dose in neovascular AMD patients was 0.5 mg. Repeated, monthly, intravitreal injections of ranibizumab had a good safety profile, and were associated with improved visual acuity and decreased leakage from CNV [19, 46]. It is suggested to be used in combination with PDT [26]. Ranibizumab is not approved by the FDA to date.

• **Anecortave acetate** (Retaane) – a novel steroid (a synthetic cortisone chemically modified into cortisene) devoid of glucocorticoid activity with a potent anti-angiogenic potential (it inhibits the proteolysis required for vascular endothelial cell migration, thereby inhibiting ocular neovascularization) [21, 37, 48]. Anecortave acetate as a slow-release depot suspension may be delivered at a dose of 15 mg as an extraocular (juxtascleral; sub-Tenon retrobulbar) injection at six-month intervals. Retaane has not final FDA approval yet.

• **Triamcinolone acetonide** – an intravitreal treatment option for various intraocular edematous and proliferative disorders. In most studies the drug was used at a dosage of 4 mg/injection, although in some centers the tested dosage equaled 20–25 mg. Triamcinolone acetonide may be helpful as an adjunct therapy for exudative AMD, possibly in combination with PDT [3, 21, 23, 37].

• **Squalamine lactate** (Evizon) – a naturally occurring steroidal compound conjugated to spermidine at position C-3. Its mechanism of antiangiogenic action remains to be explored, yet it seems to inhibit the membrane Na^+/H^+ exchanger and to function as a calmodulin chaperone, which finally leads to suppression of endothelial cell proliferation [44].

New potential anti-VEGF therapeutics being still under investigation include:

• **Sirna-027** (small interfering RNA, siRNA) – specifically targeting VEGF-R1; it caused significant reduction of VEGF-R1-mRNA and significantly suppressed CNV and retinal neovascularization [29, 37, 50].

Cand5 is another drug in the siRNA series; its target is VEGF-mRNA [29].

• **VEGF-Trap** (VEGF-$Trap_{R1R2}$; soluble decoy receptor) – a high-affinity "antagonist" of VEGF consisting of the Ig-2 domain of VEGF-R1 receptor and Ig-3 domain of VEGF-R2 receptor, fused to the Fc fragment of IgG1; it binds all isoforms of VEGF-A (but not VEGF-C or VEGF-D), as well as placenta growth factor (PlGF) [29, 31, 37, 47].

Endogenous anti-angiogenic factors that can be used as possible future therapeutics include:

• **angiostatin**, **endostatin**, and **PEDF** [9, 11, 29, 37]. An obvious positive feature of PEDF is its additional neuroprotective potential [5], which may be clinically advantageous. PEDF undergoes already clinical trials as adenoviral vector-delivered agent (AdPEDF.11) applied intravitreally offering a promising therapy for antagonizing CNV [11].

Additional therapy – antioxidant supplementation

In addition to the currently used and forthcoming-future treatments, a short notice should be given to so-called preventive category of treatments. Tobacco smoking is a consistently identified a preventable AMD risk factor; thus, its elimination should be one of the first and principal therapeutic recommendations. Preventive treatments also include dietary supplementation with antioxidants and minerals, such as vitamin E (α-tocopherol) and C (ascorbic acid), zinc, glutathione, and especially macular carotenoids, such as lutein and zeaxanthin [20, 56, 57]. Lutein and zeaxanthin, being present in photoreceptors and RPE cells, are physiological pigments which absorb light in the blue-green region of the visible spectrum (serving as a filtering apparatus for light), likely playing a double role: to improve visual function and to act as an antioxidant to protect the macula from damage by oxidative stress [15, 32]. According to the latest data [27], lutein and zeaxanthin are capable of quenching singlet oxygen (being more effective than α-tocopherol in this respect) and suppressing lipofuscin pigments (e.g. A2E) photooxidation, showing a protective potential against harmful photooxidative processes taking place in the course of lipofuscinogenesis with its impact on AMD development. Lutein and zeaxanthin are not synthesized within the body and, therefore, they have to be provided by dietary intake [56]. Although dietary supplementation with antioxidants as a supportive (or preventive) treatment in AMD seems reason-

able (yet, more experimental data and especially randomized controlled clinical trials are needed to support their real therapeutic value), its composition in terms of a single- or multiple-drug formula (lutein and/or zeaxanthin and/or vitamin E, etc.), as well as dosing of particular drug/s, requires scientific and practical verification, as well as standardization, for at least two reasons: numerous antioxidant formulas, containing individual drugs/minerals or their various combinations (including antioxidant plant extracts), are widely available as over-the-counter non-prescription preparations, and there are various, sometimes not entirely correct market (pharmaceutical company- and/or mass media-promoted) opinions on its/their therapeutic value.

A note for today and future

The results of recent studies using proteomic, immunohistochemical, and molecular biology approaches, and focussed on diseases of aging, such as AMD, Alzheimer's disease, Parkinson's disease, atherosclerosis, glomerular basement membrane disease (glomerulonephritis type II), elastoses or amyloidoses, generate an intriguing picture pointing out their common feature – the buildup of extracellular deposits (containing many shared molecular constituents) that contribute to their pathogenesis and progression [2, 17, 34, 59]. In all the mentioned diseases there is an association to the local activation of pro-inflammatory pathways, thereby leading to concurrent deposition of activated complement components, acute phase reactants, immune modulators, and other inflammatory mediators. Thus, an emerging concept for today, and especially for near future, would be to design a therapeutic strategy with which to both counteract the generation of cytotoxic intra- and extracellular deposits and to prevent inflammation. Such a strategy is highly needed in the case of AMD, as currently used therapies are only poorly effective.

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