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Submacular tissue repair and fibrosis in neovascular macular degeneration: A predictable outcome secondary to a chronic age-related endotheliopathy

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Fibrosis is strictly a histopathological term that refers to the replacement of functional tissue with permanent deposition of nonfunctional extracellular matrix (ECM), following an injury or disease, and can occur in any tissue in the body. In this histological setting, there is no overt difference between fibrosis and scarring. However, in the clinical context, fibrosis tends to be associated with chronic disease, as it ensures ongoing ECM deposition. This could be considered "excessive" when compared to ECM deposition in acute or end-stage chronic disease. This perspective highlights how fibrosis in neovascular age-related macular degeneration follows a stereotypical tissue repair process similar to that seen in other tissues and how salient biologic processes, such as aging and metabolic health, impact fibrosis development. In addition, we highlight the emerging and pivotal profibrogenic role played by progressive endothelial cell (EC) dysfunction, together with secondary blood flow impedance in the neovasculature. This results in abnormal vascular permeability, endothelial-to-mesenchymal transition, and EC senescence-associated secretory phenotype, processes that could potentially be targeted therapeutically. Finally, the dramatic impact of anti–vascular endothelial growth factor therapy, by primarily targeting permeability of the nascent microvasculature, on the natural history of fibrosis in neovascular age-related macular degeneration indirectly highlights the potentially significant role of ECs in fibrosis development and points toward how novel future targeting of these cells could further modulate the development of fibrosis.

The challenge of defining fibrosis: In recent years, fibrosis has gained traction as a therapeutic target in neovascular age-related macular degeneration (nAMD). In the strictest sense, fibrosis is a histopathological diagnosis that refers to the permanent deposition of extracellular matrix (ECM; predominantly collagen and elastin) and can occur in virtually any tissue in the body as a result of an injury, usually altering the structure or function of that tissue [1]. In this context, many authors include "excessive" ECM deposition in their definition, implying that fibrosis is pathological and different from the scarring associated with normal tissue repair [2]. Because humans are incapable of tissue regeneration (the ability to replace damaged tissue with identical functioning tissue) ex utero following a significant disease, fibrosis in this sense could be deemed pathological where there is no or only minimal restoration of tissue function.

We can further refine our understanding and definition of fibrosis by considering the clinical context in which fibrosis occurs. We can broadly classify any "fibrotic" disease as either chronic (e.g., idiopathic pulmonary fibrosis [IPF], alcoholic or nonalcoholic fatty liver disease, chronic renal fibrosis) or acute (e.g., following myocardial infarction). This differentiation is crucial as it is the chronicity of disease that explains why the fibrotic event can be inevitable, progressive, and potentially destructive (IPF) or both self-limiting and essential to preserve life and thus protective (as in the acute situation [myocardial infarction]). In short, fibrosis is inevitable and can be considered part of a stereotypical healing response irrespective of the tissue involved. Its pathological consequences are dependent on whether the disease is acute or chronic. Both imply the replacement of diseased "normal" tissue with fibrotic matrix, but only in chronic disease (in which the injury persists) is fibrosis progressive, as the disease spreads to involve newly injured adjacent tissue.

Fibrosis and aging: Fibrosis can occur at any age, but it is generally accepted that both risk and severity of fibrosis increase with age. Biologic aging affects all cells in the body, leading to both stromal and immune cell telomere attrition, epigenetic alterations, defective proteostasis, mitochondrial dysfunction, and others [3]. Aging also promotes immune and stromal cell senescence, stem cell exhaustion, and "inflammaging" (the process of an age-related elevation in inflammatory markers in the absence of an overt immunological trigger). In addition, age-related remodeling of the ECM alters its mechanical properties [4-11]: excessive collagen

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production, lysyl oxidase–induced abnormal crosslinking of collagen fibers, and compromised tissue elasticity lead to shifting the local tissue environment from one that supports normal cell function to one that promotes disease progression [12,13]. The net result of these changes to the ECM structure and properties is the entrapment of immune cells and growth factors within the matrix, altered adhesion, migration and proliferation of myofibroblasts, and ultimately reinforcement of the fibrotic feedback loop [14].

Clinically, it is the impact of age through these age-related effects on the fibrotic process that can make fibrosis "pathological." Coupled with the diseases of aging, themselves characterized by chronicity (e.g., dementia, age-related macular degeneration [AMD], atherosclerosis, and osteoarthritis), fibrotic lesions tend to be larger as the pathological process spreads to involve injured/diseased adjacent tissue that must be "plugged" by fibrous deposition, a process that is already compromised by aging.

In the retina, compare, for example, the natural history of myopic choroidal neovascularization (CNV) and CNV in nAMD before the advent of anti–vascular endothelial growth factor (VEGF) therapy: in myopic CNV, the end-stage fibrotic lesion (Forster-Fuchs spot) is usually smaller than in nAMD, and recurrent CNV is unusual in a setting of myopia [15]. When CNV develops in the context of pathological myopia in younger patients, the lesions are smaller because of a more efficient wound-healing process [15]. The visual outcomes of myopic CNV are also influenced by age, with younger patients showing better outcomes both with and without treatment [16]. In contrast, in nAMD, the overall lesion is larger and takes longer to heal probably due to age-related poorer healing abilities (antagonistic pleiotropy; see next section) but also because the lesion continues to grow to involve adjacent diseased areas within the macula [17]. It is noteworthy that myopic CNV lesions, when occurring in elderly patients, tend to be similar in size to lesions seen in nAMD, absent the diffuse thickening of Bruch's membrane, the presence of drusen, and pigment epithelial detachments, the hallmarks of AMD [18,19]. This further underscores the different response elicited in an aged individual.

Fibrosis, senescence, and antagonistic pleiotropy: The decline in an individual's ability to execute optimum repair due to age can be explained by a process called antagonistic pleiotropy [20,21]. In short, antagonistic pleiotropy is an evolutionary theory to explain the rationale of biologic senescence in vertebrates. It argues that enhanced fitness in early life (up to reproductive maturity) is ensured at the expense of a trade-off in later life, when there is an age-related somatic decline as a protective fail-safe mechanism against the development of cancer. In short, the trade-off for a reduced cancer risk in later life is compromised tissue repair as we age. Moreover, the theory posits that this fail-safe mechanism is activated by the process of telomere shortening, which limits cellular proliferation (Hayflick limit) with increasing age [22,23]. The consequence of this antagonism is a progressive decline in tissue structure and, by extension, tissue function (referred to as epigenetic/histological entropy). Arguably, nowhere is this more apparent than in tissue repair, which requires both robust cellular proliferation and optimal tissue structure for optimal executive function. Thus, we can posit that the biologic consequence of antagonistic pleiotropy in tissue repair is not only excessive but also more disordered fibrosis with age.

Antagonistic pleiotropy may also explain why observations in in vivo experimental models of disease almost always translate poorly to the clinic [21]. Essentially, laboratory breeding protocols for rodents are optimized to increase reproductive output, the consequence of which is the strong selection against reproductive senescence, which simultaneously eliminates selection that would favor tumor suppression. This is confirmed by the elongated telomeres noted in laboratory mice (making them in effect "superhealers"), thus making these animals suboptimal models for the study of age-related senescence and cancer and, by extension, tissue repair and fibrosis in aging.

Fibrosis and metabolic health: In terms of longevity, a desirable aspiration at the end of life is for our health span (the number of years someone is healthy without chronic and debilitating disease) to equal our natural life span (the total number of years we live). In biologic terms, this translates into good metabolic health and a functioning, robust immune system, the combination that ensures tissue homeostasis throughout life [5]. Both these systems are tightly coordinated and codependent. The hallmark of metabolic dysfunction is the generation of pathological oxidative stress (physiologic oxidative stress is essential for life) that generates tissue damage at the cellular and subcellular levels. The intracellular processes that mitigate oxidative damage are the antioxidant defense system, autophagy, and the unfolded protein response [24-27]. Meanwhile, the immune system, through the generation of tissue-specific inflammatory responses, also provides essential housekeeping and reparative executive functions. With age-related stromal senescence, both the metabolic and the reparative demands grow steadily, adding increasing pressure on both intracellular protective pathways and the immune system, which is itself aging (immunosenescence) [28]. The systemic manifestation of this rise in workload on the immune system is the progression from basal, to para-,

and to chronic inflammation that occurs with increasing age, hence the term *inflammaging* [29-31]. When the intracellular compensatory pathways become overwhelmed and the immune system can no longer cope with the reparative demands, then age-related chronic disease is the inevitable result [29]. The progressive clinical manifestation of this combined failure of metabolic health and the immune system is exemplified by the development of insulin resistance, as well as the progression to metabolic syndrome and eventual type 2 diabetes [32]. This is probably the single most significant factor today in explaining the expanding gap between life span and health span in the developed world [33]. In other words, we can speculate that lifestyle choices such as poor diet, sedentary behaviors, and smoking in genetically predisposed individuals progressively compromise metabolic health, imposing such an additional reparative burden on the finite resources of the immune system that the chronic age-related diseases (Alzheimer disease, AMD, atherosclerosis, osteoarthritis, and cancer) are inevitable consequences [5]. An additional consequence of this immune failure is chronicity of the tissue repair response and, therefore, additional profibrotic tendencies [34]. Moreover, the normal decline in cellular respiration secondary to age-related mitochondrial dysfunction will further hinder the reparative response [35].

Fibrosis in nAMD: The emerging and pivotal role of endothelial cells: The conventional paradigm around the pathogenesis of fibrosis in nAMD is that it results from a progressive, aberrant, exaggerated, and ultimately destructive wound-healing response, leading to excessive ECM deposition by myofibroblasts. However, as outlined in the foregoing sections, we could argue that fibrosis is inevitable due to aging: a physiologic response to injury with a pathological outcome consequent to aging. Immune and stromal senescence in a setting of recurrent/persistent injury (lifestyle and environmental factors) confers a chronic disease state in genetically predisposed individuals (Figure 1).

The actual source of myofibroblasts appears varied, but it is generally accepted that they mainly derive from the process of the epithelial-to-mesenchymal transition, with the most obvious source being the retinal pigment epithelium. However, there is also the recognition that endothelial cells (ECs; through the endothelial-to-mesenchymal transition [EndMT]), macrophages (through macrophage-to-mesenchymal transition [MMT]), pericytes, and even bone marrow–derived cells all have the capabilities to transition to myofibroblasts [36]. It is beyond the scope of the current review to delve individually into what is known about the role of these respective cells, but for a detailed review, see [36]. Here, we focus not only on the evidence that it could be the humble EC that is the driver and master regulator of the entire fibrotic process but also on how these cells could be targeted therapeutically.

It is an interesting observation that the presence of a new microvasculature appears to be both ubiquitous and essential for the development of fibrosis in nAMD, thus begging the question of its potential role in the profibrotic mechanism. This is vitally relevant when considering the therapeutic approaches. In other words, it is the presence of ECs that differentiates fibrosis in nAMD (strictly chronic ECM deposition secondary to fibrovascular proliferation) from fibrocellular disease seen, for example, in proliferative vitreoretinopathy or epiretinal membrane formation. In these latter examples, the pathobiology is driven by the dedifferentiation of cells to a fibroblastic phenotype, whereas in nAMD, the invasion of the neurosensory retina (NSR) by ECs is a prerequisite for fibrosis development [37]. Another curious aspect of fibrovascular tissue development in acquired retinal disease is the observation that violation of a basement membrane (BM) seems an additional prerequisite to generate the fibrosis phenotype (in nAMD, the retinal pigment epithelium BM, and proliferative diabetic retinopathy, the inner limiting membrane that contains the BM of the Müller cells). Even in retinal angiomatous proliferation, it is noteworthy that there seems to be an absence of fibrovascular tissue development until the anastomotic communication is established between the retinal angiomatous proliferation lesion and emerging subretinal blood vessels from the choroid, at least in eyes treated with anti-VEGF therapy [38]. Thus, there seems to be something inherently pathological about the violation of the BM and the development of fibrovascular tissue. We can speculate that violation of this BM permits access/activation of myofibroblast precursors into the NSR, which, in combination with neovessels, gives rise to the respective phenotypes observed in both nAMD and proliferative diabetic retinopathy.

Of course, one of the defining features of nAMD is the development of vascular permeability from immature neovascularization. The resulting exudation that includes fibrinogen (a precursor of fibrin), thrombin, fibronectin, and proinflammatory and lipid mediators stretches the NSR, inducing a type of pathological tissue “stiffness” of the ECM. This initiates a wound-healing response that includes the liberation of latent tissue transforming growth factor β from cryptic locations within the ECM [39]. Thus, it is plausible that tissue stiffness secondary to abnormal neovascular permeability could ultimately be the initiating event leading to the eventual recruitment of myofibroblasts and thus permanent matrix deposition [40,41].

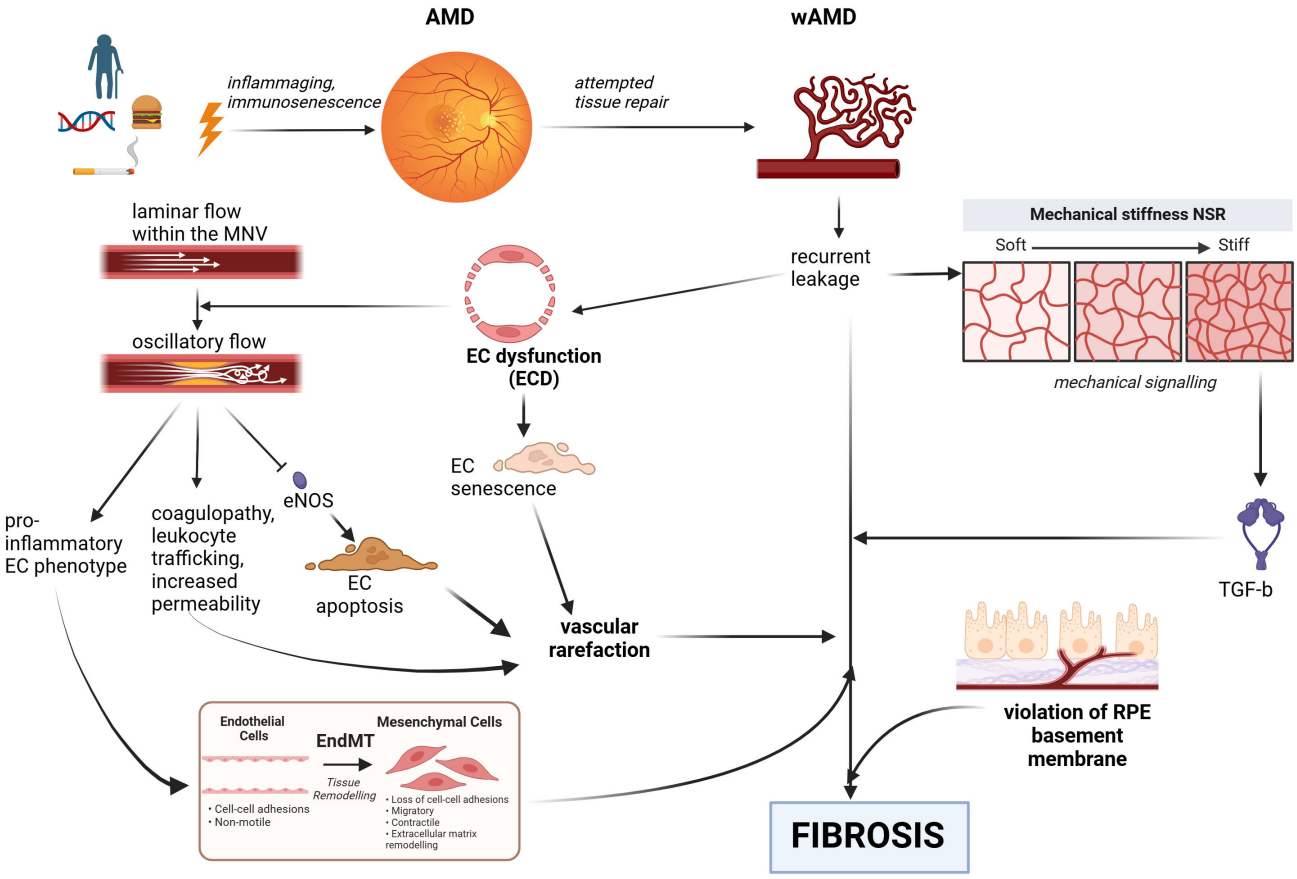

Figure 1. Endothelial cell-mediated pathway leading to fibrosis in neovascular age-related macular degeneration (nAMD). A combination of factors, including aging, lifestyle, and genetic predisposition, causes an injury that leads to AMD. In some cases, a reparative attempt, which includes the generation of new vessels that penetrate the retinal pigment epithelium/Bruch's membrane complex (choroidal neovascularization [CNV]), is initiated. Abnormal vascular permeability induces abnormal blood flow (oscillatory instead of laminar flow), resulting in oscillatory shear stress that has several consequences [1]: a change in the stiffness of the extracellular matrix of the neurosensory retina (NSR), which leads to a mechanical signaling that includes liberation of cryptic transforming growth factor β (TGF-β), a profibrotic growth factor [2], and inactivation of endothelial nitric oxide synthase (eNOS) that generates endothelial cell dysfunction (ECD), leading to fibrosis through several pathways, including a proinflammatory EC phenotype, increased generation of oxidants in the presence of decreased antioxidants, coagulopathy, increased leukocyte trafficking, EC senescence (producing a senescence-associated secretary phenotype [SASP]), apoptosis and endothelial to mesenchymal transition (EndMT), and ultimately fibrosis and vascular rarefaction. Created in BioRender. Garcia Armendariz, B. (2025).

Another consequence of vascular permeability is the development of endothelial cell dysfunction (ECD) [42]. Laminar blood flow and the associated laminar shear stress are considered pivotal to EC health and endothelial nitric oxide synthase (eNOS) production, while oscillatory shear stress appears pathological and leads to the inactivation of eNOS [43-45]. The consequences of this alteration in blood flow are multiple and include a proinflammatory EC phenotype, downregulation of antioxidant defensive systems, increased mitochondrial superoxide production, and upregulation of the proinflammatory activator protein 1 and hypoxia-inducible factor 1α [46-48]. The resultant ECD, in turn, precipitates further defective permeability, coagulopathy, and leukocyte trafficking [49]. Ultimately, the ECs secrete an abundance of profibrogenic factors, cause downregulation of matrix metalloproteinases (MMPs), and promote EndMT, microvascular rarefaction, and premature EC cellular senescence [50].

In this setting of aging (stromal senescence and immunosenescence with metabolic dysfunction) and the chronic disease that is nAMD, chronic and progressive ECD can be considered an endotheliopathy (chronic EC injury) [51].

Table 1. Indirectly modulating late stage fibrogenic potential by early targeting of the neo-microvasculature in nAMD in keeping with the concept of dynamic reciprocity.

Target pathway	Objective/ Rationale
Permeability (beyond anti-VEGF)	Prevention of ECM 'stretching' and liberation of latent TGF beta Prevention of EC-induced production of abundant profibrogenic factors, downregulation of MMPs, EMT, microvascular rarefaction and premature cellular senescence. Promoting laminar flow and eNOS production Prevention of EC injury (leukocyte trafficking, recurrent leakage, coagulation)
Vascular maturation	Reduce permeability/neutralize hypoxia and therefore is another mechanism to target the downstream consequences of vascular permeability [58] Restoration of laminar blood flow Restoration of eNOS production Prevention of EC injury and apoptosis
Senescent ECs	Improved immune surveillance, elimination/reduction of SASP
Endothelial cell dysfunction (ECD)	Prevention of premature EC senescence Prevention of EndMT Prevention of vascular rarefaction
EC-associated vascular niche/ angiocrine factors	Promotion of vascular normalization in tissue repair/fibrosis

AMD, age-related macular degeneration. ECD, endothelial cell dysfunction. ECM, extracellular matrix. EMT, endothelial to mesenchymal transition. eNOS, endothelial nitric oxide synthase. MMPs, matrix metalloproteinases. SASP, senescence associated secretory phenotype. TGF, transforming growth factor. VEGF, vascular endothelial growth factor.

This dysfunctional EC phenotype is a shared stereotypical response to chronic EC injury that occurs across many vascular beds (both macro- and microvascular) in a variety of diseases (including diabetes, hypertension, atherosclerosis, autoimmune diseases such as systemic lupus erythematosus, and septic shock) [52].

In nAMD, choroidal endothelial cells display a similar EC phenotype and molecular commonalities, including upregulation of adhesion molecules (e.g., intercellular adhesion molecule 1, vascular cell adhesion molecule 1), downregulation of eNOS, and elevated expression of angiogenic and proinflammatory mediators (e.g., VEGF, interleukin 6) [53-55]. Framing nAMD-related choroidal endothelial cell dysfunction as a localized ocular endotheliopathy underscores its parallels with systemic vascular pathologies and may guide future therapeutic exploration beyond VEGF suppression alone.

An additional consequence of ECD and disturbed laminar shear flow-induced perturbation of eNOS is further EC injury that leads to apoptotic EC death [45]. This induces additional impedance of blood flow that contributes further to vascular rarefaction [56-58]. Vascular rarefaction is defined as the loss of capillaries or small blood vessels, resulting in reduced vascular density, a key process that occurs during the tissue-remodeling phase of scarring/fibrosis as the mature fibrotic tissue proceeds toward quiescence. By promoting rarefaction, EndMT indirectly promotes fibrosis [59]. Another likely contributor to the fibrosis puzzle is EC senescence through both stress-induced premature senescence and a senescence-associated secretory phenotype [45]. In short, progressive ECD with secondary impedance of blood flow, together with EndMT and the senescence-associated secretory phenotype, all make significant contributions to the development of vascular rarefaction and, by extension, fibrosis. Finally, with the recognition of these EC processes mechanistically driving the fibrogenic process forward, it follows that therapeutically preventing, reversing, or at least stalling these processes raises the spectrum of targeting them therapeutically (Table 1). Of note, the aim of therapy should not be to prevent fibrosis but rather to modulate it so that adequate repair can occur without compromise of the delicate outer NSR (preventing repair is inherently profibrotic) [60].

In recent years, specialized vascular niches, established by ECs, have been identified in different tissues that could also be attractive targets to modulate fibrosis in nAMD [61]. These provide a reservoir of so-called angiocrine factors that not only help maintain tissue homeostasis but also orchestrate organ repair by promoting the normalization of the neovasculature. This, in turn, reestablishes laminar flow, further decreasing vascular permeability and ultimately improving tissue perfusion (and even the efficacy of drug delivery), all key aspects that abrogate the profibrotic environment [61,62].

Directly targeting the neovasculature in nAMD is also supported by observations in renal fibrosis. Early alteration

and perturbation of the peritubular capillaries appear fundamental for the initiation of renal fibrosis. Present at the outset of the disease is the biologic ecosystem that drives fibrosis (in keeping with dynamic reciprocity: defined as the ongoing, bidirectional interaction among cells and their surrounding microenvironment). This ecosystem even precedes the activation of immune cells and myofibroblasts [63-65]. The potential therapeutic implications are clear: early targeting of the ECs to improve rheology, barrier permeability, and vessel maturation could provide the key to ultimately solving the fibrosis puzzle, making ECD the primary initiating event in a process that lasts years. Thus, it may be timely to move beyond the current paradigm of the so-called angiofibrotic switch of the epithelial-to-mesenchymal transition, MMT, and so on and simply consider angiofibrosis as a continuum, driven primarily by ECD, as a component of a tissue repair response in the aging macula, rather than a one-time switch. That anti-VEGF therapy and its beneficial effects on EC function have such a profound fibrosis-modulating effect versus the natural history of nAMD would support such a premise (see fibrosis in nAMD- lessons from the anti-VEGF era).

Fibrosis in nAMD: Lessons from the anti-VEGF era: If the deposition of ECM is required for healing, then any potential therapy must be aimed at promoting repair while modulating the fibrotic response such that there is maximal preservation of the overlying NSR. It is an immutable law of tissue repair in human adult disease that an incomplete reparative response leads to a profibrotic chronic disease status. This is why we prefer the use of the term *fibrosis-modulating* versus *antifibrotic therapy* when considering nAMD. The therapeutic challenge in mitigating fibrosis in any age-related chronic disease is therefore a formidable one, but the incredible success of anti-VEGF therapy in nAMD over the past 20 years, which has become the gold standard for nAMD, allows us to be cautiously optimistic and provides important insights on how we could proceed when considering fibrosis in nAMD.

Anti-VEGF therapy: A potent modulator of fibrosis: Prior to the anti-VEGF era, clinical recognition of the so-called end-stage disciform scar was a signature feature of the natural history of nAMD. Characterized on clinical examination and color fundus imaging by a large circular yellowish-white mound of tissue beneath the NSR with an "active" edge, it usually occupied a significant area within the temporal vascular arcades. Fast forward to the current therapeutic era, and such an end-stage phenotype has become a rarity. Essentially, the near-total absence of the typical disciform lesion points to the potent fibrosis-modulating effects, whatever the precise mechanism of action, of anti-VEGF therapy in nAMD. Yet, despite these impressive therapeutic inroads, there are still opportunities for further novel add-on therapies to modulate the fibrotic response, as the profibrotic trigger seems to be ever-present in the evolving CNV lesion despite ongoing treatment.

What is it about anti-VEGF therapy that is so impactful? As its primary mechanism of action is to inhibit permeability, we can speculate that this ultimately reduces the exposure of the delicate NSR to repeated injury from the constituents of the blood and therefore the development of fibrosis (see section: fibrosis in nAMD). In fact, the presence of hemorrhage and repeated exposure of the NSR to fluid components are some of the main risk factors for fibrosis development in nAMD [66,67]. It is also noteworthy that in nonproliferative diabetic retinopathy, there can be extensive leakage and hemorrhage into the NSR, yet no intraretinal fibrosis is observed, pointing to the requirement of BM violation (see section: fibrosis in nAMD).

We can further speculate that anti-VEGF therapy is not so much antiangiogenic in nAMD but a promoter of vascular remodeling. This phenomenon occurs in all tissue repair situations where the proliferative phase is characterized by excessive angiogenesis that remodels as repair proceeds [68]. In experimental models, anti-VEGF therapy accelerates this remodeling and effectively promotes tissue repair, thus reducing the time window for excessive fibrosis, a finding that is welcome in the context of aging [69]. Finally, as these anti-VEGF effects are specific to the nascent vasculature of the CNV, they highlight the inaccuracy of using the term *fibrosis*. In reality, what we call "fibrosis" in nAMD is a mature fibrovascular lesion, as supported by both histopathological and angiographic observations [70]. Moreover, we can speculate that ongoing anti-VEGF treatment may prevent further enlargement of the fibrotic component despite the overall enlargement of the neovascular lesion with time [71-73].

There is also some evidence that anti-VEGF therapy may have direct effects on fibrosis development, although there has not been a clear clinical answer to this question yet. It is known, for example, that VEGF promotes ECM turnover by upregulating MMPs, by stimulating fibroblast activity and enhancing production of fibronectin and collagen. By inhibiting VEGF signaling, anti-VEGF agents reduce this MMP activity, dampen fibroblast activation, and may even attenuate EndMT, collectively leading to stabilization of the ECM and suppression of excessive fibrotic deposition [55]. Additionally, VEGF blockade impacts immune–stromal interactions by limiting macrophage recruitment and inflammatory cytokine release, further reducing these profibrotic

stimuli [74]. Thus, the net result is that these additive effects may be, both directly and indirectly, blunting the overall fibrotic response in nAMD.

More recently, the first novel agent beyond anti-VEGF therapy for nAMD has been added to our therapeutic armamentarium with the approval of faricimab (F. Hoffmann-La Roche Ltd., Basel, Switzerland) [75]. This combination therapy of anti-VEGF and antiangiopoietin 2 offers greater durability and vessel stability, and therefore may translate into less fibrosis in the long-term [76]. This, together with the association of disease chronicity with both fibrosis and outer retinal atrophy, raises the tantalizing possibility of ultimately developing combination therapies that address both fibrosis and atrophy simultaneously as we embrace the next therapeutic frontier in the treatment of chronic nAMD [77].

In summary, anti-VEGF therapy reduces fibrosis indirectly (via its direct effects on the permeability process) or, potentially, directly (through ECM remodeling). In whichever case, its success supports the notion that additional fibrosis-reducing therapies should be aimed at further reducing leakage over that which is currently obtained with standard of care. Furthermore, the outcome of anti-VEGF therapy in preventing the typical disciform lesion highlights the importance of prompt and early treatment in nAMD. In other words, early intervention ensures modulation of the late-stage fibrotic phenotype. Moreover, this early therapeutic approach, as outlined in section: fibrosis in nAMD, highlights the concept of dynamic reciprocity in the therapeutic modulation of fibrosis and predicts that any fibrosis-modulating therapy should be delivered early in the disease process to ensure maximal impact on the overall fibrotic process [78,79].

Finally, the authors are not advocating a solely vascular-centric approach to modulating fibrosis in nAMD. On the contrary, and reflecting the unifying stereotypical tissue repair response to chronic injury irrespective of the organ involved (persistent fibroblast activation, ECM accumulation, transforming growth factor β signaling), it is relevant to consider other treatment strategies (either alone or in combination with anti-VEGF therapy) that are employed or under consideration in other fibrotic diseases. For example, in IPF, approved antifibrotic agents such as pirfenidone and nintedanib that slow the progression of fibrosis clinically are also under evaluation for other fibrosing conditions [80,81]. Meanwhile, exploratory gene therapy and gene editing approaches that target fibrosis in the liver and lung, which demonstrate preclinical feasibility, could be considered for modulating fibrosis in nAMD. Galectin 3 inhibitors have also demonstrated attenuation of liver fibrosis in human trials [82], while more novel modalities, including microRNA-based and enzyme/nanoparticle strategies (e.g., collagenase nanocapsules), are also showing promise in preclinical fibrosis models by directly targeting ECM deposition and fibroblast behavior [83,84]. Specifically in nAMD, though, several therapies focusing on addressing fibrosis have failed in the clinic (for a recent review, see [85], highlighting the need to come up with new approaches in this area).

In conclusion, fibrosis must be considered in a clinical context. First, it is a natural consequence of tissue repair, and in that sense, it is inevitable. To posit this from a different perspective, if the human body did not have the ability to deposit scar tissue in a wound, one could ask whether this alternative phenotype, absent fibrotic tissue, would be even more destructive for the tissue. Second, the impact of aging on fibrosis cannot be overstated. If there is a pathological aspect that can be considered, then it is the degree to which it may compromise the overlying NSR by promoting atrophy [86,87]. Herein may be the opportunity to consider effective therapy, not in the context of aiming to prevent fibrosis, but to modulate the amount of fibrous deposition akin to that seen with the use of antimetabolites in glaucoma fistulizing surgery, where scar tissue deposition is modulated, but healing still takes place so that tissue repair can be completed [88]. Actual prevention of fibrosis prevents “wound” closure and ensures a chronic wound that does not heal—it is, by extension, inherently profibrotic. Moreover, in the context of aging, where fibrosis is inevitable and occurs despite optimal therapy, there may have to be some refinement of our therapeutic expectation in that restoration of normal or near-normal vision may not be a realistic endpoint once CNV (i.e., tissue repair) is underway. Finally, extrapolating from the most recent observations on fibrosis elsewhere in the body, current evidence supports the primacy of ECD as the main pathogenic driver in initiating fibrosis, preceding even inflammatory cell infiltration or myofibroblast transition. This observation, together with the profound fibrosis-modulating effects of anti-VEGF therapy, supports the notion that future and effective targeting of the fibrotic process should be directed from the outset at improving EC function and normalizing the neovasculature in nAMD.

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