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ANGIOTENSIN-(1-7)/MAS AXIS AND VASCULAR INFLAMMATION

Guang Yang
Department of Nephrology,
Heinrich-Heine-University Duesseldorf, Germany
Fanxing Meng, PhD
Department of Animal Science, Jilin Agricultural University, China
Jialin Wang, MD
Department of Nephrology, RWTH University Aachen, Germany
Yanping Zhao
Department of Family Medicine and Primary Care,
University of Hong Kong, China
Linlin Zhao
Department of Systems Biology,
Heinrich-Heine-University Duesseldorf, Germany

Abstract

Atherosclerosis, as a potentially serious condition, has become one of the most prevalent causes of mortality over the world. RAS (Renin-angiotensin-system) is recognized to be a key role in the development of atherosclerosis, which considered as a chronic inflammatory disease. Ang II (angiotensin II) is proven to cause atherosclerosis, hypertension and aortic aneurysms. While activation of Mas receptors by Ang-(1-7) [angiotensin-(1-7)] shows an important role in prevention of atherosclerosis. The activation of Ang-(1-7)/Mas receptor axis counteracts Ang II-induced hypertension, inflammation, fibrosis and apoptosis responses. We have concluded that, the relationship between Ang-(1-7)/Mas axis and vascular inflammation could be the paving-stone of the avoidance and novel treatment for atherosclerosis. The scope of this study is to review the relationship between Ang-(1-7)/Mas axis and vascular inflammation in the development of atherosclerosis.

Keywords: Atherosclerosis, Angiotensin II, Angiotensin-(1-7), Mas receptor, Vascular inflammation

Atherosclerosis

Atherosclerosis, as vascular disease is observed commonly in

patients, is a potentially serious condition which has become one of the most prevalent causes of mortality in developed and developing countries (Leong, Ng, & Jaarin, 2015). More than 50% of the cause of deaths is related to atherosclerosis in the USA, Europe and Japan (Ross, 1993). Atherosclerosis is an insidious disease, which exists in humans for a long-term without any symptom. Nevertheless, it is usually accompanied by ischemia, angina, myocardial infarction, stroke and cardiac failure (Husain, Hernandez, Ansari, & Ferder, 2015; Moss & Jaffe, 2015). All these are global health challenges in recent years.

Dozens of years ago, atherosclerosis used to be considered as a chronic disease caused by the accumulation of cholesterol and thrombotic debris in the artery wall (Libby, 2012). In the 1970s, researchers suggested that the proliferation of smooth muscle cells is the nidus of atherosclerotic lesion plaques (Ross & Glomset, 1976a, 1976b). However, in recent decades, more and more experiments demonstrated that atherosclerosis is a chronic inflammatory process caused by the cardiovascular risk factors and the vascular remodeling (Libby, 2012). The storage of fatty substances, cholesterol, connective tissue, thrombus, calcium and fibrin is the main reason for the formation of atherosclerotic plaques inside the arteries. This leads to the thickening of the arterial wall and narrowing of the arteries. And finally, it causes the arteries sclerosis and elastic loss (Finn, Nakano, Narula, Kolodgie, & Virmani, 2010). In general, the increasing accumulation of adipocytes can augment the release of free fatty acid, enhance the physiological stress and promote the generation of ROS (reactive oxygen species). These stress factors can induce the release of inflammatory adipokines, such as IL-6 (interleukin- 6), Serum amyloid A and MCP-1 (monocyte chemotactic protein 1). Then the inflammatory adipokines enter the circulation, promote the activated monocytes differentiate into the arterial wall and adipose tissue. Also, the monocytes can differentiate into macrophages, which can release cytokines. The released cytokines also promote the inflammatory process (Gustafson, 2010). Apart from aorta, and the cardiac coronary artery, cerebral artery and renal artery are the main formative parts of atherosclerosis. It may lead to aneurysm rupture, thrombosis and stenosis to occlusion, which show disorders of blood supply in some organs. The pathological process of atherosclerosis is complex, and the influencing factors are multifaceted.

ACE2/Ang-(1-7)/Mas axis was found to play a vital role in the treatment of atherosclerosis (McKinney, Fattah, Loughrey, Milligan, & Nicklin, 2014). Most of the experiments show evidences that activated Ang-(1-7)/Mas axis attenuates the inflammatory process. Accordingly, it makes sense to study the ACE2/Ang-(1-7)/Mas axis to better understand the prevention mechanism of atherosclerosis. Meanwhile, this could provide new

ideas for the prevention and treatment of atherosclerotic vascular disease. Thus, we focus on the recent discovery of Ang-(1-7)/Mas axis and vascular inflammation, as well as its future prospects.

Renin-Angiotensin System

As a major human health challenge, atherosclerosis attracts increasing attention from the researchers. Pathological processes, preventive strategies and therapeutic methods come to light progressively. RAS (Renin-angiotensin system) plays a central role in the pathogenesis of cardiovascular disease, including atherosclerosis, AAA (abdominal aortic aneurysm) and hypertension (Ferrario & Strawn, 2006; Guang, He, Yu, & Yao, 2015; Husain et al., 2015). There are two main axes in the research of RAS：ACE/Ang II/AT1R axis and ACE2/Ang-(1-7)/Mas axis. Activation of ACE/Ang II/AT1R axis aggravates the development of atherosclerosis. In opposite, activation of ACE2/Ang-(1-7)/Mas axis improves the Ang II-induced effects in atherosclerosis.

Angiotensin II

Ang II is an important peptide in RAS, can induce endothelial dysfunction, hypertension, inflammation, atherosclerosis and cardiac hypertrophy (Weiss, Kools, & Taylor, 2001). Ang II degraded from Ang I (angiotensin I) through the enzymatic degradation of ACE (angiotensin-converting enzyme). And then, Ang II activates AT1R (Angiotensin II Type I Receptors) and AT2R (Angiotensin II Type II Receptors) to regulate the physiological effects (Savoia, Burger, Nishigaki, Montezano, & Touyz, 2011). Daugherty et al. first found that Ang II accelerated the development of atherosclerosis and AAA in ApoE knockout (ApoE-KO) mice in 2000 (Daugherty, Manning, & Cassis, 2000). Macrophage in filtration, T cell infiltration and B cell infiltration was observed in the vascular wall. This plays a central role in vascular inflammation. Besides, Ang II is involved in the development of atherosclerosis via stimulating the proliferation of VSMC (vascular smooth muscle cells), and it also induces associated symptoms via hypertension. Since increasing pressure of the vascular wall is considered to be a pro-inflammatory stimuli (Taylor, 1998). In addition, it causes fibrosis, vasoconstriction and angiosteosis through disrupting the growth and apoptosis of VSMC (Savoia et al., 2011; Simoes e Silva, Silveira, Ferreira, & Teixeira, 2013). ROS and peroxide production are highly related to the procedure (Mehta & Griendling, 2007). Additionally, over-expression of inflammatory factors have also been approved in this process (Xie, Sun, Yang, & Sun, 2006). Ultimately, development of AAA and atherosclerosis is independent of hypercholesterolemia and high blood pressure (Cassis et al., 2009). This was confirmed in clinical researches and

animal experiments.

Angiotensin-(1-7) and Mas receptor

Ang-(1-7) is the endogenous ligand for G-protein-coupled Mas receptors (Gironacci et al., 2011; Kostenis et al., 2005). It is confirmed that Ang-(1-7) plays a prevention role in RAS, and it also shows many effects in related physiology and pathology (Stegbauer, Vonend, Oberhauser, & Rump, 2003). Ang-(1-7) is degraded from Ang II by PEP (prolyl endopeptidase), PCP (prolyl carboxypeptidase) or ACE2. Also, after the hydrolysis by PEP or EP (endopeptidase), Ang I can be degraded into Ang-(1-7). Or Ang I can be degraded into Ang-(1-9) primarily by ACE1, and then Ang-(1-9) will be degraded into Ang-(1-7) by ACE or EP (Savoia et al., 2011). Especially, Ang II (protein sequences: NH_2-Asp-Arg-Val-Tyr-Ile-His-Pro-Phe) is degraded into Ang-(1-7) (protein sequences: NH_2-Asp-Arg-Val-Tyr-Ile-His-Pro) by ACE2 is considered to be the main pathway.

Mas receptor, encoded from MAS1 oncogene, is a G protein-coupled receptor which activated by Ang-(1-7), the metabolite of Ang II. What's more, Mas receptor is a seven transmembrane receptor (Young, Waitches, Birchmeier, Fasano, & Wigler, 1986). It is widely expressed in brain, but little in heart, liver, lung, kidney, spleen and skeletal muscle (Metzger et al., 1995). The human Mas receptor is composed of 325 amino acid residues, meanwhile, the Mas receptor from rat and mouse is composed of 324 amino acid residues. Furthermore, Mas receptors are highly conserved. For example, the encoded protein homology is 97% between rat and mouse, and 91% between human and mouse (Metzger et al., 1995).

Activated ACE2/Ang-(1-7)/Mas axis shows an antagonism effect to activated ACE/Ang II/AT1R axis. Therefore, Mas receptors' agonists and Ang II receptors' antagonists show the same treatment effect in hypertension (Santos & Ferreira, 2006). Since Ang-(1-7) can suppress the migration of leukocytes, expression of cytokines and fibrosis in inflammatory response (Simoes e Silva et al., 2013). It inhibited early atherosclerotic lesions via protecting the endothelial cells, and suppressing the proliferation and migration of smooth muscle cells. Ang-(1-7) enhanced plaque stability through attenuates the inflammatory response and MMP's expression and activities (Masson et al., 2009). Potthoff et al. shown that, Ang-(1-7) actives the Mas receptors to mediate the vascular function that attenuates pressor response to Ang II in ApoE-KO mice by reducing ROS-mediated p38 MAPK (mitogen-activated protein kinase) activity (Potthoff et al., 2014). Rodrigo A. Fraga-Silva (Fraga-Silva et al., 2014) observed that, compare to the oscillatory shear stress-induced plaque, Ang-(1-7) increased intra-plaque collagen content in aortic root region, reduced shear stress-induced carotid plaques, decreased MMP-9 content, and declined neutrophil

and macrophage infiltration in ApoE-KO mice treated with Western-type diet. And in vitro incubation with Ang-(1-7) did not influence the expression and apoptosis of ICAM-1 in cultured endothelial cells. Furthermore, many experiments demonstrated that deletion of ACE2 gene in ApoE-KO mice leads to the decrease of Ang-(1-7). In the meantime, vascular cell adhesion molecules (VCAM), cytokines, chemokines and matrix metalloprotease (MMP) are increased. This aggravates the vascular inflammation and atherosclerosis (Thomas et al., 2010). But over expression of ACE2 severe cardiac fibrosis, which adverse response to the organism (Masson et al., 2009). Extensive researches have shown that, Ang-(1-7) dose-dependently ameliorates atherosclerosis (Yang et al., 2013). In contrast, Ang-(1-7) caused the pathological outcome by aggravating the inflammatory response, because Mas receptor deficiency depressed NF-κB activation (Esteban et al., 2009). And this is independently from Ang II receptors. Consequently, treatment with an oral formulation of Ang-(1-7) can reduce inflammation and enhance a more stable phenotype in carotid atherosclerotic plaques. In summary, Mas receptors as an essential part of RAS are important for future researches in cardiovascular therapeutics and the drug development.

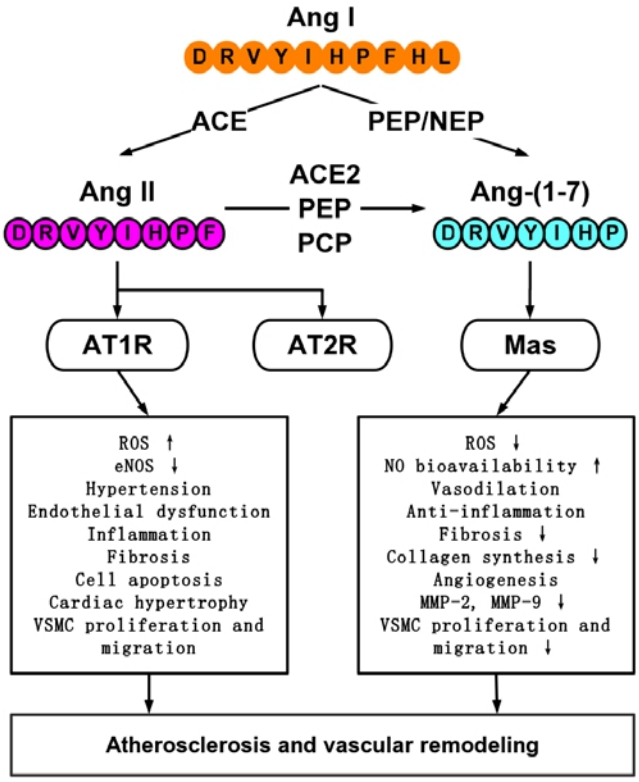

Figure 1

The RAS is a central regulation system in the development of atherosclerosis. The main effector peptides are mainly generated by the actions of ACE and ACE2. Activated ACE/Ang II/AT1R axis increases ROS production, decreases eNOS, and causes hypertension, endothelial dysfunction, tissue inflammation, fibrosis, cell apoptosis, cardiac hypertrophy and VSMC proliferation and migration. While, activated ACE2/Ang-(1-7)/Mas axis decreases oxidative stress, inflammation and fibrosis levels, increases NO bioavailability, and causes vasodilation and angiogenesis. It also reduces collagen synthesis, MMP-2 and MMP-9 expression levels. All of these cases are related to the development of atherosclerosis and vascular remodeling. ACE, angiotensin converting enzyme; PEP, prolyl-endopeptidase; NEP, neutral endopeptidase; PCP, prolyl-carboxypeptidase.

Atherosclerosis and Vascular Inflammation

Atherosclerosis leads to the vascular endothelial cells dysfunction, influences the migration, proliferation and apoptosis of vascular smooth muscle cells. Also it promotes the differentiation of monocytes, accumulation of macrophages and release of cytokines. Furthermore, atherosclerosis causes the vascular remodeling, and influences the synthesis and degradation processes of extracellular matrix. Nonetheless, the mechanism relationship between adventitia and ACE2/Ang-(1-7)/Mas axis remains unclear.

Macrophage

Macrophage, is a type of white blood cell in a process called phagocytosis, derived from monocytes differentiation. Both macrophages and monocytes are phagocytes. They are involved in innate immune cells and immune process. Beyond increasing inflammation and stimulating the immune system, macrophages also play a vital important anti-inflammatory role and can release cytokines to decrease the immune reaction. In some metabolic diseases situations, such as hyperlipoidemia, hypertension and diabetes mellitus, macrophages will be activated. And then macrophages keep in influencing vessels during the period from the early atherosclerotic arterial phase to clinical complications stage (Libby, 2012). Hyperlipemia can increase monocytes through encouraging the pro-inflammatory cytokines release from peripheral blood monocytes. Afterwards, monocytes invasive into the sub-endothelium space and differentiate into macrophages through the adhesion molecules (Koga & Aikawa, 2012). This process is called macrophage infiltration. Significant invasion of macrophages is the characteristic of vulnerable plaque (Yang et al., 2013). And then, the oxLDL will store in the macrophages to form foam cells. Activated macrophages

will release varies inflammatory factors and adhesion molecules, such as MCP-1 that further exacerbate the increase of macrophages. Thus, macrophages are considered as an important factor in the formation of atherosclerotic plaques. As a matter of fact, macrophages play a key role in atherosclerosis throughout the pathological processes. Meanwhile, Ang-(1-7) reduces the development of atherosclerosis through attenuating the inflammatory response caused by macrophages (Souza & Costa-Neto, 2012).

Ang-(1-7) reduced the macrophages level in coronary plaques and enhanced the plaque stability (Yang et al., 2013). Larura (Souza & Costa-Neto, 2012) found that, Ang-(1-7) decreased LPS induced inflammatory response induced in macrophages. The expression of TNF-α and IL-6 has been suppressed. But the inhibition of pro-inflammatory cytokines was not observed under the activation of A779, the antagonist of Mas receptors. Interleukin-6 (IL-6), as an inflammatory marker of local coronary plaque and blood circulation, can aggravate the development of atherosclerosis and even cause aneurysms rupture (Wang, Liu, Wang, & Jin, 2014). Tumor necrosis factor alpha (TNF-α) is a cytokine involved in systemic inflammation, and it was mainly secreted by monocytes and macrophages. It mediates cell survival, proliferation and apoptosis (Ma et al., 2014). Ang-(1-7) decreased the phosphorylation level of Lyn in this process (Souza & Costa-Neto, 2012). Consequently, Ang-(1-7) has anti-inflammatory role via mediating the Src kinases activities to decrease the expression of pro-inflammatory cytokines.

Macrophages have different subpopulations. Atherosclerotic lesion plaques are mainly contained two subpopulations, pro-inflammatory macrophages (M1) and anti-inflammatory macrophages (M2). The excessive ratio of M1/M2 will lead to lesion formation and plaque vulnerability in the lesion area (Koga & Aikawa, 2012). Ang-(1-7) can reduce the ratio of M1/M2. It was also found that the M2 related genes Arg-1 and CCL9 were positive regulated, and the M1 related genes CD86 and iNOS (inducible nitric oxide synthase) was negative regulated. At the same time, the expression of TNF-α, IL-6 and MCP-1 was obviously decreased (Yang et al., 2013). Additionally, MMPs are produced by a range of cells including macrophages and VSMC (Ng, Morris, & Golledge, 2015). MMP-2 and MMP-9 have been suggested playing an important role in vascular remodeling through extracellular matrix degradation. Ang-(1-7) caused the noticeable reduction of pro-MMP-2、MMP-2、pro-MMP-9、MMP-9 in aortic plaques. However, Ang II increased the mRNA expression of MMP-2、MMP-9 in macrophages. As a consequence, Ang-(1-7) can attenuate the inflammatory responses in plaques and the expression of inflammatory cytokines in macrophages.

Vascular Endothelial Cells

Vascular endothelium is the inner part of the vessel, and is involved in endocrine and paracrine to regulate the vascular wall function. Endothelial dysfunction is considered to be the initial process of atherosclerosis (Onat, Brillon, Colombo, & Schmidt, 2011). At the same time, vascular endothelium is one part about the production and action of Ang-(1-7) (Verano-Braga et al., 2012). Many inflammatory factors seem to be related to this process. Many experimental results showed that, Ang-(1-7) decreased the migration of white blood cells, expression of chemokines and fibrosis. ACE2 deficiency augmented monocytes adhesion and inflammatory factors release to endothelial cells in mice (Z. Zhang, Chen, Zhong, Gao, & Oudit, 2014). As a consequence, vascular dysfunction is considered as a key factor during the whole development of atherosclerosis. The research of vascular endothelial cells and its related risk factors has a positive meaning in the understanding of pathological process of atherosclerosis.

Stegbauer (Stegbauer et al., 2011) found that, Ang-(1-7) attenuated the renal vascular dysfunction in ApoE-KO mice with Western-type diet. The possible reason is that Ang-(1-7) mediated NO (nitric oxide) production so that increased the bioavailability of NO. This may be caused by the activation of Mas receptors through Ang-(1-7). In summary, Ang-(1-7)/Mas pathway modulates vascular function, and the activated Mas receptor attenuates pressor response to Ang II in ApoE-KO mice by reducing reactive oxygen species-mediated p38 mitogen-activated protein kinase activity (Potthoff et al., 2014). Thiago (Verano-Braga et al., 2012) studied the human aortic endothelial cells treated with Ang-(1-7). The results suggest that the anti-proliferative activity of Ang-(1-7) is owing to the activation or inactivation of several target phosphoproteins, such as FOXO1 (fork head box protein O1), mitogen-activated protein kinase 1 and AKT1S1 (proline-rich AKT1 substrate 1). Zhang (F. Zhang, Ren, Chan, & Chen, 2013) found that, Ang-(1-7) attenuates the inflammatory process via Mas-receptor activation that reducing the expression of VCAM-1 and NF-kappaB in the vascular endothelial cells. The AT1 receptor antagonist can increase the expression of ACE2/Ang-(1-7)/Mas axis, thereby, reducing the expression of pro-inflammatory factors TNF-α, IFN-γ, IL-1β and IL-6. And it also induces the expression of anti-inflammatory factors, such as IL-10 (Simoes e Silva et al., 2013). Thus, Ang-(1-7)/Mas pathway plays an active role in the maintenance of endothelial function and inflammatory process.

Vascular cell adhesion molecule 1 (VCAM-1) also known as vascular cell adhesion protein 1 or cluster of differentiation 106 (CD106), which is encoded by the *VCAM1* gene in human body (Cybulsky et al., 1991). VCAM-1 stimulates lymphocytes, monocytes, eosinophils and basophils adhere to the vascular endothelium. It involves the cell identification, cell

activation and signal transduction, also mediates the stretching, movement, growth and differentiation of the cells. Experimental results suggest that VCAM-1 mainly stimulates monocytes adhere to vascular endothelium in early disease process period of atherosclerosis. Moreover, the adhesion of T-lymphocytes and monocytes to vascular endothelial cells means the beginning of atherosclerosis inflammation. Consequently, VCAM-1 is considered playing an important role in the physiological and pathological processes of inflammation, thrombosis and atherosclerosis.

In the research of vascular endothelium, Ang II enhanced the mRNA expression of VCAM-1 (F. Zhang et al., 2013). But there was no effect when EC were only treated with Ang-(1-7). However, Ang-(1-7) significantly suppressed the gene expression of VCAM-1 when EC treated together with Ang II and Ang-(1-7), and it also decreased the promoter activity of VCAM-1. At the same time, the translocation of NF-kappaB is also reduced. At the same time, when EC were treated with Ang II, Ang-(1-7) and A-779 together, the inhibition of VCAM-1 promoter and translocation of NF-kappaB were not observed. Thus, Ang-(1-7) is an integral part of the RAS, can regulate ECs though Mas receptors, also suppress the expression of VCAM-1 activated by Ang II via decreasing the translocation of NF-kappaB.

Vascular Smooth Muscle Cells

Vascular smooth muscle cells (VSMC）is one of the main components of the vascular wall, can cause the change of blood pressure. Excessive vasoconstriction can increase blood pressure. Conversely, excessive vasodilation can decrease the blood pressure. The proliferation and migration of VSMC are considered to be one of the early features of atherosclerosis (Yang et al., 2013). VSMC is related to a variety of mechanisms of vascular disease. In addition, the activated VSMC in atherosclerotic lesion parts can produce diversity of cytokines and proteases (Koga & Aikawa, 2012). In the lesion area with inflammation, MMPs are over expressed by macrophages. And in the fibrous cap, VSMC will produce excess collagen-degrading enzymes. The terrible result is the rupture of the lesion plaque because of the thinner vascular. Moreover, Ang II is not only shown regulations in cardiovascular and renal steady, but also showed functions in cardiovascular disease, atherosclerosis, hypertension and cardiac failure. Activation of MAPKs by Ang II can cause the migration, proliferation and inflammation of VSMC (Eguchi, Dempsey, Frank, Motley, & Inagami, 2001; Rateri et al., 2014). At the same time, the activation of Ang-(1-7)/Mas shows an antagonist function to it. Thus, the inflammatory mechanism research of VSMC is a key point for the therapy of atherosclerosis and aortic aneurysm.

Yang (Yang et al., 2013) found that, Ang II increased the proliferation

and migration of VSMC, and it also increased the phosphorylation level of ERK/P38 and JAK/STAT, promoted the mRNA expression of MMP-2 and MMP-9. But all the conditions were normal when co-infusion with Ang II and Ang-(1-7) together. This means that, Ang-(1-7) offset the adverse effects of Ang II to VSMC. The qPCR results show that, Ang-(1-7) increased the mRNA level of AT2R, but nothing observed in the mRNA level of AT1R and Mas. Ang-(1-7) adjusted the composition of coronary plaques and increased the VSMC collagen content. Thereby enhanced the stability of the plaques. SM22 α is a cytoskeletal protein, which can modify the VSMC phenotype to limit plaque growth (Feil, Hofmann, & Feil, 2004). This is important functional role in vascular remodeling. Ang-(1-7) can enhance the protein expression of SM22 α in artery media of ApoE-KO mice (Yang et al., 2013). Previous studies showed that, Ang II activated the ERK, JNK and p38MAPK signaling pathway in VSMC (Eguchi et al., 2001). These MAPKs can regulate the inflammation, proliferation, differentiation, apoptosis and survival processes via inducing the expression of inflammatory factors. In the study of Ang-(1-7) agonist, AVE0991 decreased the Ang II-induced VSMC proliferation, and it also significantly decreased the ROS and p38 MAPK phosphorylation level. But these results were not observed by the primary treated with A779, an antagonist of Ang-(1-7) (Sheng-Long et al., 2012). The animal experimental results show that Ang II caused loss of smooth muscle cells, elastin fragmentation, and presence of adventitial inflammation (Rateri et al., 2014)。

Adventitia

Atherosclerosis was considered related to adventitial inflammation for many decades (Schwartz & Mitchell, 1962). In 1985, Kohchi et al.(Kohchi, Takebayashi, Hiroki, & Nobuyoshi, 1985) found significant adventitial inflammation of the coronary artery in patients with unstable angina. This study demonstrated that adventitial inflammation possibly related to macrophage infiltration. Until recent years, the relevance of adventitial inflammation and atherosclerosis attracts the focus from researchers. Daugherty et al.(Daugherty et al., 2000) observed that macrophages accumulated in adventitia of abdominal aortic part in Ang II-induced mice model. Then, several studies showed that T and B cells also aggregated in adventitia (Akhavanpoor et al., 2014). All these results lead to increased local expression of cytokines and growth factors, which evoking an inflammatory response. Thus, there is one hypothesis is that the mechanisms of vascular inflammation started from adventitia inward toward the intima. But, the relevance between Ang-(1-7)/Mas axis is still unclear.

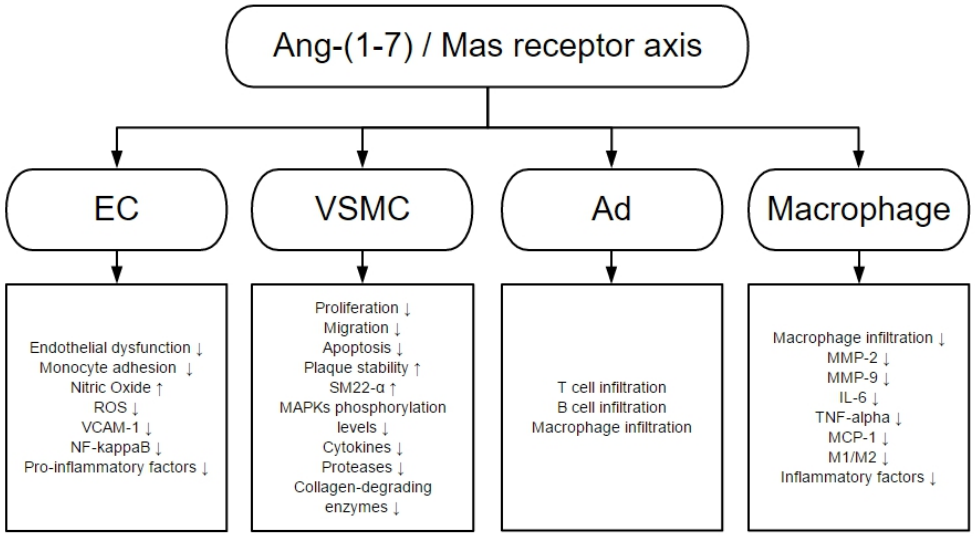

Figure 2

Activation of the Ang-(1-7)/Mas receptor axis improves vascular inflammation. But the prevention mechanism of Ang-(1-7)/Mas receptor axis in adventitia is still unknown. EC, endothelial cells; VSMC, vascular smooth muscle cells; Ad, adventitia.

Conclusion and perspectives

There are two pathways in RAS, ACE/Ang II/AT1R axis and ACE2/Ang-(1-7)/Mas axis. Both of them act an important role in all the stages of atherosclerosis, hypertension and aneurysm. Ang II, as a key factor in RAS, induces hypertension and increases the atherosclerosis incidence. And Ang-(1-7) shows a prevention mechanism in the development of atherosclerosis, including vasodilation, anti-proliferation, anti-inflammation and anti-fibrosis. In addition to this, the expression of many inflammatory factors will be reduced by the activated ACE2/Ang-(1-7)/Mas axis in order to improve the development of atherosclerosis. However, Ang-(1-7) is not enough to be a commercial product as it's easy to be degraded by the proteases. Therefore, many agonists appeared in the view of researchers for clinical application. For instance, CGEN-856S and AVE0991 can activate Ang-(1-7)/Mas axis. Both A779 and D-Pro-angiotensin-(1-7) are the antagonists of Ang-(1-7). AR244555 is an inverse agonist of Mas receptor. All of them have made contributions in the research of RAS.

In summary, Ang-(1-7) and its Mas receptors are widely expressed in many organs of the human body. It plays a central role in the avoidance of atherosclerosis. In recent years, studies in ACE2/Ang-(1-7)/Mas axis have made significant progress. Not with standing, there are many questions still

unclear. More pathological mechanisms need to be resolved and detected. Research in the ACE2/Ang-(1-7)/Mas axis can improve our understanding to the pathological process of atherosclerosis. This will provide us a more theoretical basis for prevention strategy, treatment method and drug development from the molecule level in future.

References:

Akhavanpoor, M., Wangler, S., Gleissner, C. A., Korosoglou, G., Katus, H. A., & Erbel, C. (2014). Adventitial inflammation and its interaction with intimal atherosclerotic lesions. *Front Physiol, 5*, 296. doi: 10.3389/fphys.2014.00296

Cassis, L. A., Gupte, M., Thayer, S., Zhang, X., Charnigo, R., Howatt, D. A., . . . Daugherty, A. (2009). ANG II infusion promotes abdominal aortic aneurysms independent of increased blood pressure in hypercholesterolemic mice. *Am J Physiol Heart Circ Physiol, 296*(5), H1660-1665. doi: 10.1152/ajpheart.00028.2009

Cybulsky, M. I., Fries, J. W., Williams, A. J., Sultan, P., Eddy, R., Byers, M., . . . Collins, T. (1991). Gene structure, chromosomal location, and basis for alternative mRNA splicing of the human VCAM1 gene. *Proc Natl Acad Sci U S A, 88*(17), 7859-7863.

Daugherty, A., Manning, M. W., & Cassis, L. A. (2000). Angiotensin II promotes atherosclerotic lesions and aneurysms in apolipoprotein E-deficient mice. *J Clin Invest, 105*(11), 1605-1612. doi: 10.1172/JCI7818

Eguchi, S., Dempsey, P. J., Frank, G. D., Motley, E. D., & Inagami, T. (2001). Activation of MAPKs by angiotensin II in vascular smooth muscle cells. Metalloprotease-dependent EGF receptor activation is required for activation of ERK and p38 MAPK but not for JNK. *J Biol Chem, 276*(11), 7957-7962. doi: 10.1074/jbc.M008570200

Esteban, V., Heringer-Walther, S., Sterner-Kock, A., de Bruin, R., van den Engel, S., Wang, Y., . . . Walther, T. (2009). Angiotensin-(1-7) and the g protein-coupled receptor MAS are key players in renal inflammation. *PloS one, 4*(4). doi: 10.1371/journal.pone.0005406

Feil, S., Hofmann, F., & Feil, R. (2004). SM22alpha modulates vascular smooth muscle cell phenotype during atherogenesis. *Circ Res, 94*(7), 863-865. doi: 10.1161/01.RES.0000126417.38728.F6

Ferrario, C. M., & Strawn, W. B. (2006). Role of the renin-angiotensin-aldosterone system and proinflammatory mediators in cardiovascular disease. *Am J Cardiol, 98*(1), 121-128. doi: 10.1016/j.amjcard.2006.01.059

Finn, A. V., Nakano, M., Narula, J., Kolodgie, F. D., & Virmani, R. (2010). Concept of vulnerable/unstable plaque. *Arterioscler Thromb Vasc Biol, 30*(7), 1282-1292. doi: 10.1161/ATVBAHA.108.179739

Fraga-Silva, R. A., Savergnini, S. Q., Montecucco, F., Nencioni, A., Caffa, I.,

Soncini, D., . . . da Silva, R. F. (2014). Treatment with Angiotensin-(1-7) reduces inflammation in carotid atherosclerotic plaques. *Thromb Haemost, 111*(4), 736-747. doi: 10.1160/TH13-06-0448

Gironacci, M. M., Adamo, H. P., Corradi, G., Santos, R. A., Ortiz, P., & Carretero, O. A. (2011). Angiotensin (1-7) Induces Mas Receptor Internalization. *Hypertension, 58*(2), 176-181. doi: 10.1161/Hypertensionaha.111.173344

Guang, Y., He, X., Yu, P., & Yao, H. (2015). Cross talk of angiotensin-(1-7)/Mas receptor axis and vascular inflammation in atherosclerosis. *Journal of Southwest University for Nationalities (Natural Science Edition), 41*(1), 17-23.

Gustafson, B. (2010). Adipose tissue, inflammation and atherosclerosis. *J Atheroscler Thromb, 17*(4), 332-341.

Husain, K., Hernandez, W., Ansari, R. A., & Ferder, L. (2015). Inflammation, oxidative stress and renin angiotensin system in atherosclerosis. *World J Biol Chem, 6*(3), 209-217. doi: 10.4331/wjbc.v6.i3.209

Koga, J., & Aikawa, M. (2012). Crosstalk between macrophages and smooth muscle cells in atherosclerotic vascular diseases. *Vascul Pharmacol, 57*(1), 24-28. doi: 10.1016/j.vph.2012.02.011

Kohchi, K., Takebayashi, S., Hiroki, T., & Nobuyoshi, M. (1985). Significance of adventitial inflammation of the coronary artery in patients with unstable angina: results at autopsy. *Circulation, 71*(4), 709-716.

Kostenis, E., Milligan, G., Christopoulos, A., Sanchez-Ferrer, C. F., Heringer-Walther, S., Sexton, P. M., . . . Walther, T. (2005). (G)-protein-coupled receptor Mas is a physiological antagonist of the angiotensin II type 1 receptor. *Circulation, 111*(14), 1806-1813. doi: 10.1161/01.Cir.0000160867.23556.7d

Leong, X. F., Ng, C. Y., & Jaarin, K. (2015). Animal Models in Cardiovascular Research: Hypertension and Atherosclerosis. *Biomed Res Int, 2015*, 528757. doi: 10.1155/2015/528757

Libby, P. (2012). Inflammation in atherosclerosis. *Arterioscler Thromb Vasc Biol, 32*(9), 2045-2051. doi: 10.1161/ATVBAHA.108.179705

Ma, L., Gong, H., Zhu, H., Ji, Q., Su, P., Liu, P., . . . Xu, Y. (2014). A novel small-molecule tumor necrosis factor alpha inhibitor attenuates inflammation in a hepatitis mouse model. *J Biol Chem, 289*(18), 12457-12466. doi: 10.1074/jbc.M113.521708

Masson, R., Nicklin, S. A., Craig, M. A., McBride, M., Gilday, K., Gregorevic, P., . . . Baker, A. H. (2009). Onset of Experimental Severe Cardiac Fibrosis Is Mediated by Overexpression of Angiotensin-Converting Enzyme 2. *Hypertension, 53*(4), 694-U207. doi: 10.1161/Hypertensionaha.108.122333

McKinney, C. A., Fattah, C., Loughrey, C. M., Milligan, G., & Nicklin, S. A.

(2014). Angiotensin-(1-7) and angiotensin-(1-9): function in cardiac and vascular remodelling. *Clin Sci (Lond), 126*(12), 815-827. doi: 10.1042/CS20130436

Mehta, P. K., & Griendling, K. K. (2007). Angiotensin II cell signaling: physiological and pathological effects in the cardiovascular system. *Am J Physiol Cell Physiol, 292*(1), C82-97. doi: 10.1152/ajpcell.00287.2006

Metzger, R., Bader, M., Ludwig, T., Berberich, C., Bunnemann, B., & Ganten, D. (1995). Expression of the mouse and rat mas proto-oncogene in the brain and peripheral tissues. *FEBS Lett, 357*(1), 27-32.

Moss, M. E., & Jaffe, I. Z. (2015). Mineralocorticoid Receptors in the Pathophysiology of Vascular Inflammation and Atherosclerosis. *Front Endocrinol (Lausanne), 6*, 153. doi: 10.3389/fendo.2015.00153

Ng, E., Morris, D. R., & Golledge, J. (2015). The association between plasma matrix metalloproteinase-9 concentration and endoleak after endovascular aortic aneurysm repair: A meta-analysis. *Atherosclerosis, 242*(2), 535-542.

Onat, D., Brillon, D., Colombo, P. C., & Schmidt, A. M. (2011). Human vascular endothelial cells: a model system for studying vascular inflammation in diabetes and atherosclerosis. *Curr Diab Rep, 11*(3), 193-202. doi: 10.1007/s11892-011-0182-2

Potthoff, S. A., Fahling, M., Clasen, T., Mende, S., Ishak, B., Suvorava, T., . . . Stegbauer, J. (2014). Angiotensin-(1-7) modulates renal vascular resistance through inhibition of p38 mitogen-activated protein kinase in apolipoprotein E-deficient mice. *Hypertension, 63*(2), 265-272. doi: 10.1161/HYPERTENSIONAHA.113.02289

Rateri, D. L., Davis, F. M., Balakrishnan, A., Howatt, D. A., Moorleghen, J. J., O'Connor, W. N., . . . Daugherty, A. (2014). Angiotensin II Induces Region-Specific Medial Disruption during Evolution of Ascending Aortic Aneurysms. *Am J Pathol, 184*(9), 2586-2595. doi: 10.1016/j.ajpath.2014.05.014

Ross, R. (1993). The pathogenesis of atherosclerosis: a perspective for the 1990s. *Nature, 362*(6423), 801-809. doi: 10.1038/362801a0

Ross, R., & Glomset, J. A. (1976a). The pathogenesis of atherosclerosis (first of two parts). *N Engl J Med, 295*(7), 369-377. doi: 10.1056/NEJM197608122950707

Ross, R., & Glomset, J. A. (1976b). The pathogenesis of atherosclerosis (second of two parts). *N Engl J Med, 295*(8), 420-425. doi: 10.1056/NEJM197608192950805

Santos, R. A., & Ferreira, A. J. (2006). Pharmacological effects of AVE 0991, a nonpeptide angiotensin-(1-7) receptor agonist. *Cardiovasc Drug Rev, 24*(3-4), 239-246. doi: 10.1111/j.1527-3466.2006.00239.x

Savoia, C., Burger, D., Nishigaki, N., Montezano, A., & Touyz, R. M.

(2011). Angiotensin II and the vascular phenotype in hypertension. *Expert Rev Mol Med, 13*, e11. doi: 10.1017/S1462399411001815

Schwartz, C. J., & Mitchell, J. R. (1962). Cellular infiltration of the human arterial adventitia associated with atheromatous plaques. *Circulation, 26*, 73-78.

Sheng-Long, C., Yan-Xin, W., Yi-Yi, H., Ming, F., Jian-Gui, H., Yi-Li, C., . . . Hong, M. (2012). AVE0991, a Nonpeptide Compound, Attenuates Angiotensin II-Induced Vascular Smooth Muscle Cell Proliferation via Induction of Heme Oxygenase-1 and Downregulation of p-38 MAPK Phosphorylation. *Int J Hypertens, 2012*, 958298. doi: 10.1155/2012/958298

Simoes e Silva, A. C., Silveira, K. D., Ferreira, A. J., & Teixeira, M. M. (2013). ACE2, angiotensin-(1-7) and Mas receptor axis in inflammation and fibrosis. *Br J Pharmacol, 169*(3), 477-492. doi: 10.1111/bph.12159

Souza, L. L., & Costa-Neto, C. M. (2012). Angiotensin-(1-7) decreases LPS-induced inflammatory response in macrophages. *J Cell Physiol, 227*(5), 2117-2122. doi: 10.1002/jcp.22940

Stegbauer, J., Potthoff, S. A., Quack, I., Mergia, E., Clasen, T., Friedrich, S., . . . Rump, L. C. (2011). Chronic treatment with angiotensin-(1-7) improves renal endothelial dysfunction in apolipoproteinE-deficient mice. *Br J Pharmacol, 163*(5), 974-983. doi: 10.1111/j.1476-5381.2011.01295.x

Stegbauer, J., Vonend, O., Oberhauser, V., & Rump, L. C. (2003). Effects of angiotensin-(1-7) and other bioactive components of the renin-angiotensin system on vascular resistance and noradrenaline release in rat kidney. *J Hypertens, 21*(7), 1391-1399. doi: 10.1097/01.hjh.0000059074.43904.80

Taylor, W. R. (1998). Mechanical deformation of the arterial wall in hypertension: a mechanism for vascular pathology. *Am J Med Sci, 316*(3), 156-161.

Thomas, M. C., Pickering, R. J., Tsorotes, D., Koitka, A., Sheehy, K., Bernardi, S., . . . Tikellis, C. (2010). Genetic Ace2 deficiency accentuates vascular inflammation and atherosclerosis in the ApoE knockout mouse. *Circ Res, 107*(7), 888-897. doi: 10.1161/CIRCRESAHA.110.219279

Verano-Braga, T., Schwammle, V., Sylvester, M., Passos-Silva, D. G., Peluso, A. A., Etelvino, G. M., . . . Roepstorff, P. (2012). Time-resolved quantitative phosphoproteomics: new insights into Angiotensin-(1-7) signaling networks in human endothelial cells. *J Proteome Res, 11*(6), 3370-3381. doi: 10.1021/pr3001755

Wang, X. H., Liu, S. Q., Wang, Y. L., & Jin, Y. (2014). Correlation of serum high-sensitivity C-reactive protein and interleukin-6 in patients with acute coronary syndrome. *Genet Mol Res, 13*(2), 4260-4266. doi: 10.4238/2014.June.9.11

Weiss, D., Kools, J. J., & Taylor, W. R. (2001). Angiotensin II-induced hypertension accelerates the development of atherosclerosis in apoE-

deficient mice. *Circulation, 103*(3), 448-454.
Xie, Q. Y., Sun, M., Yang, T. L., & Sun, Z. L. (2006). Losartan reduces monocyte chemoattractant protein-1 expression in aortic tissues of 2K1C hypertensive rats. *Int J Cardiol, 110*(1), 60-66. doi: 10.1016/j.ijcard.2005.07.046
Yang, J. M., Dong, M., Meng, X., Zhao, Y. X., Yang, X. Y., Liu, X. L., . . . Zhang, C. (2013). Angiotensin-(1-7) dose-dependently inhibits atherosclerotic lesion formation and enhances plaque stability by targeting vascular cells. *Arterioscler Thromb Vasc Biol, 33*(8), 1978-1985. doi: 10.1161/ATVBAHA.113.301320
Young, D., Waitches, G., Birchmeier, C., Fasano, O., & Wigler, M. (1986). Isolation and characterization of a new cellular oncogene encoding a protein with multiple potential transmembrane domains. *Cell, 45*(5), 711-719.
Zhang, F., Ren, J., Chan, K., & Chen, H. (2013). Angiotensin-(1-7) regulates Angiotensin II-induced VCAM-1 expression on vascular endothelial cells. *Biochem Biophys Res Commun, 430*(2), 642-646. doi: 10.1016/j.bbrc.2012.11.098
Zhang, Z., Chen, L., Zhong, J., Gao, P., & Oudit, G. Y. (2014). ACE2/Ang-(1-7) signaling and vascular remodeling. *Sci China Life Sci, 57*(8), 802-808. doi: 10.1007/s11427-014-4693-3