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Review article

# Cellular distribution and interaction between extended renin-angiotensin-aldosterone system pathways in atheroma

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ABSTRACT

The importance of the renin-angiotensin-aldosterone system (RAAS) in the development of atherosclerotic has been experimentally documented. In fact, RAAS components have been shown to be locally expressed in the arterial wall and to be differentially regulated during atherosclerotic lesion progression. RAAS transcripts and proteins were shown to be differentially expressed and to interact in the 3 main cells of atheroma: endothelial cells, vascular smooth muscle cells, and macrophages. This review describes the local expression and cellular distribution of extended RAAS components in the arterial wall and their differential regulation during atherosclerotic lesion development.



## 1. Introduction

Atherosclerosis remains the main cause of death and morbidity in the world, mainly in developed countries [1]. Extensive studies were done to elucidate the mechanisms by which atherosclerosis develops, however, many aspects of the disease remain unclear. Nevertheless, recent advances revealed different mechanisms involved in atherosclerosis development and progression, one of which is the renin-angiotensin-aldosterone system (RAAS) [2].

RAAS is a complex bioactive system that comprises different pathways involved in the conversion of angiotensinogen into diverse bioactive peptides that exert various cellular effects through selective receptors. The specific combination of peptides and receptors defines the final response of a tissue toward the system. RAAS is involved in numerous atherogenic mechanisms such as cellular growth, proliferation, differentiation, migration and apoptosis, extra cellular matrix (ECM) remodeling and inflammation [3].

We recently proposed an extended RAAS (extRAAS) [4] system at the local tissue level (Fig. 1). The expression of extRAAS components have been demonstrated in the arterial wall and during atherosclerotic lesion development [5]. This review will focus on the local differential expression and production of extRAAS components during atherosclerotic lesion development.

## 2. The substrate angiotensinogen (AGT)

Several polymorphisms in angiotensinogen (*AGT*) gene were shown to be associated with atherosclerotic events and their risk factors [6,7]. *AGT* mRNA was detected in several normal rat arterial beds [8–10]. AGT mRNA and protein are mainly expressed by medial vascular smooth muscle cells (VSMCs) and adventitial fibroblast cells in both normal and atherosclerotic arterial wall from rats and human, but also Ldl receptor-deficient ($Ldlr^{-/-}$) mice macrophages [9–12]. The expression of extRAAS components and their cellular distribution in atheroma are presented in Fig. 2. In VSMCs, AGT expression is influenced by risk factors of atherosclerosis such as hypertension, type 2 diabetes (T2D) and high cortisol [13].

## 3. Angiotensin (Ang)–I generating enzymes

In fact, AGT is cleaved into the decapeptide Ang-I by the tightly regulated enzyme renin (Fig. 1), which is considered the rate-limiting enzyme due to its high ligand affinity and specificity. Renin inhibition *in vivo* in $Ldlr^{-/-}$ mice reduced atherosclerotic lesion size in both the aortic arch and root [14]. Although renin

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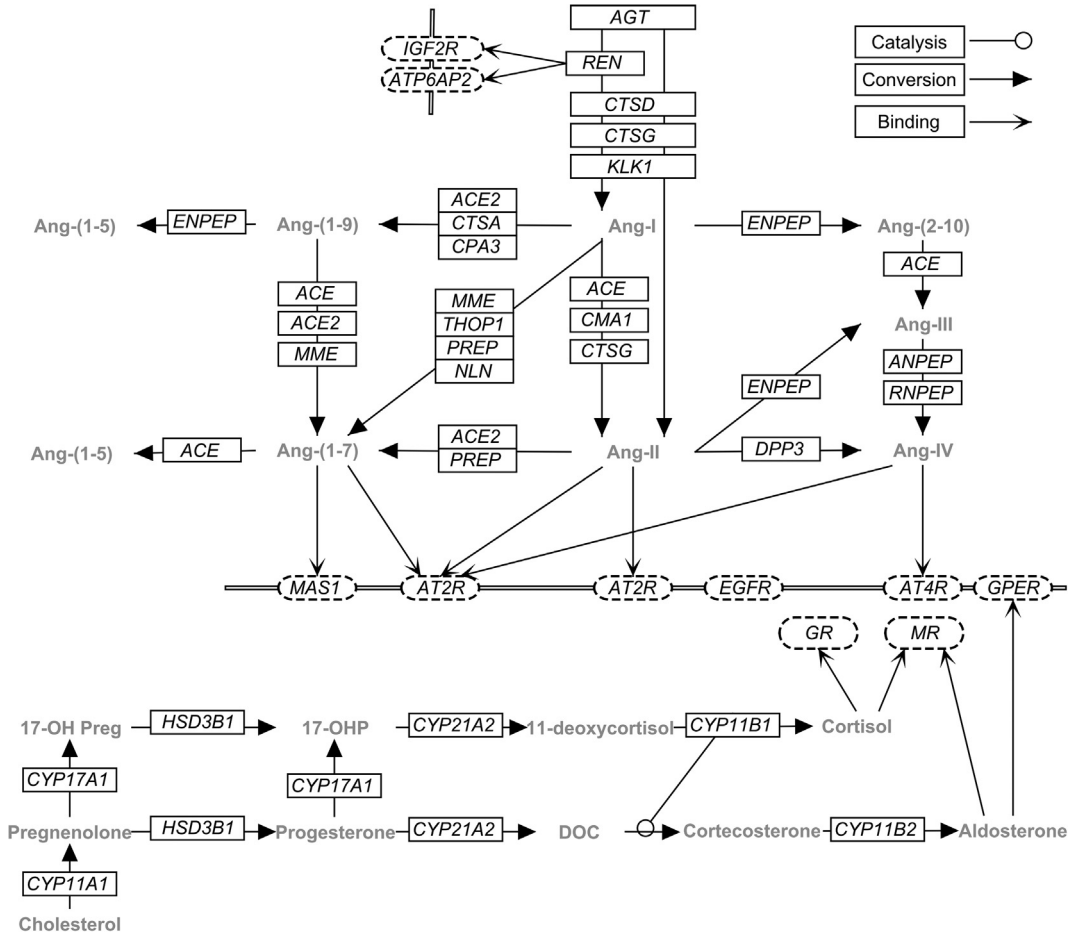


**Fig. 1.** Extended Renin Angiotensin Aldosterone System (ExtRAAS).
Enzymes and receptors are represented using gene symbols. Angiotensin peptides and steroid hormones are represented in grey using their usual abbreviation. Ang, angiotensin; Preg, pregnanolone; Prog, progesterone; DOC, 11-deoxycorticosterone; 17-OHP, 17-OH progesterone.

mRNA was not detected in human atheroma [11], renin mRNA, protein and activity were shown to be present *in vitro* in canine VSMCs [15], bovine endothelial cells (ECs) [16] and mouse macrophages [14] (Fig. 2). In the latter study, co-culture with renin-expressing macrophages increased monocyte adhesion to ECs. Similarly, renin protein was detected *in vivo* in the cap region and shoulders of atherosclerotic lesions in *Ldlr*$^{-/-}$ mice [12]. In addition, vascular (Pro)Renin receptor (PRR) expression was found to be associated with renin activity in human and rat VSMCs from several arterial beds [17–19], where it may also exert direct effects on atherosclerotic cells independent of AngII generation [20].

Alternatively, Ang-I can be produced by other enzymes, such as cathepsin D (CTSD), tonins and aspartyl proteases (Fig. 1). CTSD mRNA and protein were upregulated in atheroma-related human synthetic and rat hypertensive VSMCs, compared to normal contractile VSMCs [21,22] (Fig. 2). Of importance, CTSD protein was upregulated in human atherosclerotic lesions and further in abdominal aortic aneurysm (AAA), suggesting an alternative role for this enzyme in ischemic events [23,24].

## 4. AngII pathway

Ang-I is cleaved by angiotensin converting enzyme (ACE) (Fig. 1) to generate the bioactive octapeptide, AngII. Compelling evidence support that AngII exerts various effects involved in atherosclerotic lesion initiation and progression [25]. In fact, AngII blockade via ACE inhibitors (ACEi) or angiotensin type 1 receptor (AT1R) blockers (ARBs) ameliorates the formation, progression and acute complications of atherosclerotic lesions in mice, independent of hypertension and other risk factors of atherosclerosis [25,26].

AngII formation was shown to be higher in human atherosclerotic and aneurysmal lesions, compared to normal aortas [27,28] (Fig. 2). ACE is thought to be the major AngII-generating enzyme in the intima of both normal and atherosclerotic human vessels [29]. In healthy carotid human arteries, ACE protein was found to be restricted to both luminal and *vasa vasorum* ECs [30] (Fig. 2). However, in human and mouse atherosclerotic lesions, ACE protein is predominantly expressed by macrophages, macrophage-derived foam cells (MFCs), lymphocytes and synthetic VSMCs [12,22,31,32] (Fig. 2). In line with this difference in ACE expression between normal and atherosclerotic lesions, EC-specific deletion of ACE had no effect on atherosclerosis whereas SMC-specific deficiency of ACE significantly attenuated hypercholesterolemia-induced atherosclerosis in both male and female mice [32]. Nevertheless, vascular AngII production was not completely suppressed by ACEi in canine arteries, which suggests the presence of alternative AngII producing enzymes [33].

Indeed, ACE-independent pathways (Fig. 1) are responsible for 40% of AngII generation in the human vessel wall [34]. Although most of AngII forming activity *in vitro* was chymase-dependent in both normal and atherosclerotic human aortas, chymase protein levels were not different between the two tissues [27], which