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Age-Related Macular Degeneration and Intracrine Biology: An Hypothesis

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This laboratory has studied the intracellular actions of angiotensin II and other signaling proteins that can act in the intracellular space—peptides/proteins we have called intracrines. Moreover, we have suggested that general principles of intracrine action exist and can help explain the progression of some chronic degenerative diseases such as diabetic nephropathy and congestive heart failure. Here, a similar analysis is carried out in the case of age-related macular degeneration. We propose that intracrine mechanisms are operative in this disorder. In particular, we hypothesize that intracrine loops involving renin, angiotensin II, transforming growth factor-beta, vascular endothelial growth factor, bone morphogenetic protein-4, and p53, among other factors, are involved. If this analysis is correct, it suggests a commonality of mechanism linking chronic progressive renal diseases, congestive heart failure, and macular degeneration.

Keywords: *Angiotensin II, macular degeneration, renin-angiotensin system, transforming growth factor-beta*

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INTRODUCTION

Age-related macular degeneration (AMD) is a common cause of vision loss and blindness in the elderly. While the specific causes of this disorder are not known, age and smoking are risk factors. The pathology of AMD is complex, and while the typical features are well described, the relationship between the various abnormalities is unclear.[1] Briefly, the earliest form of the disorder is characterized by drusen, punctate yellow or pale retinal deposits. These lesions appear to develop in association with retinal pigment cells, although leakage from choriocapillaries may play a role (Figure 1). Retinal pigment epithelial atrophy is also present. The disorder can progress to severe degeneration of the retinal pigment epithelium with secondary loss of photoreceptors (called geographical atrophy) and, in some cases, also to the growth of vessels into the retinal pigment epithelium and/or the subretinal space.[1-5] Clinical disease is usually categorized as dry macular degeneration or wet macular degeneration. Dry AMD is associated with loss of retinal pigment cells and secondary pathologies, while the wet form is complicated by neovascularization and vessel leakage. The pathological findings in these disorders are complex and are well described in the literature. The factors that determine disease progression and disease phenotype are unknown. While agents targeting vascular endothelial growth factor (VEGF) have been partially effective in controlling wet AMD, no effective therapy is available for the dry form other than vitamins and nutritional supplements. More important, both forms of disease frequently, but not always, progress.[1-5] These characteristics of AMD find parallels in other progressive chronic degenerative diseases such as chronic renal disease (CRD) and congestive heart failure (CHF).[6-8] Like AMD, these disorders are associated with age and smoking and often progress in the face of currently available optimal therapies. In addition, local renin-angiotensin systems (RAS) have been reported in heart, kidney, and retina, as have other growth-regulating peptide hormones. We have proposed a novel role for the RAS and these other intracrine systems in the pathogenesis of CRD and CHF and here extend these arguments to AMD.[6-8]

INTRACRINE BIOLOGY

In recent decades, this laboratory has studied the intracellular action of the vasoactive peptide angiotensin II (AngII). Based on our findings, we defined what we termed intracrine action—the intracellular action of extracellular signaling proteins/peptides, either in their cells of synthesis or after internalization by target cells.[9-13] It became apparent that intracrine action was associated with proteins/peptides other than hormones or growth factors. A wide variety of moieties, including hormone growth factors, cytokines, enzymes, DNA binding proteins, and others, can act in an intracrine fashion—that is, act as extracellular signaling proteins/peptides and also act in the intracellular space. Intracrines have been shown to traffick between cells after secretion, in exosomes, and possibly via nanotubes. We defined basic principles of intracrine action such as their tendency to form intracellular positive feedback loops that have the potential to be self-sustaining. Based on these proposals, we suggested that self-reinforcing loops involving RAS components along

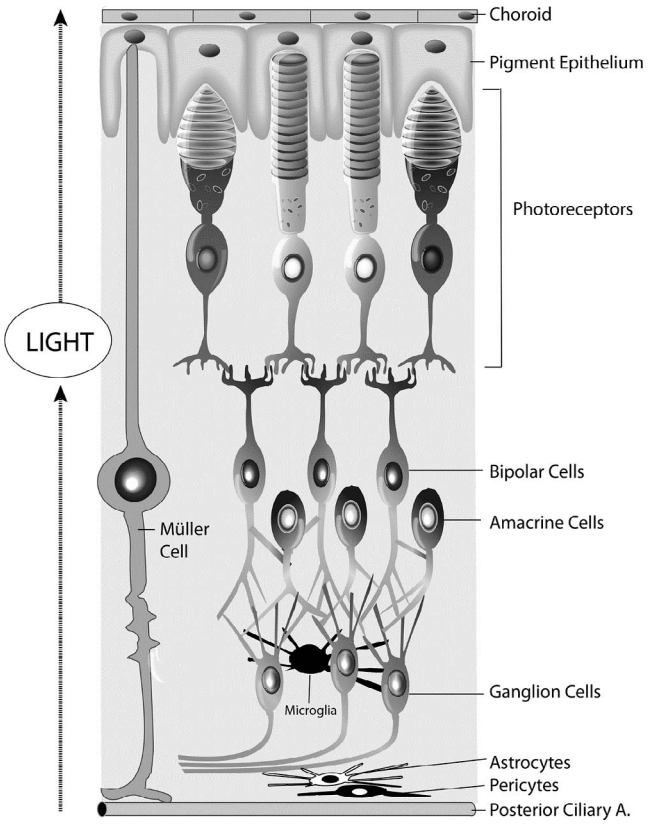

Figure 1. A schematic cross-sectional diagram of the retina. Müller cells span the retina. Pigment epithelial cells are located deep in the retina adjacent to the choroid. Posterior Ciliary A, posterior ciliary artery.

with other loops could participate in the progression of CRD and CHF, even after instigating insults were removed or mitigated.[9-28] For example, diabetic nephropathy progresses even after blood glucose is controlled. We have also proposed an interaction of the RAS and the mineralocorticoid receptor (MR) in diabetic nephropathy.[7,8] This interaction involved AngII-mediated MR upregulation acting to support a pathological intracrine loop in the kidney, which could explain the therapeutic benefit derived from MR inhibition in diabetic nephropathy. These ideas are discussed in detail elsewhere.[6-8] Here, we ask if similar intracrine mechanisms/loops could be playing a role in macular degeneration.

INTRACRINES IN THE RETINA

Consistent with the notion that intracrine biology plays a role in retinal disease, many intracrines are found in the retina and are known to often regulate one another in one tissue or another.[1,2,4,29-96] These interactions will be touched upon, but it must be understood that the interactions discussed here are not exhaustive. Also, the intracrines' actions and interactions described here are often context and cell-type specific, and so, except in cases in which data have been developed in retinal cells/tissues, they represent an extrapolation of data from cells/tissues other than the retina and must be considered potential rather than proven.[6-9,12]

Renin-Angiotensin System

All components of the RAS exist in the eye.[29-38] Message encoding renin, angiotensinogen (AGT), and angiotensin-converting enzyme (ACE) can be detected in the retina, and renin, prorenin, AGT, ACE, and AT-1 receptors for AngII (AGTR1) have been identified in the retina.[29,31] The concentration of AngII in the eye is several fold higher than in the blood. Of note, AngII, prorenin/renin, AGT, angiotensin (1-7), and ACE are intracrines.[6,9] In the retina, it appears that glial cells, and in particular Müller cells, are the main (but not the sole) sources of AngII. Müller cells express renin and prorenin receptors, as well as AGTR1. AGT is present in these cells, and they secret AngII; renin enzymatic activity is most pronounced at Müller cell endfeet adjacent to retinal blood vessels.[32,33] Prorenin receptors are found on retinal pigment epithelial cells, and the expression of these receptors is increased in hypertensive patients with adult-onset macular degeneration. Type I collagen is upregulated in these pigment epithelium cells, and this upregulation, along with in vitro studies, suggests that prorenin, acting through the prorenin receptor, may be involved in extracellular matrix remodeling. Retinal pigment epithelial cells also express renin, prorenin, AGTR1, and ACE proteins, although it is not clear to what extent these proteins are synthesized by the cells themselves.[31,34-38] Any interaction between prorenin and its receptor is not likely to form a positive feedback loop because in these cells prorenin downregulates its receptor.[34] However, other possible feed-forward loops in retinal epithelial cells are discussed below.

Vascular Endothelial Growth Factor

Normal vascular homeostasis in the retina is produced through a balance of angiogenesis factors such as VEGF and antiangiogenic factors.[39-43] For example, in a model of ischemia-induced neovascularization in rats, neovascularization was associated with an upregulation of VEGF and a downregulation of the antiangiogenic factor pigment epithelium-derived factor (PEDF).[39] AngII upregulates VEGF in the retina. This stimulation is mediated by both AGTR1 and AGTR2.[41] VEGF protein expression is located in the ganglion cell layer, Müller cells, the inner nuclear layer, glial cells, and the retinal pigment epithelium; VEGF expression is normally low but is upregulated in diabetes and to a lesser extent in AMD.[30,31] In a study of choroidal neovascular membranes from patients with AMD or proliferative diabetic retinopathy, increased expression of VEGF (compared to levels in epiretinal membranes from patients with nonischemic proliferative retinopathies such as rhegmatogenous retinal detachment) was found in a variety of cells, including Müller cells. Of note, in these tissues, some Müller cells expressed both VEGF and the angiogenic protein fibroblast growth factor-2 (FGF-2).[42]

Transforming Growth Factor-Beta

Considerable evidence suggests an interaction (intracellular or otherwise) between AngII and transforming growth factor-beta (TGF-β1) in the kidney and vasculature, with AngII upregulating TGF-β1; TGF-β1 in turn produces cellular hypertrophy and extracellular matrix thickening.[6-9,44] Indeed, in kidney cells, intracellular AngII has been reported to upregulate TGF-β1. Because AngII

can upregulate TGF-β1 transcription in isolated nuclei of renal cells, this TGF-β1 upregulation could involve direct intracellular AngII action.[6,45,69] We have previously suggested that an intracrine loop can exist in the kidney and the heart in which AngII upregulates TGF-β1 that then indirectly upregulates AngII synthesis.[6-8] In the retina, these interactions may be different.[46-51] Human Müller cells have been shown to express message for TGF-β1 and TGF-β2, as well as for type I and type II TGF-β receptors. In cultured human Müller cells, however, TGF-β2 predominately was secreted. The observation that TGF-β2 blocks the proliferative effects of several growth factors on glial cells suggests a role for the protein in eye disorders, although not necessarily that of TGF-β1 in cardiorenal disorders.[46,47] Moreover, Müller cells inhibit the proliferation of microvascular retinal endothelial cells.[48] However, it remains an open question whether TGF-β1, which is produced by Müller cells, could participate in producing retinal pathology in vivo as it does in renal disease. This possibility is supported by the observation that both TGF-β2 and TGF-β1 are upregulated in Müller cells in a model of retinal detachment, although the cells appear to only secrete TGF-β2.[49] Also, TGF-β1 is upregulated in a mouse model of oxygen-induced neovascularization. Here, TGF-β1 intracellular immunoreactivity is found, apparently in the nuclei, of endothelial cells in regions of retinal neovascularization. This finding assumes additional importance given that all forms of TGF-β can increase the synthesis and secretion of VEGF by retinal pigment epithelial cells.[50,51] Similarly, TGF-β1 can upregulate the proangiogenic protein platelet-derived growth factor (PDGF) in pigmented retinal epithelial cells.[52] Moreover, injury causes retinal pigment epithelial cells to upregulate a variety of factors including TGF-β1, TGF-β2, and connective tissue growth factor (CTGF); this upregulation causes the cells to adopt a persistent mesenchymal state and reduces cell survival.[53-56] Because retinal pigment epithelial cells have TGF-β receptors, the secretion of TGF-β moieties during injury potentially can produce a positive feedback loop. Indeed, because TGF-β1 has been located in mitochondria and the TGF-β type I receptor has been shown to traffick to the nucleus following ligand binding, any such positive loop could be dependent on intracellular TGF-β1 action.[57-59]

Fibroblast Growth Factor-2/Angiogenin/Hepatocyte Growth Factor/Heparin-Binding–Epidermal Growth Factor-Like Growth Factor

FGF-2 is synthesized by Müller cells and is upregulated by ischemia and inflammatory cytokines. Thus, in the case of prolonged ischemia, the synthesis of intracrines by Müller cells shifts from those that inhibit neovascularization (PEDF, thrombospondin, prolactin, TGF-β1) to those promoting it (FGF-2, VEGF). FGF-2 upregulates VEGF in retinal endothelial cells and Müller cells.[48] In addition, FGF-2 upregulates hepatocyte growth factor and heparin-binding epidermal growth factor-like growth factor (HB-EGF).[60-62] Also, the angiogenic factor angiogenin is expressed in both the normal vasculature and the pathologic endothelium of eyes showing neovascular membranes, and it is found in some drusen, suggesting a permissive role in the pathogenesis of macular degeneration.[4]

Intracrine Interactions

Although the above list of growth factors operating in the retina is not exhaustive, the list contains those most likely to be important in retinal disease progression. It is remarkable that all the protein factors mentioned here have been shown to be intracrines.[63-65] These factors regulate one another in the retina and, although it is not known to what if any extent these interactions involve intracellular peptide action, it seems likely that some do. This is so if only because FGF-2, angiogenin, and VEGF indirectly cooperate in an intracellular intracrine fashion in angiogenesis, and angiogenesis is a key feature of wet macular degeneration. The evidence for an intracellular mechanism linking these 3 intracrines in angiogenesis comes from the observation that (1) VEGF and FGF-2 upregulate angiogenin in the nuclei of endothelial cells; (2) knocking down angiogenin downregulates FGF-2 and VEGF expression (indicating a positive feedback loop) and reduces the proliferative action of externally added FGF-2 and VEGF; and (3) blocking angiogenin trafficking to the nucleus with the drug neamine not only blunts the growth of some tumor explants in vivo but also reduces angiogenesis.[66,67]

POTENTIAL INTRACRINE LOOPS

The growth factor interactions discussed above could serve as the substrate for the formation of regulatory networks and in particular for the genesis of intracrine positive feedback loops. As noted earlier, we have previously suggested the existence of specific positive feedback intracrine loops—including loops employing the intracellular actions of intracrines—in CRD and CHF. These involve the RAS, TGF-β1, VEGF, and parathyroid hormone-related protein, as well as other intracrines.[6-8] In the retina, the situation is arguably more complex. Interactions between intracrines are more easily identified, suggesting the possible existence of regulatory loops, but there is less evidence for intracellular intracrine action in the retina. Nonetheless, it is reasonable, given the available data, to suggest several such positive feedback loops. These loops must be viewed as potential in that it is unclear to what extent, if any, they are active in any given case. Presumably these self-reinforcing loops are not normally active, but one or more could develop to cause disease, with the likelihood of that happening dependent upon genetic predisposition and environmental factors.

AngII—p53—AGT—AngII

As is the case in the heart and kidney, the RAS is expressed in the retina where it could play an important role in the pathogenesis of macular degeneration. AngII can upregulate the transcription of renin, AGT, and PDGF in isolated hepatic nuclei, and intracellular AngII upregulates renal tubule production of AGT in vivo. This upregulation suggests the possible production of an AngII—AGT—AngII positive loop.[68,69] Also, it has been shown in the heart that AngII upregulates p53 activity and that in turn upregulates AGT (thereby possibly producing a positive loop given the presence of local renin) and promotes senescence and/or apoptosis.[6-8] Thus, if a stimulus upregulates the retinal

pigment epithelial cell RAS, the secondary increase in p53 activity and apoptosis could create a self-sustaining loop and progressive cell dropout. This progressive cell dropout would push the retina toward the formation of drusen and dry AMD. The process would likely be compounded by other pathological loops discussed below. The initial stimulus to AngII upregulation could be ischemia given that hypoxia upregulates (pro)renin in the eye. Müller cells synthesize prorenin and secrete AngII; retinal pigment epithelial cells express the prorenin receptor (which has the capability to bind and transiently activate prorenin enzymatic activity) and they express prorenin, renin, AGTR1, and ACE. So there appear to be multiple paths by which AngII can be produced in the retina, including in retinal pigment epithelial cells.[29-37] Moreover, because Müller cells both synthesize AngII and express AGTR1, the potential for a positive feedback loop in these cells is real; in fact, AngII is known to upregulate the AT-1 receptor in these cells.[33-38] Such a loop could lead to ongoing p53 activation as has been shown to occur in cardiac myocytes and to cell dropout. A similar process could occur in pigment epithelial cells; even if retinal pigment epithelial cells do not themselves synthesize all components of the RAS, loops in Müller and other retinal cells could provide the needed components and lead to p53 upregulation, oxidative stress, and cell dropout.[31] If the RAS loop in any cell type upregulates synergizing loops in Müller cells, retinal pigment epithelial cells, or other retinal cells, disease progression could accelerate.

An additional point is that many tissues apparently can synthesize small amounts of aldosterone that could stimulate local MRs. Irrespective of the local synthesis of aldosterone, AngII can directly upregulate and activate the MR as can angiotensin-induced oxidative stress.[7] Because MR activation has been reported to upregulate AGTR1 and ACE in cardiac myocytes and endothelial cells, it therefore potentially upregulates AngII. This mechanism could provide a supportive loop sustaining upregulation of the RAS.[7,8]

AngII—TGF-β1—AGT—AngII; TGF-β1—TGF-β1; AngII—TGF-β1—VEGF; AngII—FGF-2—VEGF (the latter two are not self-sustaining loops but expand the AngII network)

AngII is known to upregulate TGF-β1 in multiple cell types, while TGF-β1 has been shown to upregulate AGT, ACE, and AGTR1 as well as its own synthesis (the latter loop is possibly important in wound healing) in some tissues/circumstances.[6-8,44,45,53,54,69] Indeed, in some cells, intracellular angiotensin at the nucleus upregulates TGF-β1.[45] Thus, multiple self-sustaining loops exist between the RAS and TGF-β1 (Figure 2). TGF-β1, 2, and 3 all stimulate VEGF release by pigment epithelial cells.[49-55] Thus, not only could loops linking AngII, p53, and TGF-β1 participate in retinal pigment epithelial cell apoptosis, but a higher level of expression could trigger VEGF secretion and therefore participate in the switch from dry to wet macular degeneration. TGF-β1 and 2 can stimulate HB-EGF in some cells. Similarly, AngII can upregulate FGF-2, an angiogenic factor, in vascular smooth muscle cells. It can also upregulate VEGF and thereby further link the RAS with angiogenesis.[30,44,60,61,70-75]

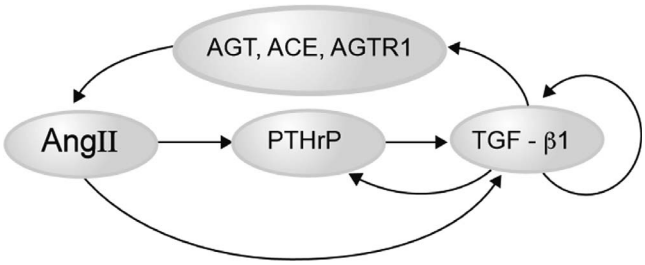

Figure 2. The proposed angiotensin II—TGF-β1 network. Arrows indicate stimulation, and therefore self-sustaining loops are possible. ACE, angiotensin-converting enzyme; AGT, angiotensinogen; AngII, angiotensin II; PTHrP, parathyroid hormone-related protein; TGF-β1, transforming growth factor-beta.

TGF-β1,2—HB-EGF—VEGF—HB-EGF; FGF-2—HB-EGF—VEGF—HB-EGF

HB-EGF upregulates VEGF secretion by retinal pigment epithelial cells and stimulates their proliferation, while VEGF upregulates HB-EGF in endothelial cells. Thus, the potential exists for a self-sustaining loop in the retina. This self-sustaining loop could also help potentiate neovascularization while maintaining any pathological actions of HB-EGF.[63,71-76] At the same time, it must be understood that intracrine loops such as those regulating VEGF can be cell and context specific. For example, AngII upregulation of p53 activity in cardiac microvascular cells actually established a positive feedback loop between p53 and the notch ligand Jagged1 with the net effect of suppressing VEGF secretion.[75,77]

MMP-9—VEGF—MMP-9

Matrix metalloproteinase 9 (MMP-9) directly stimulates VEGF synthesis in retinal pigment epithelial cells, and VEGF can similarly upregulate MMP-9 synthesis by the cells, thereby producing a positive feedback loop. Of note, MMP-9 is not known to be an intracrine. This self-sustaining loop could play a role in the switch from dry to wet disease.[78]

AngII—BMP-4—senescence—p53—AGT—AngII

Retinal pigment epithelial cells express bone morphogenetic protein (BMP-4).[79-81] In dry macular degeneration, BMP-4 is upregulated and can mediate oxidative stress-induced cell senescence. In wet macular degeneration, it is downregulated.[2,71] In the aorta, AngII upregulates BMP-4. If this upregulation occurs in the retina, the potential for a self-sustaining loop acting through cell senescence upregulation of AngII exists.[80] Moreover, the BMP-4 in this loop could play a role in preventing the switch from dry to wet disease.[2,78-81]

PATHOGENESIS AND THE DRY TO WET SWITCH

It is generally assumed that the switch from dry to wet macular degeneration involves the upregulation of angiogenic factors such as VEGF and FGF-2 and the downregulation of antiangiogenic factors such as PEDF and BMP-4; VEGF and TGF-β can also upregulate CTGF which modifies the actions of other factors.[2,48,64,65,82-84] The cause of this change in secretion pattern is unknown. The loops described above may shed some light on this. It is possible

that aging causes an upregulation of the retinal RAS. For example, in the rat left ventricle, aging is associated with upregulation of AGTR1, AGT, and ACE which would be expected to increase AngII signaling and internalization.[85,86] The extent to which this upregulation could occur in the retina is likely genetically determined and modified by environmental factors such as smoking and local retinal ischemia. If sufficient upregulation occurs, the AngII—p53—AGT—AngII and the AngII—BMP-4—senescence—p53—AGT—AngII loops could develop, leading to retinal pigment cell apoptosis and eventually to drusen, photoreceptor dropout, and dry macular degeneration. With still more upregulation, again likely genetically and environmentally determined (with oxidative stress playing a role in VEGF upregulation), the AngII—TGF-β1—AGT—AngII, TGF-β1—TGF-β1, AngII—TGF-β1—VEGF, AngII—FGF-2—VEGF, FGF-2—HB-EGF—VEGF—HB-EGF, and MMP-9—VEGF—MMP-9 loops could be activated.[96] This activation would lead to angiogenesis and conversion to wet macular degeneration. Moreover, it has been suggested that downregulation of BMP-4 is associated with the dry to wet switch because retinal BMP-4 expression is elevated in dry macular degeneration and reduced in wet disease; the loss of the antiproliferative action of BMP-4 contributes to a shift from antiangiogenic to angiogenic loops.[2] Because in some cell types, including fetal pigment epithelial cells, BMP-4 is downregulated by tumor necrosis factor-alpha (TNF-α), the latter factor may play a role.[2,87] Retinal TNF-α is upregulated in eye disorders such as glaucoma, and TNF-α can be a component of the senescence-associated secretory phenotype (SASP) that is induced in cells by genotoxicity-induced senescence and involves the secretion of a variety of factors, some in exosomes.[10] Therefore, if sufficient cellular/genomic damage occurs in retinal cells during the development of dry macular degeneration, it is possible that p53 induces TNF-α secretion by senescent cells as part of the SASP; this would help trigger the switch from dry to wet disease by downregulating BMP-4.[6-8,10,87-89] A more likely mechanism for TNF-α involvement centers on the observation that damaged neurons and Müller cells upregulate TNF-α. This observation suggests that if intracrine loops produce sufficient damage in Müller cells, TNF-α could be upregulated and play a role in triggering the phenotype change.[88] According to this view, the phenotypic switch is not so much a switch as it is the progression of disease.

It is accepted that a switch from retinal production of antiangiogenic factors to proangiogenic factors accounts for the switch from dry to wet disease. Here, it is argued that this phenotypic switch is caused by an imbalance between the various intracrine networks operative in the diseased retina. Intracrine biology offers additional candidate interactions for this shift, but the most likely candidate appears to involve the loops discussed. The relative activities of these networks can result from genetic predispositions or environmental factors, but if this line of thought is correct, networks responsible for the switch are the appropriate therapeutic targets. Also, if this argument is correct, it suggests an important role for the RAS in disease onset and progression. Although RAS activation is unlikely to be the sole trigger for disease given the large number of interacting growth factors in the retina, it could nonetheless be the most frequent initiating mechanism. Epidemiological evidence suggests that the prevalence of ACE inhibitor use in hypertensive patients with macular degeneration was the same in patients with wet and dry disease. This need not, however, imply that AngII is not involved in disease initiation or in the switch. Disease-initiating RAS action could involve the intracellular action of RAS components and so be relatively unaffected by most AngII receptor blockers and ACE inhibitors; also, intracellular AngII can be formed by mechanisms that do not involve ACE, and these pathways would make ACE inhibitors ineffective.[6,8] Further, once disease-causing loops are established, the AngII loop might no longer be necessary given the upregulation of the other loops. For example, if disease was initiated by AngII, it is possible that sufficient TGF-β1 upregulation could occur to produce TGF-β1 self-upregulation and eventually VEGF and HB-EGF upregulation, leading to wet disease. Similarly, retinal injury could upregulate TGF-β1,2 as well as CTGF, leading to the loss of retinal pigment cell viability; further TGF-β upregulation could trip the dry to wet switch.[49,53-56] Finally, the available data do not adequately address the effect, if any, of RAS inhibition on the initiation of disease. There is evidence that ACE inhibitors and angiotensin AT-1 blockers can cause regression of choroidal neovascularization in rodent models, but the significance of this is as yet unclear.[90]

IMPLICATIONS FOR THE DEVELOPMENT OF NEW THERAPIES

Many growth factors and cytokines operate in the retina to maintain health and at other times to produce disease. These factors, virtually all intracrine, form regulatory networks. Moreover, there is redundancy in their actions such that blocking the action of one factor need not produce a desired result because of the existence of a second agent with similar function. Also, downregulating one or another factor to achieve a result such as suppression of angiogenesis can, depending on context, produce collateral harms because the factors active in the retina often function in multiple ways.[2,48] This situation therefore suggests 3 approaches to therapy. First, because disease initiation may involve dysregulation of a single growth factor, identifying and targeting any such factor before it enlists other factors and establishes self-perpetuating loops would be expected to provide benefit in terms of disease prevention. Second, in established disease, targeting multiple cooperating factors with the intent to reduce cell death and/or neovascularization while interrupting positive feedback loops should be undertaken, but partial inhibition of these factors should be employed so that the homeostatic actions they appear to provide in the retina are not eliminated.[96] Third, because most of the relevant factors are intracrines and because several of these appear capable of supporting feed-forward networks by acting in the intracellular space, optimal therapy will likely require the development of intracellularly active agents.

With these approaches in mind, several prototype therapies can be suggested for testing in experimental models of disease. First angiotensin receptor blockers, especially those active in the intracellular space such as losartan, should be studied, particularly in the early stages of the disease. So too, MR blockers and a low-salt diet could

be investigated to inhibit MR activation/function and so lessen MR amplification of the AngII loops and TGF-β1 loops.[7,8,91,92] Because angiogenesis is the defining abnormality in wet disease, neamine, a derivative of neomycin, should be studied. Neamine blocks nuclear trafficking of the intracrine angiogenin and therefore blocks its action. Because blocking angiogenin action partially inhibits angiogenesis induced by FGF-2 and VEGF, neamine could be the prototype of a novel therapy.[66,67] In addition, inhibitors of noncanonical and unconventional intracrine actions should be sought to better suppress intracrine interactions. Included in the latter category would be an inhibitor of direct prorenin action at its receptor and inhibitors of the intracellular generation of AngII from angiotensin (1-12).[93,94] Finally, an intracellularly active inhibitor of TGF-β1 was recently shown to block PDGF-induced intracellular action of TGF-β1 in pulmonary artery smooth muscle cells.[95] This observation suggests that agents of this kind could be helpful in AMD, CHF, and CRD. Moreover, this observation suggests a commonality of intracrine mechanism between these diseases and primary pulmonary hypertension.[8,95]

CONCLUSION

A complex interplay of growth factors takes place in the retina during the development of macular degeneration. These factors are virtually all intracrine, and some of their interactions occur in the intracellular space. Moreover, these factors may form self-sustaining loops based on signaling at the external cell membrane or at intracellular loci. This formulation suggests novel directions for experimentation into disease pathogenesis and for the development of new therapies. Moreover, if these proposals are correct, they point to a commonality in the pathogenesis of CRD, CHF, and AMD.

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