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Chapter 25

# ACE2 Cell Biology, Regulation, and Physiological Functions

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## INTRODUCTION

The classical renin–angiotensin system (RAS) pathway regulating the cardiovascular system primarily through the hormone angiotensin II (Ang II) has evolved over a period of some 60 years into a complex network of angiotensin mediators and receptors influencing multiple physiological pathways at both intracellular and endocrine levels. In the simplified linear pathway from precursor protein (angiotensinogen) to the vasoconstrictor octapeptide, Ang II, two key proteolytic enzymes are involved: the aspartic protease renin cleaving the decapeptide Ang I from angiotensinogen and the metallopeptidase angiotensin-converting enzyme (ACE) converting Ang I to Ang II. Both of these proteases have served as primary targets for the development of antihypertensive drugs: for example, aliskiren for renin and captopril and its many successors for ACE. ACE also inactivates the vasodilator bradykinin, providing an intricate dual regulation of blood pressure. The discovery of Ang-(1-7) as a functional angiotensin mediator,[1] subsequently shown to counterbalance the action of Ang II,[2] set the scene for the hunt for the Ang-(1-7)-forming enzyme(s) and its cognate peptide receptor (Mas receptor[3]). Not until both of these entities were identified did the physiological significance of Ang-(1-7) become widely accepted.

## ACE2: DISCOVERY AND BASIC BIOLOGY

ACE is a highly glycosylated, transmembrane protein existing in two differentially spliced forms: the two-domain somatic ACE (N- and C-domains) with similar but not identical substrate specificities, which is important for cardiovascular regulation, and the single-domain testicular form important for male fertility through metabolism of an unidentified peptide substrate. Somatic ACE also plays important roles in developmental processes, inflammation and immunity, and neurodegenerative disease (reviewed in Ref. [4]). For almost 50 years from the discovery of ACE, the existence of a human "ACE2" remained undiscovered and unpredicted notwithstanding the importance of ACE inhibitors to pharmacology and therapeutics, despite the known existence of ACE homologues in invertebrate species. For example, *Drosophila* expresses two ACE-like genes and catalytically active protein products (Ance and Acer) important in insect development and physiology.[5] It was on this basis that a search of human expressed sequence tags led us to identify, clone, and characterize a human ACE homologue, designated ACE2.[6] Shortly afterward and quite independently, Donoghue and colleagues identified the *ACE2* gene as one upregulated in a human heart failure cDNA library.[7] Despite the high sequence similarities between ACE and ACE2, there were some surprising differences in substrate specificity in that ACE2 functions exclusively as a carboxypeptidase removing a single C-terminal amino acid from Ang II generating Ang-(1-7) or, much less efficiently, from Ang I forming Ang-(1-9). In contrast, ACE principally acts as a carboxydipeptidase (peptidyldipeptidase) removing the C-terminal dipeptide from Ang I to form Ang II. ACE2 activity is also not affected by classical ACE inhibitors. Detailed structural and mutagenesis studies have revealed the important features leading to these specificity differences between ACE and ACE2.[8,9] It is these synergies in angiotensin metabolism, with ACE forming Ang II and ACE2 removing it by conversion to Ang-(1-7), that provides the counterbalancing of angiotensin metabolism by these two homologous enzymes providing metabolites that act through three distinct receptors, $AT_1$, $AT_2$, and Mas. ACE2, however, is not the only metabolic route to Ang-(1-7), which can also be formed directly from Ang I by neprilysin (NEP), and other peptidases (prolyl endopeptidase and thimet oligopeptidase) may also participate in Ang-(1-7) biosynthesis depending on tissue or cell type. However, kinetic analysis indicates that the most efficient pathway for Ang-(1-7) generation is directly from Ang II via ACE2.[10] A unique metallopeptidase may function to inactivate Ang-(1-7) to Ang-(1-4), at least in the brain.[11]

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ACE and ACE2 both serve a multiplicity of functions. Unlike ACE, ACE2 degrades [des-Arg9]-bradykinin but not bradykinin itself.[6] Since [des-Arg9]-bradykinin is the ligand for the B1 bradykinin receptor, ACE2 may function to turn off signaling at this receptor. Other substrates for ACE2, at least *in vitro*, include apelin-13/17, neurotensin (1-11), dynorphin A (1-13), and ghrelin.[12] There appears to be a close interplay between the inotropic and cardioprotective peptides apelin and ACE2 since ACE2 is downregulated in apelin-deficient mice and apelin acts as a positive regulator of ACE2 expression in failing hearts *in vivo*.[13] The recent discovery of a new player in the RAS, alamandine, has shown that this peptide can be formed from angiotensin A by ACE2 action and acts through a Mas-related gene receptor (MrgD).[14] Angiotensin A is itself formed by decarboxylation of the N-terminal aspartyl residue of Ang II to an alanyl residue.[15]

Roles for both ACE and ACE2 are emerging in Alzheimer's disease (AD), specifically the ability of both enzymes to hydrolyze the amyloid-β (Aβ) peptide. ACE can cleave Aβ40 at internal sites in the peptide reducing its aggregation.[16] It can also hydrolyze the more hydrophobic Aβ-(1-42) to the less neurotoxic form (Aβ40) with ACE inhibition enhancing Aβ deposition.[17] The larger Aβ43 species is also found in AD brain and Aβ43 is the earliest-depositing Aβ species in APP transgenic mouse brain.[18] We have now demonstrated[19] that ACE2 can efficiently hydrolyze Aβ43 to Aβ42 that is then further degraded to Aβ40 by ACE. The discovery that NEP was a major Aβ-degrading enzyme *in vivo* led to a cessation of developments of NEP inhibitors as novel antihypertensives because of the potential for promoting the onset of AD through enhanced Aβ accumulation and aggregation. This, then, begs the question as to whether ACE inhibitors, by promoting the accumulation of more toxic Aβ species in the brain, might also predispose to AD. To date, there are no epidemiological data to support this concept, and ACE inhibition with captopril even retards the development of signs of neurodegeneration in an animal model of AD.[20] This is most likely explained by the greater protective vascular effects on the brain of ACE inhibition, AD itself having a major vascular component in its etiology. Furthermore, ACE overexpression in myelomonocytes prevents Alzheimer's-like cognitive decline.[21] A comparison of the substrate specificities of ACE and ACE2 is provided in Table 1.

ACE2 also plays distinct biological roles independent of its enzymic activity.[22] The ACE2 protein appears to be a chimera composed of an ACE-like domain fused to a collectrin-like domain. The collectrin protein is one that regulates renal amino acid transport and pancreatic insulin secretion. Likewise, ACE2 regulates transport of intestinal neutral amino acid transporters of the $B^0AT1$ family to the plasma membrane and has been implicated in the pathology of Hartnup's disease, a disorder of amino acid homeostasis.[22] Through this process, ACE2 also appears to regulate intestinal inflammation and diarrhea, hence modulating the gut microbiome.[23] Other disease processes in which ACE2 is involved are infection and pathology induced by the severe acute respiratory syndrome (SARS) virus through its serendipitous function as the cell-surface receptor for the virus facilitating viral RNA entry in the lungs.[24] The consequent downregulation of surface ACE2 levels leads to increased local levels of Ang II, which probably contribute to the significant mortality rates resulting from the acute lung injury and fibrosis caused by SARS.[25,26] ACE2 may also be protective against liver fibrosis and other fibrotic diseases,[27] again through reduction in Ang II levels (or elevated Ang-(1-7) levels).

**TABLE 1 Comparison of Substrate Specificities of ACE and ACE2 for Angiotensin, Bradykinin, and Amyloid-β (Aβ) Peptides**

| | ACE | ACE2 |
|---|---|---|
| Ang I | AspArgValTyrIleHisProPhe↓HisLeu | AspArgValTyrIleHisProPheHis↓Leu |
| Ang II | Not cleaved | AspArgValTyrIleHisPro↓Phe |
| Ang-(1-9) | AspArgValTyrIleHisPro↓PheHis | Not cleaved |
| Ang-(1-7) | AspArgValTyrIle↓HisPro | Not cleaved |
| Ang A | Not cleaved | AlaArgValTyrIleHisPro↓Phe (alamandine) |
| BK | ArgProProGlyPheSerPro↓PheArg | Not cleaved |
| [des-Arg9]-BK | Not cleaved | ArgProProGlyPheSerPro↓Phe |
| Aβ42 | Aβ-(1-42) → Aβ-(1-40) | Not cleaved |
| Aβ43 | Aβ-(1-43) → Aβ-(1-41) | Aβ-(1-43) → Aβ-(1-42) |

↓ indicates the site of enzyme cleavage. ACE primarily acts as a peptidyldipeptidase removing the C-terminal dipeptide in susceptible substrates. For some other peptide substrates (e.g., substance P), it can, however, act as an endopeptidase (not shown). ACE can also exhibit endopeptidase cleavage at a number of internal sites in both Aβ40 and Aβ42 (see Refs. [17,18] for further details). ACE2 converts Ang II to Ang-(1-7) approx 70-fold more efficiently than it does Ang I to Ang-(1-9), making it principally an Ang-(1-7)-forming enzyme under normal physiological conditions.[10] ACE2 hydrolysis of Ang A generates the peptide alamandine that acts through the Mas-related gene receptor MrgD14. ACE2 can also hydrolyze some other regulatory peptides, most notably apelin, which in turn regulates ACE2 levels, as does Ang II (see text).

## ACE2 REGULATION

The discovery of ACE2 and its role in the RAS led to its rapidly becoming a focus as a novel cardiovascular target emphasized by studies of ACE2-null mice, revealing the enzyme as a key protective regulator of cardiovascular function.[28] Subsequent gene deletion models have not consistently reproduced the ACE2-null phenotype, perhaps reflecting their different genetic backgrounds, and it may be that ACE2 functions as a modulator of responses to injury rather than a primary mediator of cardiac phenotype (reviewed in Ref. [29]). The generally cardioprotective role of ACE2 has limited the development of ACE2 inhibitors since they are unlikely to be of therapeutic benefit in cardiovascular or other disease states where, instead, upregulation of ACE2 expression or activity is required. Nevertheless, given the knowledge of ACE2 structure, mechanism, and specificity, a number of ACE2 selective inhibitors of nM potency have been developed including MLN-4760 (GL1001), DX-600, and 416F2 (see Ref. [30] for a review). More interesting from a therapeutic perspective has been the rational development of ACE2 activator small molecules that lower blood pressure in animal models.[31] A structurally related antitrypanosomal drug (diminazene aceturate) also activates ACE2[32] and exhibits beneficial cardiovascular activity.[33] However, the biological effects of these compounds *in vivo* may be ACE2-independent so some caution is needed in the interpretation of these data at present.[34]

ACE2, like ACE, is shed into plasma in catalytically active form. The constitutive ACE-shedding enzyme remains to be unequivocally identified although in some stimulated conditions may involve the A disintegrin and metalloproteinase 9.[35] ACE2 shedding is mediated by ADAM17 (also known as TACE) both *in vitro* and *in vivo*.[36,37] Ang II induces ADAM17-mediated shedding of myocardial ACE2 providing a positive feedback mechanism in the RAS.[37] The cleavage of ACE2 at the plasma membrane, through binding of soluble ACE2 to integrins, can regulate integrin signaling modulating cell–extracellular matrix interactions and hence influence cardiac remodeling processes.[38] Furthermore, soluble circulating ACE2 may serve as a biomarker in hypertension and heart failure.[39]

While numerous agents have been shown to modulate ACE2 expression, including angiotensin peptides and some other peptide and steroid hormones, relatively little is known about the molecular details of transcriptional regulation of ACE2.[40] The regulatory element responsible for Ang II stimulation of human ACE2 gene expression in human cardiofibroblasts has, however, been identified in its promoter.[41] Hepatocyte nuclear factor (HNF) transcription factors, for example, HNF1α, upregulate ACE2 expression at least in pancreatic islets and HEK293 cells.[42,43] Cell energy stress including hypoxia, cytokine action, and AMP kinase activation lead to epigenetic control of ACE2 expression via the histone deacetylase SIRT1.[44] At the posttranscriptional level, a number of microRNA (miR) species have been reported to regulate ACE2 expression,

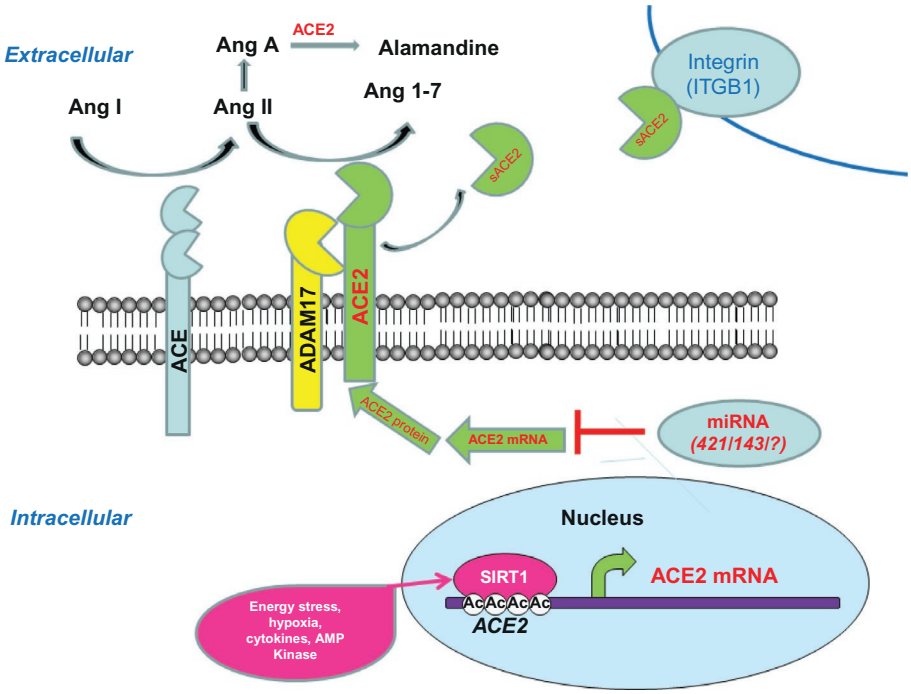


**FIGURE 1** Some aspects of the biology, regulation, and function of ACE2 with particular reference to the protective arm of the RAS. Illustration of ACE2 regulation at the transcriptional/epigenetic,[43,44] posttranscriptional[45,46] (miRNA), and posttranslational[36,37] (plasma membrane shedding) levels as discussed in this chapter and its relevant angiotensin substrates in the RAS in conjunction with ACE, which interact with their specific receptors (AT1/2 and MrgD) (not shown). Shed ACE2 (sACE2) can interact with integrins modulating signaling as can membrane-bound ACE2 modulating cell–cell interactions.[38]

including miR-421 and miR-143.[45,46] All of the above transcriptional regulatory sites may provide mechanisms for future modulation of ACE2 levels as cardioprotective strategies. The metabolic and regulatory aspects of ACE2 function are summarized in Figure 1.

In summary, ACE2 is a multifunctional protein in health and disease, which serves as a counterregulatory component of the RAS functioning in a cardioprotective role. Hence, its transcriptional upregulation, activation of its catalytic activity, or administration of the recombinant protein[47] could well provide new strategies in hypertension and heart failure. Additionally, ACE2 modulation (and hence alteration of the circulating Ang II/Ang-(1-7) balance) may have relevance to diabetes, acute lung injury and fibrotic disease, and even dystrophic muscular conditions.[48] But much still remains to be explored in terms of the basic aspects of ACE2 cellular function and its regulation to be able to exploit these opportunities effectively and safely.

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