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Review

Angiotensin converting enzyme 2 and atherosclerosis

Yutang Wang [a], Chris Tikellis [b], Merlin C. Thomas [b], Jonathan Golledge [a,b,*]

[a] The Vascular Biology Unit, Queensland Research Centre for Peripheral Vascular Disease, James Cook University, Townsville, Queensland 4811, Australia
[b] Division of Diabetic Complications, Baker IDI Heart and Diabetes Institute, Melbourne, VIC 8008, Australia

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ABSTRACT

Angiotensin converting enzyme 2 (ACE2) is a homolog of angiotensin converting enzyme (ACE) which generates angiotensin II from angiotensin I. ACE, its product angiotensin II and the downstream angiotensin type I receptor are important components of the renin–angiotensin system (RAS). Angiotensin II, the most important component of the RAS, promotes the development of atherosclerosis. The identification of ACE2 in 2000 opened a new chapter of research on the regulation of the RAS. ACE2 degrades pro-atherosclerotic angiotensin II and generates anti-atherosclerotic angiotensin 1–7. In this review, we explored the importance of ACE2 in protecting experimental animals from developing atherosclerosis and its involvement in human atherosclerosis. We also examined the published evidence assessing the importance of ACE2 in different cell types relevant to atherosclerosis and putative underlying cellular and molecular mechanisms linking ACE2 with protection from atherosclerosis. ACE2 shifts the balance from angiotensin II to angiotensin 1–7 inhibiting the progression of atherosclerosis in animal models.

Contents

1. Introduction

It is established that the renin–angiotensin system (RAS) plays an important role in many processes including regulation of blood pressure. Angiotensinogen is hydrolyzed by renin to form the decapeptide angiotensin I (Ang I); and Ang I is then metabolized to a biologically very active peptide angiotensin II (Ang II) by angiotensin converting enzyme (ACE) [1] (Fig. 1). Ang II can interact with both angiotensin II type 1 (AT1R) and type 2 receptors (AT2R), with most of the effects of Ang II being mediated via AT1R. The ACE/Ang II/AT1R axis has long been thought to be the main pathway of the RAS. This pathway has been implicated in many physiology processes including blood pressure control, cardiovascular function, immune function and aging [2]. Inhibition of various parts of the RAS, such as renin, the ACE and the AT1R has been previously

* Corresponding author. The Vascular Biology Unit, Queensland Research Centre for Peripheral Vascular Disease, James Cook University, Townsville, Queensland 4811, Australia. Tel.: +61 7 4796 1417; fax: +61 7 4796 1401.
E-mail address: jonathan.golledge@jcu.edu.au (J. Golledge).

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Abbreviations

ACE	angiotensin converting enzyme
ACE2	angiotensin converting enzyme 2
ADAM	a disintegrin and metalloproteinase
Akt	protein kinase B
Ang	angiotensin
Ang1–7	angiotensin 1–7
Ang1–9	angiotensin 1–9
Ang I/II	angiotensin I/II
Apoe	apolipoprotein E
AT1R	angiotensin II type 1 receptors
AT2R	angiotensin II type 2 receptors
EC	endothelial cell
ERK	extracellular signal-regulated kinase
HUVEC	human umbilical vein endothelial cell
IL	interleukin
JAK	Janus kinase
Ldlr	low-density lipoprotein receptor
MAPK	mitogen-activated protein kinase
MCP-1	monocyte chemoattractant protein-1
MMP	matrix metalloproteinase
NF-κB	nuclear factor-κB
PCNA	proliferating cell nuclear antigen
PI3K	phosphoinositide 3-kinase
RAS	renin–angiotensin system
ROS	reactive oxygen species
STAT	signal transducers and activators of transcription
THP-1	human acute monocytic leukemia cell line
TNF-α	tumor necrosis factor-α
VCAM-1	vascular cell adhesion molecule 1
VSMC	vascular smooth muscle cell

shown to limit development and complications of atherosclerosis in animal models and humans, respectively [3–6].

In recent years, the understanding of the RAS has rapidly expanded. One of the important developments is the discovery of angiotensin converting enzyme 2 (ACE2) in 2000 by two independent research groups [7,8]. Human ACE2 is an 805-amino-acid homolog of human ACE, which has a 42% identity in the catalytic domain [7,8] to human ACE. ACE2 can degrade both Ang I and Ang II to the putative protective peptides angiotensin 1–9 (Ang1–9) and angiotensin 1–7 (Ang1–7), respectively (Fig. 1).

Ang II increases oxidative stress and inflammation [9] and promotes the development of atherosclerosis in mice [10]. ACE2 acts to decrease the concentration of Ang II and increase the concentration of Ang1–7, an anti-atherosclerotic peptide [11], in both tissue and blood [12,13]. As such, many researchers are currently focusing on the protective effects of ACE2 on the development of atherosclerosis. This review will focus on new developments suggesting the protective role of ACE2 in atherosclerosis.

2. Function of ACE2

The ACE2 gene is localized on the X chromosome in both humans [8] and rodents [14]. This enzyme is a zinc metalloprotease.

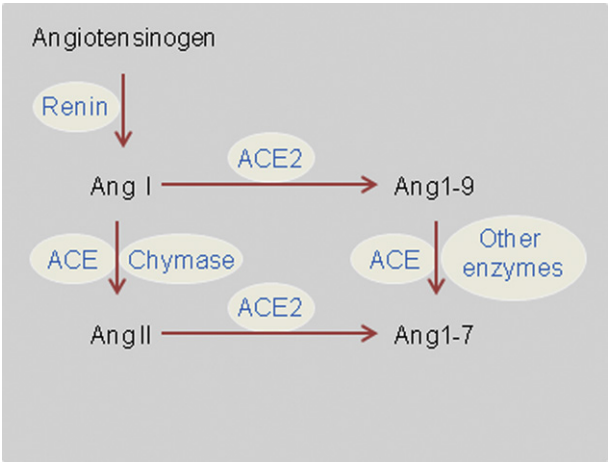

Fig. 1. Illustration of the key components of the renin–angiotensin system. Angiotensinogen is converted by renin to Ang I, which is metabolized to Ang II by ACE in the circulation or by chymase in the tissue. ACE2 converts Ang I and Ang II to Ang1–9 and Ang1–7, respectively. Ang1–9 can be further metabolized to Ang1–7 by ACE or other enzymes. The main function of ACE2 is to convert Ang II to Ang1–7.

Human ACE2 is predicted to be a type I integral membrane protein. The protein consists of a large extracellular domain with a zinc binding site with a HEXXH motif, a single transmembrane domain and a 42-amino-acid-long cytoplasmic tail.

ACE2 is able to cleave Ang I and Ang II to Ang1–9 and Ang1–7, respectively [8,15]. Ang1–9 can be further converted to Ang1–7 (Fig. 1). ACE2 metabolizes Ang II ~360-fold more efficiently than Ang I, and therefore it is believed that the main physiological function of ACE2 is to convert Ang II to Ang1–7. Ang1–7 is an endogenous ligand for the G protein-coupled Mas receptor, which is a cell surface receptor that is highly expressed within the cardiovascular system [16,17]. The ACE2/Ang1–7/Mas pathway has anti-proliferative, anti-inflammatory and anti-oxidative stress properties [16,18–20]. Ang1–7 may thus have anti-atherosclerotic properties. Indeed, subcutaneous infusion of Ang1–7 for four weeks reduces atherosclerosis development in both apolipoprotein E deficient ($Apoe^{-/-}$) [11] and low-density lipoprotein receptor deficient ($Ldlr^{-/-}$) mice [21] fed on a high fat diet.

ACE2 also exists in a soluble form. The extracellular active domain of ACE2 can be cleaved [22] and released into the circulation [23,24]. Tumor necrosis factor-alpha (TNF-α)-converting enzyme (also known as a disintegrin and metalloproteinase 17; ADAM17) mediates cleavage of ACE2 [25]. In HEK293 cells which over-express ACE2 and Huh7 cells which endogenously express ACE2, pharmacological or genetic inhibition of ADAM17 inhibits ACE2 cleavage, while over-expression of ADAM17 promotes ACE2 cleavage [25]. Soluble ACE2 activity is low within the plasma of healthy individuals, probably due to the presence of an unidentified endogenous inhibitor [26]. The importance of the soluble form of ACE2 is not yet clear. It has been suggested that soluble ACE2 might participate in regulating ACE2 expression and Ang II levels within the circulation.

The RAS exists in two distinct locations, i.e., systemic and local or tissue located. Different enzymes are involved in these two systems. For example, Ang II is mainly generated through ACE present within the circulation, as it is undetectable in plasma from ACE deficient ($ACE^{-/-}$) mice [27]. Tissue Ang II level is not controlled by ACE, as its levels in the heart, lung and kidney in $ACE^{-/-}$ mice are similar to that in wild type mice [27]. Generation of Ang II in the tissue is believed to be controlled by chymase [27] (Fig. 1). ACE2 plays an important role in regulating both the systemic and local RAS, as deficiency of ACE2 results in a 130% increase in plasma Ang II (from 111 pg/ml in wild type to 270 pg/ml in ACE2 knockout mice) and a 110% increase in tissue Ang II (from 12 pg/mg protein in wild type to 26 pg/mg protein in ACE2 knockout mice) [12]. ACE2 is also important in controlling Ang1–7