REVIEW

Angiotensin Ⅱ-related hypertension and eye diseases

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Abstract

Systemic vascular disease, especially hypertension, has been suspected as a risk factor for some eye diseases including, diabetic retinopathy and age-related macular degeneration. Hypertension can contribute to chronic diseases by hemodynamic injury and/or cellular actions induced by hypertension-related hormones or growth factors. Among the most important is Angiotensin Ⅱ (Ang Ⅱ), which controls blood pressure and induces different cellular functions that may be dependent or independent of its effect on blood pressure. Importantly, as is true for heart, kidney and other organs, the renin-angiotensin system (RAS) is present in the eye. So, even in the absence of hypertension, local production of Ang Ⅱ could be involved in eye diseases. The goal of this manuscript is to review the most relevant scientific evidence supporting the role of the RAS activation, in the development of age-related macular degeneration and diabetic retinopathy, and highlight the importance of Ang Ⅱ in the etiology of these diseases.

Key words: Renin-angiotensin system; Angiotensin Ⅱ; Angiotensin receptors; Hypertension; Retinal microvasculature; Blood flow; Angiotensin-related hypertension; Age-related macular degeneration; Diabetic retinopathy

Core tip: Association between eye diseases and systemic hypertension has been revealed. The developments of some ocular diseases, as well as, alterations in the severity of these diseases have been associated with disregulation of the ocular renin-angiotensin system and activation of the angiotensin type 1 receptor. In this paper we reviewed the importance of angiotensin Ⅱ in the etiology of age-related macular degeneration and diabetic retinopathy, two ocular diseases that can rob people of their vision.

INTRODUCTION

Knowledge of the renin-angiotensin system (RAS) has advanced remarkably over recent years from that of a classical endocrine system that explained homeostasis for maintenance of circulating intravascular volume and thereby restoration of arterial pressure to a newer concept including a number of local RASs that operate independently within several organs[1-5], including the eye[6,7].

Angiotensin Ⅱ (Ang Ⅱ), a hormone that raises blood pressure, is derived either from the circulation or from local production. Ang Ⅱ causes vasoconstriction, sympathetic nervous stimulation, release of aldosterone, and renal actions which contribute to control the blood pressure[8]. The effects of Ang Ⅱ provoke different responses in tissue, which are mostly mediated *via* the Ang Ⅱ type 1 receptor (AT1R). According to previous studies, the systemic RAS is not supposed to be directly accountable for the increase in blood pressure, it appears to be that

Table 1 Presence of renin-angiotensin system components in the eye

RAS molecule	Eye part	Species	Ref.
Prorenin	Retina	Human	Sramek *et al*[207], 1988
	Ciliary body	Human	Danser *et al*[33], 1989
	Vitreous body	Human	Danser *et al*[33], 1989
Retina	Retina	Human, rabbit	Danser *et al*[33], 1989
	Ciliary body	Rabbit	Wagner *et al*[19], 1996
	Choroid	Human, Rabbit	Ramirez *et al*[208], 1996
	Iris	Rabbit	Ramirez *et al*[208], 1996
	Vitreous	Human, rabbit	Ramirez *et al*[208], 1996
	Aqueous humor	Rabbit	Ramirez *et al*[208], 1996
Angiotensinogen	Retina	Human, rabbit	Sramek *et al*[209], 1992
	Ciliary body	Human, rabbit	Ramirez *et al*[208], 1996
	Choroid	Human, rabbit	Wagner *et al*[19], 1996
	Iris	Human, rabbit	Wagner *et al*[19], 1996
	Vitreous	Human, rabbit	Wagner *et al*[19], 1996
	Aqueous humor	Rabbit	
ACE1	Retina	Dog, monkey, human	Vita *et al*[210], 1981
		Rabbit, porcine	Weinreb *et al*[211], 1985
	Ciliary body	Human, rabbit, porcine	Immonen *et al*[212], 1987
	Choroid	Dog, monkey, human	Ramirez *et al*[208], 1996
		Rabbit, porcine	Wagner *et al*[19], 1996
	Sclera	Dog, monkey	Shiota *et al*[213], 1997
	Iris	Rabbit, porcine	Geng *et al*[214], 2003
	Cornea	Human	Savaskan *et al*[16], 2004
	Vitreous	Dog, monkey, rabbit	Savaskan *et al*[16], 2004
	Aqueous humor	Human, dog, monkey, rabbit	Savaskan *et al*[16], 2004
	Tear fluid	Human, rabbit	Savaskan *et al*[16], 2004
ACE2	Retina	Rodent	Tikellis *et al*[215], 2004
		Human	Senanayake *et al*[17], 2007
Chymase	Choroid	Dog	Shiota *et al*[213], 1997
	Sclera	Dog	Maruichi *et al*[216], 2004
	Vitreous body	Human	
AT1R	Retina	Human	Savaskan *et al*[16], 2004
	Cornea	Human	Senanayake *et al*[17], 2007
	RPE	Human	Striker *et al*[18], 2008
		Rodent	Praddaude *et al*[104], 2009
AT2R	Retina	Human	Senanayake *et al*[17], 2007
	RPE	Human	Striker *et al*[18], 2008
		Rodent	Praddaude *et al*[104], 2009
Ang Ⅰ	Retina	Porcine	Danser *et al*[22], 1994
	Choroid	Porcine	
	Vitreous body	Porcine, human	
	Aqueous humor	Human	
Ang Ⅱ	Retina	Human, porcine, rabbit	Danser *et al*[22], 1994
	Ciliary body	Human, rabbit	Ramirez *et al*[208], 1996
	Choroid	Porcine, human, rabbit	Savaskan *et al*[16], 2004
	Iris	Rabbit	Senanayake *et al*[17], 2007
	Cornea	Human	
	Vitreous body	Porcine, human, rabbit	
	Aqueous humor	Human, rabbit	
	RPE	Rodent	Praddaude *et al*[104], 2009
Ang 1-7	Retina	Human	Senanayake *et al*[17], 2007

Ang: Angiotensin; RAS: Renin-angiotensin system; AT1R: Angiotensin Ⅱ type 1 receptor; ACE1: Angiotensin-converting-enzyme 1.

the blood pressure and local blood flow (BF) adjustment are due to the local RASs[9]. Ang Ⅱ directly or indirectly also promotes apoptosis, hypertrophy, neovascularization, inflammation and fibrosis *via* AT1R activation[10-13].

Ophthalmic literature concerning the RAS started in 1977 with a study by Igić *et al*[14] on the detection of angiotensin-converting-enzyme (ACE) activity in homogenates of the retina. Since then, and as shown in Table 1, the presence of all constituent of the RAS has been confirmed in different parts of the eye (Figure 1), where

the mediators of the RAS are locally released, conferring the molecular basis for a biological function of these mediators in the eye[15-18]. However, the origin of intraocular mediators such as Ang Ⅱ and renin has been debated. Local synthesis of both renin and ACE has been suggested in the retina of rats[19]. In this way, the secretion of renin by retinal pigment epithelium (RPE) to the retinal side was demonstrated by Milenkovic *et al*[20] (2010). It has been also suggested that Ang Ⅰ, Ang Ⅱ, and angiotensinogen are not able to cross the barriers between eye
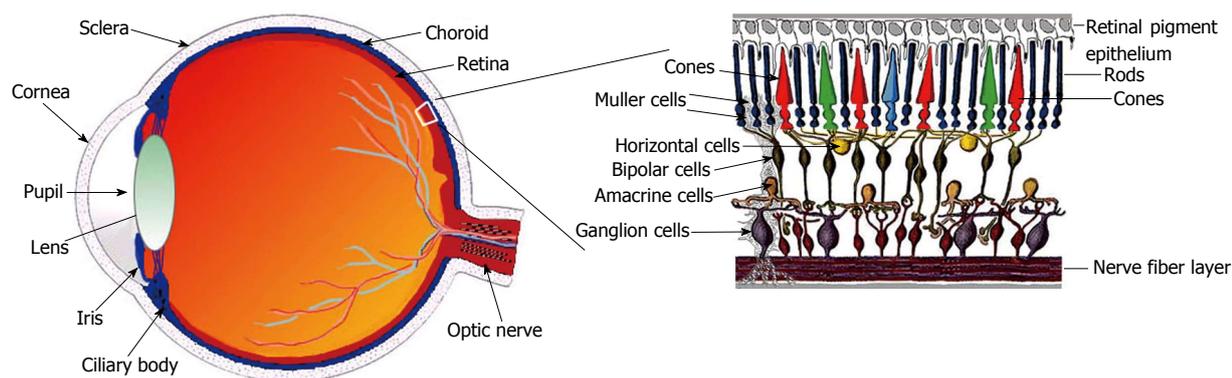
Figure 1 A drawing of a section through the human eye with a schematic enlargement of the retina [Helga Kolb from AMER Sci (2003)].

and circulating blood[21,22]. On the other hand, the presence of a ocular local production of Ang Ⅱ has been indicated[22,23]. As a result, increased local or tissue Ang Ⅱ formation in the retina in the absence of elevated circulating Ang Ⅱ may indeed be deleterious.

The RPE, a cell layer between the neurosensory retina and choroid, nourishes retinal visual cells and forms part of the blood-retinal barrier, therefore, playing a central role in maintaining retinal function. For example, the presence of the AT1R in the RPE basolateral membrane[20], indicates that the systemic RAS is a part of that retinal function signaling. Interestingly, by using electro-retinography, it was previously demonstrated that regulation of the systemic RAS changes the neuro-sensory retina activity[24-26]. Furthermore, plasma Ang Ⅱ cannot pass into the eye[7], and modifications of the renin expression in the RPE by regulators of the systemic RAS alter, have been observed[24]. Overall, these data lead to think the systemic RAS credits the presence of an intraocular RAS through the RPE.

The presence of the most important RAS components in the retina and the Ang Ⅱ actions observed in the eye (Surveying PubMed for eye, ocular, or retina, and Ang yields 734 citations dating back to 1963), imply an important role of RAS in the eye. However, its exact role, remains inadequately recognized. Of special focus are the components of the RAS and its receptors in the retina, as the RAS is increasingly recognized as a mediator of the pathogenesis of ocular diseases such as age-related macular degeneration (AMD) and diabetic retinopathy (DR)[27-36], which are two major causes of severe vision loss and blindness. Therefore, in this manuscript we review the most relevant scientific evidence supporting the function of the RAS activation, in the development of AMD and DR, and highlight the importance of Ang Ⅱ in the etiology of these two ocular diseases.

## RETINAL MICROVASCULATURE: MODULATION BY ANG Ⅱ

Given that vascular pathology in the retina is an important contributor of vision loss, the greatest research examining retinopathy and the possible role played by the RAS

has been focused on the microvasculature. The circulatory system of the retina supplies oxygen and nutrients to retinal tissue, which is essential for a correct function.

The retina circulation essentially comprises two parts: (1) a retinal circulation without autonomic innervation; and (2) a choroidal vasculature with autonomic innervations[37]. Evidence is accumulating that the retinal microvasculature is an interactive complex that includes a network of capillaries and a tertiary arteriole that links the capillaries with a secondary arteriole (Figure 2). The capillary is formed by an uninterrupted endothelium and inner pericytes[38]. Both endothelial cells and pericytes are directly communicated and share a common basement membrane[39]. It was previously demonstrated that contraction and relaxation of pericytes leads to alterations in the capillary lumen, which could regulates local perfusion[40-45]. Moreover, evidence suggests that a capillary network including pre-capillary at the tertiary arteriole form a working unit which is able to control local perfusion within the retinal vessels[39,46,47].

The retina tends to keep its BF constant through an autoregulatory response that is intrinsic[48,49]. The utoregulation of the retinal microcirculation is evaluated by some methods, including changes in systemic blood pressure[50]. The main regulators of BF are the vascular perycites[51,52], endothelium cells and the neural and glial cells[53]. One of the most important peptides playing a crucial role in the regulation of vasculature tone is Ang Ⅱ[54-58]. For instance, it has been demonstrated that Ang Ⅱ induces retinal endothelial cells apoptosis[59] and constriction of pericytes[60-63], therefore, decreasing the mean retinal arterioles and capillaries diameter, which leads to BF reduction[51,52].

Modifications in the retinal BF has been observed in some eye disorders. For example disturbances in the ocular circulation have been reported in AMD[31-33], supporting the presence of hemodynamic abnormalities in this disease. AMD is the main cause of severe visual loss and legal blindness in elderly. There are three stages of AMD: (1) early AMD, which is diagnosed by the presence of medium-sized drusen: (2) intermediate AMD, characterized by the presence of large drusen and/or pigment changes in the retina: and (3) late AMD, in which in addition to drusen, there is damage of the macula with severe
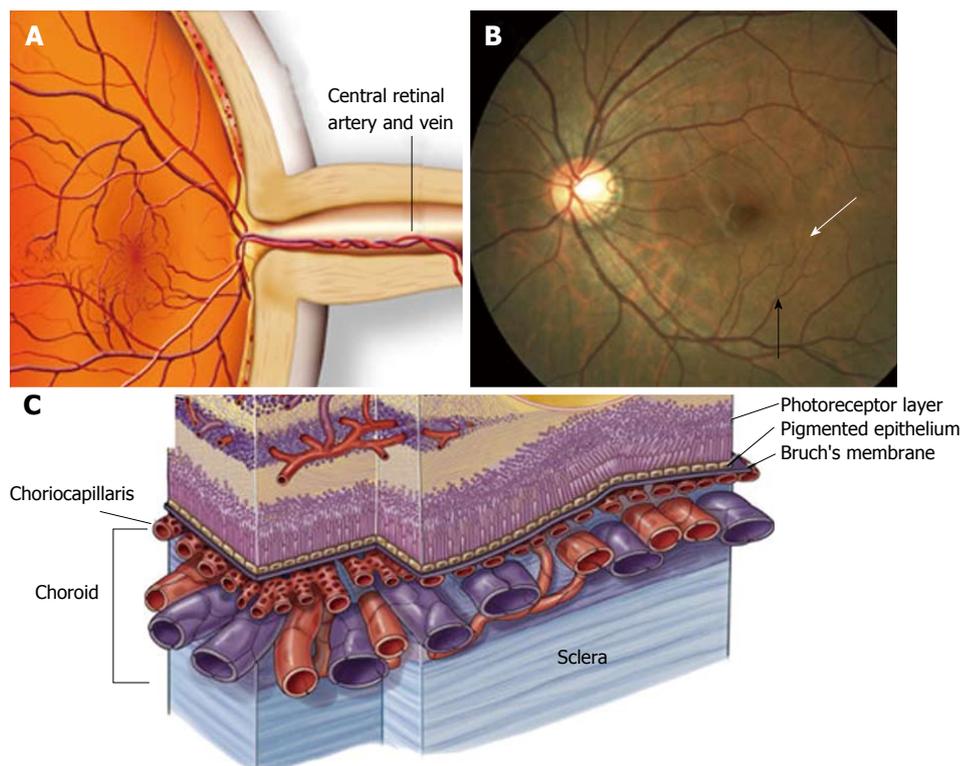
Figure 2 Anatomy of ocular circulation. A: Central retinal artery and vein respectively; B: Arteriole (black arrowhead); capillaries (white arrowhead); C: Choroidal vasculature (Anand-Apte, Hollyfield, Academic Press, Elsevier Books, 2009; 9-15).

vision loss[64]. Both local ocular and systemic vascular risk factors, such as systemic hypertension seem to be connected with the etiology of AMD. A relationship between AMD and modifications in the eye circulation was previously reported[27,29,65-72] and numerous studies have proposed a decrease in the vascularity of the choroid[73-75], reinforcing the existence of hemodynamic abnormalities in this disease. The relationship between impaired choroidal perfusion, reduced choroidal BF and clinical manifestations of AMD has been recently reported by previous studies[70,71,75-79].

Association between AMD and systemic hypertension has been studied by many epidemiological studies[80-84]. The Macular Photocoagulation Study has demonstrated that patients with both, AMD and hypertension responded less to laser photocoagulation treatment than patients with only AMD[85]. These observations, suggested that hypertension could have a harmful effect on the stages of AMD. A decrease in the choroidal BF in individuals with hypertension versus those without was previously reported[31,32]. These authors, also showed that this reduction becomes more marked with increasing AMD severity[31,32]. Therefore, the observed decrease in choroidal BF in AMD patients with hypertension suggests the implication of an ischemic mechanism in the etiology of AMD.

ANG II-RELATED HYPERTENSION IN THE PATHOGENESIS OF AMD

AMD is a slow progressing disease that can rob people of their vision. This ocular disease is a public health problem that will remain a major threat to vision.

There are two forms of AMD; early (dry) AMD and late (wet) form. Wet AMD is always preceded by early disease, and in about one-third of cases dry AMD can lead to wet macular degeneration which progresses much more rapidly and leads to greater loss of central vision. Death of photoreceptors is the ultimate cause of vision loss. However, the initial cellular target of this deseade is the RPE, its extracellular matrix, and the subjacent vascular bed (called choriocapillaris; Figure 2C), the blood supply for the outer retina.

Dry AMD is characterized by the accumulation of debris and other lipid rich extracellular deposits in form of drusen under the RPE and within Bruch's membrane (BrM) (Figure 3B)[86,87]. During aging, deposits initially accumulate between the RPE and its basement membrane (called BLD), but progression into AMD requires additional deposit formation within BrM, (called BLiD and "nodular" drusen). These are yellowish lesions that can be seen in the macula at the earliest stages of dry AMD. A finding in dry AMD that represents disease progression and can be used as a surrogate endpoint is the presence, size, and appearance of drusen. Over time, these drusen enlarge, coalesce, become pigmented, and eventually can disappear when they progress to the late form of AMD. We observed that when drusen go away, there are three possible outcomes; formation of geographic atrophy, formation of abnormal blood vessels known as wet AMD or choroidal neovascularization (CNV) (Figure 3C), or disappearance of drusen without any significant
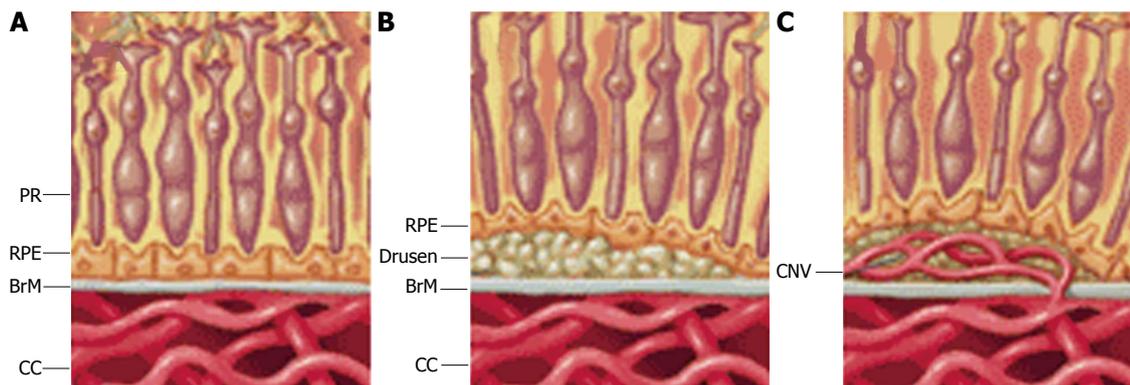
Figure 3 The pathologic changes to the retina and choroidal blood vessels typical of dry and early wet age-related macular degeneration respectively. A: Control; B: Early age-related macular degeneration (AMD); C: Wet AMD. PR: Photoreceptors; RPE: Retinal pigment epithelium; BrM: Brusch's membrane; CC: Choriocapillaries; CNV: Choroidal neovascularization (provided by the OcuCure Therapeutics' website).

anatomic abnormality. The endpoint that represents the progression of the disease is the growth and enlargement rate of drusen[88-90]. Wet AMD is always preceded by early disease.

Our understanding of this disease has increased; however, no one knows exactly what causes AMD. Age is the major factor determinant for developing AMD. However, it has been suggested that the disease results from some interactions between different issues: genetic susceptibility, environmental factors and systemic health co-factors[91-95]. Because the increasing frequency of hypertension, the RAS is of special interest among these systemic health co-factors. In this context, epidemiological demonstrated an association between hypertension and incidence of drusen[28] and with wet AMD development[29,96-98]. Exciting findings which showed a strong link between hypertension and progression of early AMD to the wet form were recently published[99]. However, the mechanism(s) by which hypertension contribute to the progression from early form to CNV was not elucidated. In recent years, evidence has revealed that Ang Ⅱ, AT1R signaling, and prorenin, may play a significant role in the mentioned pathologic processes[100-104]. Moreover, recent studies revealed the participation of AT2R, Ang I and Ang 1-7[24]. Consequently, investigation of the local RAS in the retina will allow find out new approach for the development of new treatments.

Dry (early) AMD

As mentioned previously, RPE-derived debris and other debris accumulated between the RPE and within BrM is a very well-known histopathologic sign of the dry AMD[105-108]. Studies in eyes from AMD patient found out deposits of RPE-derived debris within BrM[109]. Nevertheless, the mechanism(s) by which the debris accumulate were not studied. Based in the idea that a relationship between matrix metalloproteinases (MMPs) and inhibitors of matrix metalloproteinases and development of dry AMD exits. We proposed that the evolution of the sub-RPE deposits into BrM necessitates breakdown of the RPE basement membrane's components by diges-

tion or degradation of these compounds (*i.e.*, type Ⅳ and I collagens and laminin)[110,111], and that ECM turnover up-regulation through activation of MMP-2 and MMP-14 is required for the interruption of these physical barriers. We evaluated the regulatory effects of Ang Ⅱ and prorenin-activated prorenin receptor (PRR) on the MMP-2 and basement membrane component proteins, in the RPE. The objective of our work was to describe the expression and function of Ang Ⅱ receptors in the RPE and at explore the contribution of this hormone and PRR in the etiology of dry AMD. Mice were rendered hypertensive either by exogenous administration of Ang Ⅱ or by using a model of experimental renovascular hypertension (1K1C). Measurements of systolic blood pressure (BP) revealed a progressive increase during Ang Ⅱ infusion period reaching a peak value on day 14 and remaining at plateau through day 30. However, after 24 h of exposure to Ang Ⅱ, BP was not modified. Similarly, BP was significantly higher in 1K1C mice compared with the corresponding sham-operated group. No significant differences in BP were observed between control and sham-operated groups. Treatment using Ang Ⅱ in combination with angiotensin receptors blockers showed that the AT1R blocker eliminated the modifications in the BP due to Ang Ⅱ. However, the AT2R blocker did not alter the effect of Ang Ⅱ on systolic BP, demonstrating, that the effect on BP caused by Ang Ⅱ was AT1R mediated[104,112].

Our study in human and mouse also confirmed that both ATRs were expressed and upregulated by Ang Ⅱ in the RPE and showed that the activation of the AT1R by Ang Ⅱ increased the intracellular calcium levels[18,105]. These results clearly evidenced the functionality of the RPE's AT1R, which could be coupled to the phospholypase C-pathway. In contrast, activation of the AT2R by Ang Ⅱ did not mobilize intracellular calcium. AT2R could be coupled to the cytosolic phospholipase A2 and not to the PLC pathway as shown for other tissues[113]. Consequently, regulation of the AT2R transduction pathway is a possibility to be explored.

Ang Ⅱ also up-regulated the activity of MMP-2,

MMP-14, and basigin (also known as extracellular matrix metalloproteinase inducer or cluster of differentiation 147) as well as digestion of type Ⅳ collagen[18,104,112]. The Ang Ⅱ observed effects were blocked by the AT1R antagonist candesartan. *In vivo*, the Ang Ⅱ-derived decrease in collagen Ⅳ was AT1R/AT2R mediated, implying a synergistic effect. Therefore, Ang Ⅱ through MMP-2, MMP-14, and basigin regulation could stimulate RPE basement membrane breakdown allowing the migration of BLD and buildup of BLiD deposits or drusen.

It is important to note that the majority of intracellular effects of Ang Ⅱ in most tissues are MAPKs mediated. MAPKs are a group of serine/threonine kinases[114-116] which can be divided into three major groups: ERK, p38, and Jun N-terminus kinase (JNK) and participate in a wide array of cellular responses including proliferation, differentiation, migration, and stress responses among others[117-120]. We explored the involvement of MAPK as intracellular modulator of Ang Ⅱ-induced up-regulation of MMPs in the RPE. Our study showed that Ang Ⅱ-induced increase in MMP-2 activity is mediated by ErK(1/2) and p38 MAPK in the human RPE cell line ARPE-19. We also demonstrate that Ang Ⅱ increased the expression of MMP-14, MMP-2 activity major regulator, in an ErK(1/2) and p38 MAPK-dependent way while basigin does not appear to be involved in RPE cells. In addition, we reported that ErK/p38 MAP kinase signaling pathway is AT1R mediated, which could be an important mechanism by which Ang Ⅱ up-regulates MMPs in RPE cells. Moreover, we show that RPE from mice exposed to Ang Ⅱ for 4 wk showed increased MMP-14 and basigin protein expression as well as increased phosphorylated ErK(1/2), p38, and JNK MAPK. The increase in MMP-14 protein expression and activation of ErK(1/2), p38, and JNK MAPK were AT1 receptor-mediated, whereas the increase in basigin expression increase was mediated by AT2 receptor[112]. Blockade of extracellular signal-regulated kinases or p38 MAPK abolished the up-regulation of MMPs in RPE cells[112]. Given that MMP-14 and basigin are major inducers of MMP-2, our results lead us to speculate that MMP-14 and basigin might regulate Ang Ⅱ-induced MMP-2 activity through MAPKS- and AT1 receptor-dependent signaling pathways in the RPE. These original observations highlight the potential importance of this signaling pathway as a potential mediator of RPE response to Ang Ⅱ-induced ECM dysregulation and disruption of the RPE basement membrane believed to be involved in sub-RPE deposits progression in the pathogenesis of AMD. Based on our observations, MAPKs inhibitors and AT1R blockers may prevent these changes in the ECM, which are essential in the development of early AMD.

We also provided evidence that activation of the PRR may be involved in ECM-remodeling through increase of collagen I [121]. Interestingly, we confirmed that PRR and type I collagen were present in human retinas and that the expression of both proteins was higher in the RPE from dry AMD hypertensive donors (Figure 4), support-

ing our *in vitro* findings. Overall, our studies suggest a molecular mechanism by which hypertension may aggravate the pathology of dry AMD.

Even though dry AMD is not a retinal vascular pathology, we reviewed this form of the disease here because hypertension-related Ang Ⅱ has been implicated in dry AMD pathogenesis[28], and wet AMD is always preceded by the early form of the disease.

Wet AMD

As mentioned previously, about one-third of cases dry AMD can lead to wet macular degeneration which progresses much more rapidly and leads to loss of central vision. CNV is a retinal vasculature related pathology[120] associated with several common retinal degenerative or inflammatory diseases[87,120,122,123]. Inflammation and hypoxia are key cellular processes involved in the development of CNV[17-25], in that choroidal monocytes processes, for example, have been noted to insert into BrM deposits suggesting that these sub-RPE deposits may generate inflammatory stimulus at the BrM and sub-RPE space. Macrophage infiltration to the damaged sites by chemotactic factors may be responsible for the production of inflammatory cytokines and angiogenic factors such as intercellular adhesion molecule 1 (ICAM-1) and monocyte chemoattractant protein-1 (MCP-1)[124] and vascular endothelial growth factor (VEGF)[125] which will ultimately contribute to induction and/or progression of CNV[26-28]. Blockade of AT1R by systemic administration of telmisartan reduced CNV formation, macrophage infiltration and expression of VEGF, VEGF receptor-2 (VEGFR-1), ICAM-1 MCP-1 and interleukin 6 in eyes from a laser induced CNV mouse model of AMD[125]. This suggests that AT1R mediated up-regulation of these molecules and mediators participate in the development of CNV.

Ang Ⅱ has been shown to act as an indirect mitogenic agent for retinal vascular endothelial cells by increasing VEGFR-2 expression[23] which could lead to formation of CNV. Blockade of AT1R signaling suppresses pathologic but not normal retinal neovascularization by inhibiting inflammatory processes[34,116]. Additionally, it has been shown that excised choroidal neovascular membranes from patients with AMD express AT1R, AT2R and Ang Ⅱ on the vascular endothelium[126]. Similar findings were seen in the laser-induced mouse model of CNV[126]. As noted above, formation of CNV was suppressed with the AT1R blocker telmisartan but not with an AT2R antagonist[127]. In a laser induced model of CNV using AT1R knockout mice, the ACE inhibitor, imidapril, significantly reduced choroidal and retinal neovascularization in wild type mice to levels detected in laser treated AT1R KO mice[128]. Additionally, in a rat model of laser-induced CNV, losartan was shown to inhibit the incidence of new vessel formation from 99.5% to 72.5%[129].

Increasing evidence support the notion that increase in the production of of chemokines happens in diseases related to an inflammatory component. Several of these chemokines are expressed in the RPE cells, including
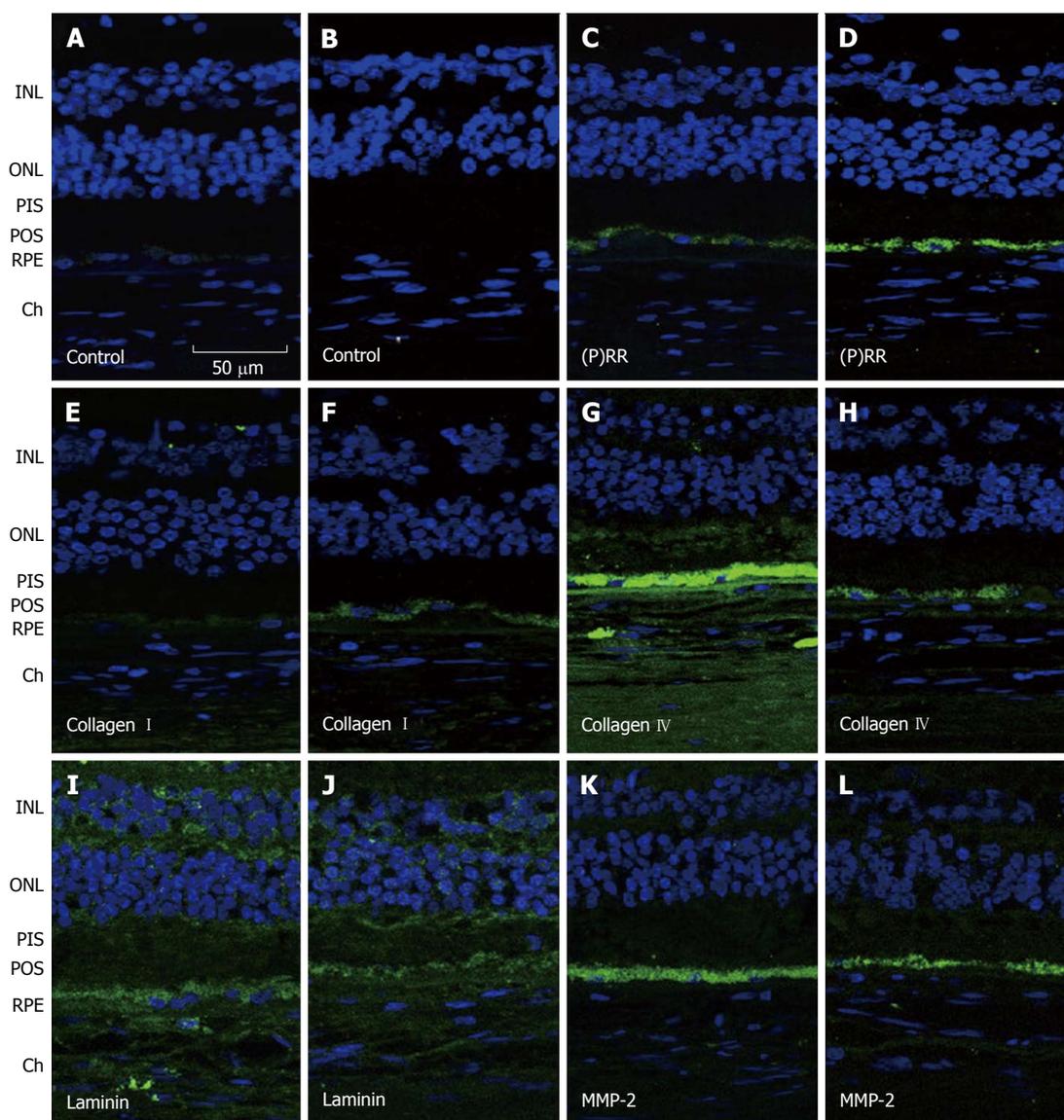
Figure 4 Representative immunofluorescent double staining of prorenin receptor, collagen types Ⅰ and Ⅳ, laminin and matrix metalloproteinase-2 (green) and nuclei (bleu) in retina sections from human donor eyes with no known eye disease (B, D, F, H, J and L), and human donor eyes with dry age-related macular degeneration and hypertension (A, C, E, G, I and K)[121]. Negative controls were generated by omission of the primary antibody (A and B). Sections were analyzed by using confocal microscopy (original magnification, × 40). INL: Inner sections were analyzed with a confocal microscope at a magnification of × 40. INL: Inner nuclear layer; ONL: Outer nuclear layer; MMP: Matrix metalloproteinase; PIS: Photoreceptor inner segments; POS: Photoreceptor outer segments; RPE: Retinal pigment epithelium; Ch: Choroid.

MCP-1[29,30], which has been proposed to be implicated in the development of dry and wet AMD[31-33]. During inflammatory responses, RPE cells have been shown to secrete MCP-1 toward the choroid, consequently, implying that RPE cells might induce recruitment of macrophage to the choroid[34]. There is clear evidence for the role of MCP-1 in angiogenesis in several angiogenic-related disorders[35-37]. Interestingly, expression of the recently discovered novel zinc finger protein MCP-1 induced protein (MCPIP) has been shown to induce tube formation in human umbilical vein endothelial cells[38].

As mentioned previously, hypoxia, which was proposed to be one of the most significant driving forces for CNV formation[130], is another key cellular process which stimulates the expression of VEGF in AMD. Angiogenic factor expression occurring secondary to hypoxia is mediated by the family of transcription regulators know as hypoxia inducible factors (HIF). HIF-1 and -2 have been found to be expressed in human choroidal neovascular membranes[131], and HIF-1 has been shown to upregulate expression of VEGF in RPE[132,133]. Hypertension-associated Ang Ⅱ is known to induce inflammation, macrophage infiltration, and angiogenesis by stimulating expression of MCP-1, HIF-1 and VEGF through the AT1R[126,134-137]. Up-regulation of MCP-1 has been demonstrated in hypoxic animals[138] and recently, it has been demonstrated that MCP-1 promotes angiogenesis *via* MCPIP, HIF-1 and VEGF induction[139]. Interestingly, previous works also suggest that the BF in the choroidal and retinal is down-regulated in AMD hypertensive
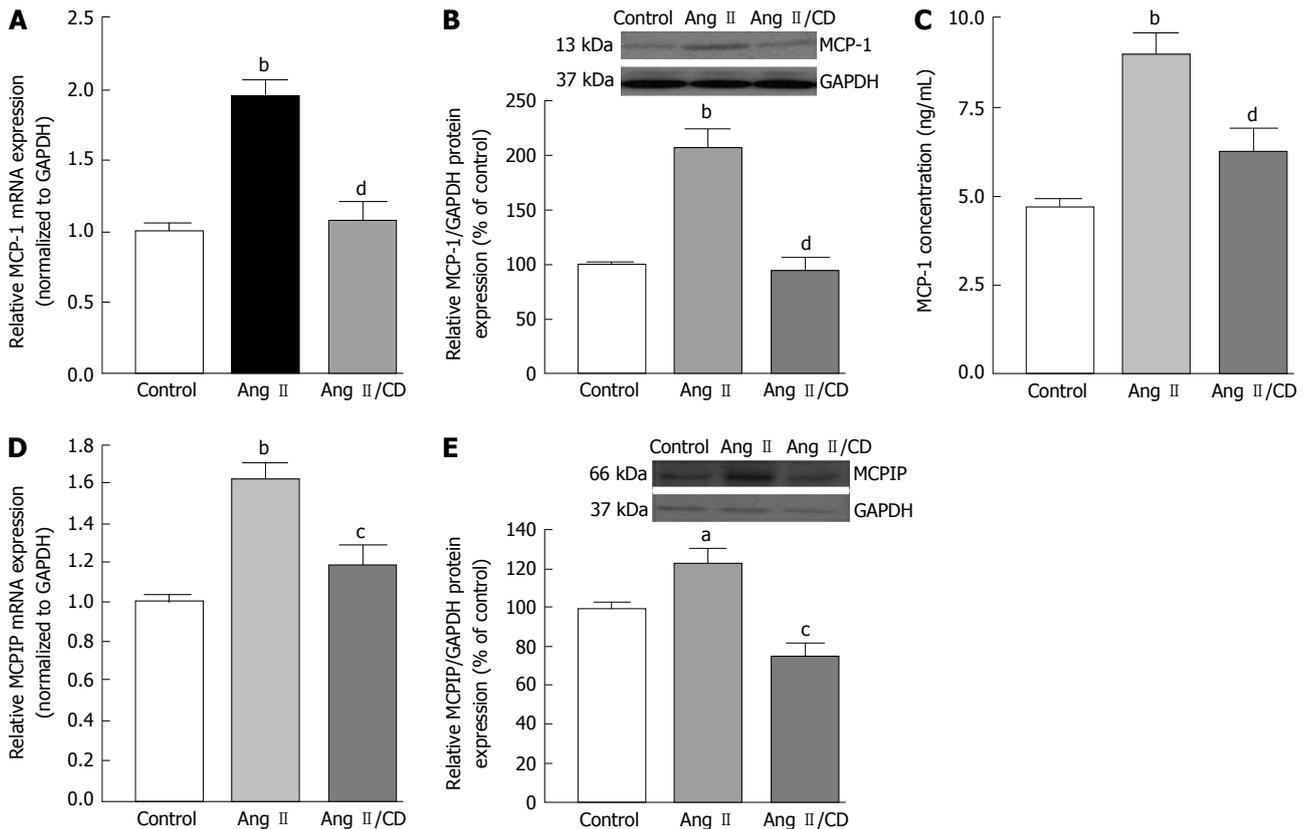
Figure 5 Hypertension-induced Angiotensin Ⅱ up-regulated monocyte chemoattractant protein-1 and monocyte chemoattractant protein-1 induced protein expression through AT1R activation in retinal pigmented epithelium-choroid[140]. C57BL 6 mice were treated with saline (1), Ang Ⅱ (2), and Ang Ⅱ in combination with candesartan (10 mg/kg per day) (3). Blood pressure was recorded before and after treatment. After 30 d of treatment, animals were sacrificed and eyes enucleated and collected for microdisection of retinal pigmented epithelium-choroid. Monocyte chemoattractant protein-1 (MCP-1) and MCP-1 induced protein (MCPIP) proteins were analyzed by real-time PCR and Western blot. MCP-1 and MCPIP mRNA expression by real-time PCR (A and D), protein expression by Western blot (B and E), and MCP-1 protein secretion by ELISA (C). GAPDH was used as control. Data are expressed as mean ± SE (n = 3). [a]$P < 0.05$, [b]$P < 0.01$ *vs* control; [c]$P < 0.05$, [d]$P < 0.01$ *vs* Ang Ⅱ-treated animals. CD: Candesartan. Ang: Angiotensin; PCR: Polymerase chain reaction; GAPDH: Glyceraldegyde 3-phosphate dehydrogenase; ELISA: Enzyme-linked immuno assay.

patients[31,32], which leads to think about the possibility that an ischaemic/hypoxia mechanism plays a role in the CNV development. Given that a positive correlation between elevated levels of circulating MCP-1 and hypertension has been previously shown, we studied whether hypertension-induced Ang Ⅱ influences the development of CNV and characterized the role played by MCP-1/MCPIP in this event. We addressed this by setting goals of understanding the mechanisms underlying the interactions between the RPE, choroidal microvascular endothelial cells (cEC) and Ang Ⅱ which may contribute to CNV development in hypertensive dry AMD patients.

Our results indicated that hypertension-induced Ang Ⅱ increases MCP-1 and MCPIP expression in mouse RPE-choroid through AT1 receptor. *In vitro*, MCP-1 and MCPIP expression was up-regulated by Ang Ⅱ in RPE cells. Moreover, MCP-1 induced expression of MCPIP in RPE cells, which led to cEC tube formation (Figures 5-7) (Marin-Castano *et al*[140] IOVS 2013; ARVO E-Abstract 6089). Therefore, our data support the hypothesis that Ang Ⅱ, through MCP-1/MCPIP may contribute to CNV, proposing a possible mechanism linking hypertension and CNV, which can provide new targets for more effective early preventive and novel therapeutic interventions.

DR AND THE RAS

The incidence of DR is alarming. A recent study emphasizes that 93 million people have DR, and that about 17 million have the blinding form of the disease[141]. Patients with type 1 or type 2 diabetes are at risk for the development of DR. The longer a person has diabetes, the more likely they are to develop DR[142]. DR is classified into two types: (1) non-proliferative DR (NPDR), the early state of the disease. In NPDR, the blood vessels in the retina are weakened causing tiny bulges called microanuerysms. The microanuerysms may leak fluid into the retina, which may lead to swelling of the macula: and (2) proliferative DR (PDR), which is the more advanced form of the disease. At this stage, the retina becomes oxygen deprived. New blood vessels can start to grow in the retina and into the vitreous causing clouding vision. If left untreated, PDR can cause severe vision loss and even blindness[143]. The progression to PDR looks like to be a result of tissue ischemia and the consequent increase in the production of angiogenic growth factors such as VEGF.

The report that some components of the RAS are augmented in blood and eyes from DR patients[46,144,145], suggests the RAS may be implicated in the pathogenesis
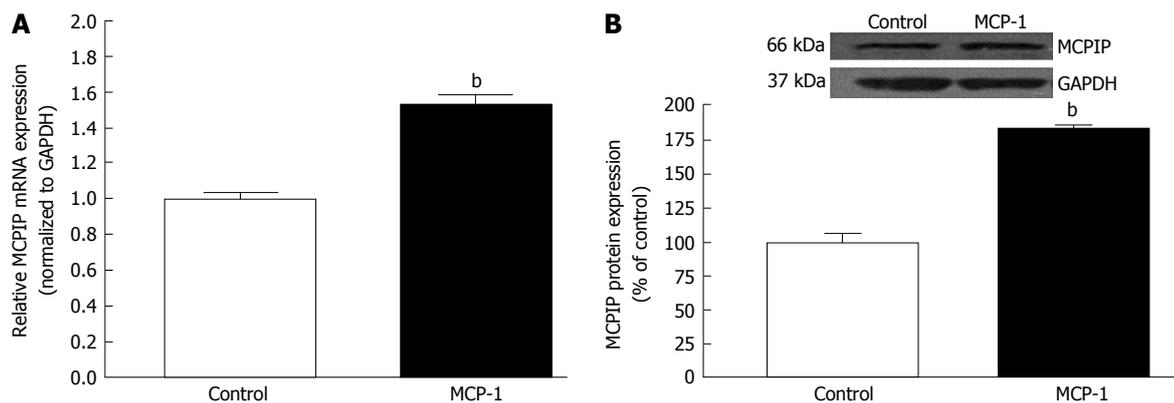
Figure 6 Monocyte chemoattractant protein up-regulates monocyte chemoattractant protein-1 induced protein expression in ARPE-19 cells[140]. Monocyte chemoattractant protein-1 (MCP-1) increases MCP-1 induced protein (MCPIP) mRNA (A) and MCPIP protein expression (B) in human retinal pigment epithelium cells. The maintenance medium was deprived of phenol red for 2 d. Medium FBS content was then brought down from 10% to 1% for 1 d. Subsequently, cells were treated with with 50 pg/mL MCP-1 for 24 h in a medium supplemented with 0.1% FBS. Cell homogenates were collected to assess MCPIP expression by real-time PCR and Western blot. GAPDH was used as control. Data are mean ± SE (n = 4). [b]P < 0.01 *vs* control cells; FBS: Medium with fetal bovine serum; PCR: Polymerase chain reaction; GAPDH: Glyceraldehyde 3-phosphate dehydrogenase.

of DR[28]. An increase of angiotensinogen, ACE, ACE2, and AT1R in retinas from diabetic animals was described previously[35,146,147]. Up to now, research addressed to find a link between the RAS and retinopathy has been based on the retinal microvasculature. Strong evidence supporting a role of Ang Ⅱ in pericytes and endothelial cells in the retinal microvasculature has been shown. Ang Ⅱ has a mitogenic effect on retinal endothelial cells[23,59,148]. This peptide also decreases the expression of pigment epithelium derived growth factor[148] and enhances proliferation of endothelial cells in retina through VEGF up-regulation[23,149]. Moreover, glucose ingestion by the retinal tissue might be instantly regulated by Ang Ⅱ[150,151]. This increase in glucose in turn could induce VEGF expression and potentates the effect of Ang Ⅱ on VEGF expression as demonstrated previously in vascular smooth muscle cells[152]. Since it is clear that reactive oxygen species (ROS) contribute to cellular damage in DR by inducing VEGF[153,154], and that both Ang Ⅱ and high glucose can lead to ROS formation,[155,156] ROS may be a common pathway linking a synergistic effect between Ang Ⅱ and high glucose on the activation of VEGF.

The actions of Ang Ⅱ on the retinal vasculature have been well described in pericytes. These microvascular cells are incriminated in the regulation of capillary tone[157], and it has been suggested they have other extra roles such as preservation of microvascular homeostasis[149]. For instance, death of pericytes has been linked to the initial sign of DR. It has been reported that Ang Ⅱ uncouples pericytes from the vasculature[48,158]. Studies *in vitro* have shown activation of pericyte migration by Ang Ⅱ through the AT1R[159,160]. Moreover, Ang Ⅱ also has an effect on pericyte viability, by increasing apoptosis[33,59]. Therefore, it is evident that Ang Ⅱ impacts the retinal microvasculature. Research in diabetic animals showed a reduction in the retinal microvascular injury by exposure to ACE inhibitors and AT1R blockers. These data revealed a decrease in the vascular leakage, acellular capillaries formation, VEGF production[161-164], leukostasis and adhesion molecules[164-167]. Comparable advantages were observed in different animal models of diabetes, which were treated with renin inhibitors[167], PRR inhibitor[35], and gene delivery of ACE2[160] respectively. Diabetes may also affect neuronal retina in DR. For example, diabetic retina may reveal releasing of pro-inflammatory factors by microglia[168], death of retinal neurons[169], apoptosis of ganglion cells[170], glial dysfunction[170] and photoreceptors loss[171]. These pathological neuronal effects may be translated to electrophysiological abnormalities[172-174]. Color vision, contrast sensitivity and dark adaption[24,175] can be altered by diabetes before the presence of any apparent pathological sign in the vessels[175]. Given that treatment with ACE inhibitors and AT1R blockers decreases these deficits in retinal function[176-179], the advantages of RAS blockade could extend to non-vascular cells.

It is also interesting to note that discovery of other important players on the RAS such as ACE2 and Ang (1-7) has resulted in the emerging new role ascribed to these RAS components beyond the classic ACE/Ang Ⅱ/AT1R axis of the RAS[179-180]. Nevertheless, the force of this novel axis stays inadequately elucidated[180,182-184]. This new protective axis antagonizes the classic role of the vasoconstrictor axis. Thus, it was assumed that a disproportion in the vasoprotective/vasodeleterious axis of the RAS, could result in the development and progression of DR. Many studies in non-ocular tissues have emphasized the beneficial effect of the balance displacement of the RAS towards the ACE2/Ang (1-7)[180,185-189]. Therefore, activation of the vasoprotective axis is currently considered to be part of the beneficial actions of ACEi and ATRs blocker drugs[180,182], which neutralize the actions of Ang Ⅱ, in spite of its origins of generation[146].

High blood pressure is a great risk factor for DR. Several studies have been addressed to elucidate if the contribution of the Ang Ⅱ to the development of DR is *via* blood pressure dependent or independent. This is an intricate search, given that blockers of some compound of the RAS decrease both blood pressure and the actions
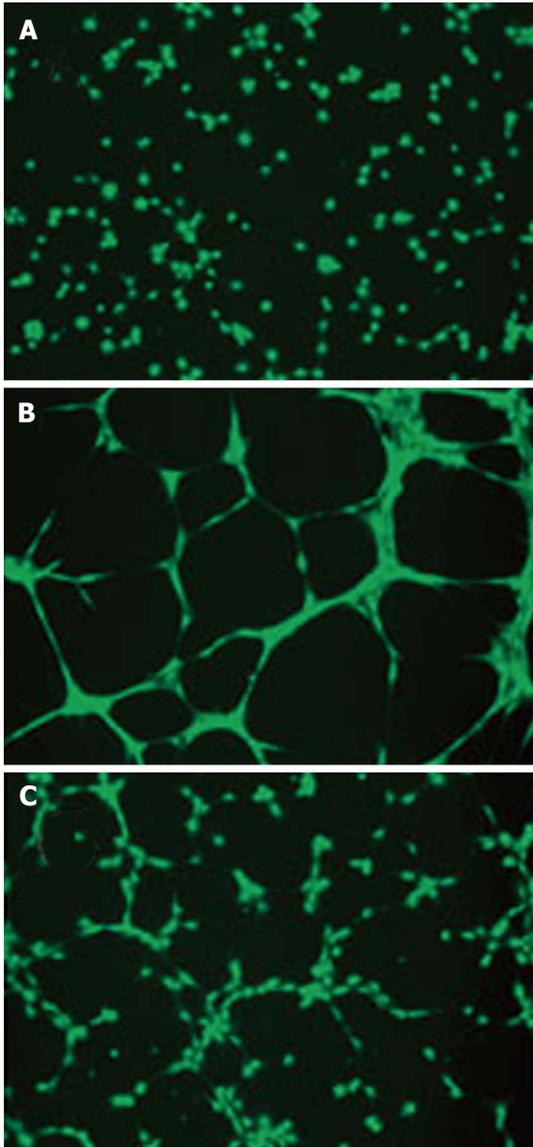
Figure 7 Conditioned medium collected from human ARPE-19 cells exposed to Ang Ⅱ promotes tube formation in choroidal microvascular endothelial through AT1 activation[140]. Cells were exposed to: (1) Ang Ⅱ alone; or (2) Ang Ⅱ in combination with candesartan for 24 h, supernatants were collected after treatment and human choroidal microvascular endothelial (cECs) were treated with the supernatants for 24 h. Thereafter, cells were trypsinized and then seeded (42000 cells/cm²) on a 24-well polystyrene plate coated with Geltrex™ (50 μL/cm²) according to the manufacturer's protocol followed by incubation in EBM medium for 24 h at 37 ℃ in 5% CO₂. At 16 h post-seeding, 2 μg/mL of Calcein, AM (Invitrogen, Cat # C3099), was added directly to the culture well and allowed to incubate for 20 min (37 ℃, 5% CO₂). Cells were visualized using a fluorescence microscope. A: Control; B: cECs exposed to conditioned medium from Ang Ⅱ-treated ARPE-19 cells; C: cECs treated with medium collected from treated retinal pigment epithelium cells. EBM: Endothelial cell basal; AM: Acetoxymethyl.

of the Ang Ⅱ at cellular levels. Studies in Ren-2 rat with hypertension showed that both AT1R and β-adrenergic blockade regularize blood pressure[158]. Nevertheless, the retinal vascular pathology only becomes better using AT1R blockers. Additional determination of the blood pressure-independent effects of the RAS blockade in DR is crucial for diabetic patients without hypertension.

The mechanism(s) by which the RAS exerts its effects in the retina are being investigated. There is proof that hypertension and mechanical stretch up-regulate the RAS and VEGF expression[190]. It has been previously demonstrated an increase of VEGF in the RPE[191] and in retinal endothelial cells[192] due to mechanical stretch. Moreover, rats with hypertension showed increased expression of the VEGFR-2 in the retina[191]. Therefore, it could be probable that the decrease in VEGF reported in DR[193] following RAS blockade could be due to the antihypertensive properties of this treatment, rather than, suppression of the growth factor effects of Ang Ⅱ. Moreover, given that a relationship between ROS and cellular damage in DR has been demonstrated and the fact that ROS production is induced by Ang Ⅱ[153,154,194,195], it is likely that ROS are essential in the pathogenesis of DR. The main origin of the ROS is nicotinamide adenine dinucleotide phosphate (NADPH, or NOX) and ROS originated from NOX have been associated with the development of DR[196,197]. Ang Ⅱ modulates NOX to generate ROS[194,198]. However, the connection between the RAS and NOX in retinopathy is not completely clarified yet[199,200]. Obviously, the link involving RAS and NOX in DR guarantees further study.

Clinical trials evaluated the influence of Ang Ⅱ in the development and progression of DR. To elucidate this, three major studies addressed to evaluate the blockade of the RAS were done: (1) the DIabetic REtinopathy Candesartan trial[201-204]; (2) the Appropriate Blood Pressure Control in Diabetes trial[205]; and (3) the Action in Diabetes and Vascular Disease Controlled Evaluation (ADVANCE) trial[206]. The first study showed that candesartan, an AT1R blocker, modestly avoid the evolution of retinopathy in type 1 diabetic patients without hypertension. From another point of view, this AT1R blocker caused reversion of retinopathy in type 2 diabetic patients in a 34% regression of retinopathy and decreased the risk of microaneurysm evolution in both types of diabetes[202]. The second trial study, showed notably benefit for RAS blockade[203], whereas the ADVANCE study reported that treatment with a combination of an ACE inhibitor and a diuretic, did not affect the retinopathy risk[205]. I summary, these data document the influence of Ang Ⅱ in the development of DR. Further evaluation of the RAS blockade in DR is still to be determined.

CONCLUSION

Hypertension is a potential link between cardiovascular pathologies and eye diseases. A large amount of information has demonstrated the presence of a RAS in the retina which is greatly spread in the vasculature. To date, findings from epidemiological studies indicate an association between AMD and hypertension. Moreover, studies *in vitro* and *in vivo* show that Ang Ⅱ contributes to sub-RPE deposit formation and CNV development and that these events can be improved by Ang Ⅱ receptor blockers (ARBs). However, the utility of ARBs for the treat-

ment of eye AMD is still to be determined. In terms of DR, there is documented evidence showing a clear contribution of Ang Ⅱ to the development of this disease. Therefore, the use of ARBs can confer retinoprotection and arrest the progression of DR.

ACKNOWLEDGMENTS

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