The first reports\(^\text{1,2}\) of the angiotensin-converting enzyme (ACE) homolog, ACE2, in mid-2000 came almost 50 years after the discovery of ACE and, remarkably, its existence had not been predicted from the known physiology of the renin-angiotensin system (RAS) at the time. There has since been an exponential growth in knowledge of ACE2 functions,\(^3\) spanning such diverse areas of biology as cardiovascular function, liver disease, nutrition (eg, Hartnup disease), pregnancy, and, perhaps most unexpectedly, acute lung injury and severe acute respiratory syndrome (SARS), with ACE2 being the SARS virus receptor.\(^4\) It is now apparent that ACE2 contributes to the RAS through counterbalancing the action of ACE by converting angiotensin II to its metabolite angiotensin-(1-7) which, probably through the Mas receptor, brings about its vasodilatory and antiproliferative actions. Hence, ACE2 was quickly recognized as a possible cardioprotective activity and a potential target in controlling blood pressure.

Strategies to investigate the physiological and pathological roles of ACE2 have used either pharmacological approaches, for example by using inhibitors of ACE2 such as MLN4760, or transgenic approaches, neither of which have provided clearcut results. Indeed, studies with different strains of ACE2-null mice themselves have been ambiguous. In the first such study,\(^5\) ACE2 deletion resulted in increased plasma and tissue angiotensin II levels combined with associated cardiomyopathy and impaired cardiac contractility. These effects were reversed in mice in which both ACE and ACE2 were deleted, providing the first direct evidence that these 2 enzymes counterbalance each other in metabolism, presumably by regulating angiotensin II levels. However, in these mice, no discernible effects on blood pressure were reported, although three hypertensive rat strains (Sabra-salt sensitive, spontaneous hypertensive [SHR], and spontaneously hypertensive stroke-prone [SHRSP]) all showed downregulation of ACE2 expression. Two other strains of ACE2-deficient mice,\(^6,7\) however, showed no differences in plasma angiotensin II levels from wild-type mice, but enhanced blood pressure increases were seen after angiotensin II infusion, probably attributable to impaired renal metabolism of angiotensin II.\(^7\) Some commonalities do emerge from these divergent studies of ACE2-deficiency in mice: namely that any effects on baseline blood pressure and cardiovascular function are relatively modest, and that these effects can be significantly modulated by the underlying genetic background of the animal. ACE2 may, however, play a more significant role in pathological conditions and in the failing heart when it appears to be upregulated. In this context it is significant that, in one of the original studies identifying ACE2, it was cloned from a human heart failure cDNA library.\(^2\)

Hence, upregulation of ACE2 may provide a novel therapeutic strategy in cardiac pathophysiology. In this issue, Rentzsch et al\(^8\) have tested this hypothesis by overexpressing ACE2 selectively in vascular smooth muscle of spontaneously hypertensive stroke-prone rats and examining the effects on the RAS, endothelial cell function, and blood pressure. Strongest expression of the transgene was seen in the aorta, but it was also significantly raised in renal and mesenteric arteries. Consistent with this, ACE2 enzyme activity in the aorta was almost 8-fold increased and angiotensin-(1-7) levels in plasma and aorta were doubled, although, perhaps surprisingly, angiotensin II levels were only modestly decreased. Nevertheless, these changes were significant enough to cause a fall in blood pressure in the ACE2-overexpressers compared with the control SHRSP rats. Most significantly, this study revealed a protective effect of ACE2 on endothelial function, both in vitro as assessed by the carbachol-dependent relaxation of aortic rings, and in vivo. These data, along with other recent studies,\(^9-11\) are sufficiently encouraging to develop novel strategies for the upregulation of ACE2 in vivo as approaches to deal with cardiac pathophysiology ranging from hypertension to atherosclerosis.

How best, though, to modulate the activity of ACE2 in vivo? Three strategies show initial promise: targeted viral delivery of ACE2 cDNA, direct administration of recombinant ACE2 protein, and structure-based design and development of ACE2 activator small molecules. In addition to the study of Rentzsch et al,\(^8\) intracardiac injection of rats with a lentiviral-ACE2 construct was shown to exert a protective influence on the heart after myocardial infarction by preserving cardiac functions\(^9\) and, in a rabbit model of atherosclerosis, local adenoviral overexpression of ACE2 significantly enhanced plaque stability through enhancing Ang-(1-7) levels.\(^10\) The cardioprotective and blood pressure-regulating effects of ACE2 may, in part, be centrally mediated as shown by adenoviral overexpression of the enzyme in the subfornical organ.\(^11\)
Although a gene therapy type approach appears an attractive option, the administration of recombinant ACE2 protein may also be a relatively effective strategy in treatment of cardiovascular disease, and its efficacy has already been validated in the case of acute lung injury. Knowledge of the structure of the ACE2 protein has allowed an ingenious and entirely different approach, that of a rational search for activators based on the conformational changes that ACE2 undergoes on binding substrate or ligand. This drug-screening program identified 2 compounds that were able to enhance ACE2 activity 2-fold while having no effect on ACE. These compounds were able to reduce blood pressure and improve cardiac function in spontaneously hypertensive rats. Dietary regime may also affect ACE2 levels and expression because the protein, which is expressed in mouse adipocytes, appears to be dysregulated by high-fat feeding, correlating with increased blood pressure.

Finally, whereas most attention has focused on ACE2 in relation to angiotensin II metabolism and Ang-(1-7) production, its ability to metabolize other regulatory peptides, eg, apelin, should not be forgotten and may well contribute to some of the cardiovascular and other effects seen on manipulation of ACE2 levels and activity. ACE2-based therapies are showing considerable promise, but much still remains to be learned of the basic biology of ACE2 and its pathophysiological relevance.

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Angiotensin-Converting Enzyme 2. Cardioprotective Player in the Renin-Angiotensin System?
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