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could the mechanism be? In the context of the known proinflammatory and proatherogenic actions of Ang II, impaired degradation of this peptide owing to ACE2 deficiency could explain their findings. In other words, Ang II accumulation systemically and/or locally within the vasculature could be responsible for the observed increases in vascular inflammation, as seen in the ACE2 KO, and enhanced plaque formation, as seen in the ApoE/ACE2 double KO. The issue, however, is complicated by the fact that genetic ACE2 ablation may or may not lead to demonstrable Ang II overactivity, as judged by increased levels of circulating or tissue Ang II levels. Marked differences have been reported between 3 different ACE2-deficient mouse lines in terms of cardiovascular phenotype and basal Ang levels.12–15 The line originally described by Crackower et al,8 which was used in this study,12 has increased levels of Ang II in kidneys, hearts, and plasma. By contrast, the other available mouse lines13,14 do not have any overt differences in the levels of these peptides. These differences in phenotypes between ACE2-deficient lines cannot be easily explained by differences in the gene disruption methodology or differences in genetic backgrounds.15 ACE2 deficiency in the other 2 ACE2-deficient lines, however, is not without consequence; rather, the metabolism of Ang II is clearly impaired, as demonstrated by increased plasma and kidney levels of Ang II when this peptide is infused. Moreover, this is associated with marked worsening of Ang II–induced hypertension.13,16

That treatment with the ACE inhibitor, perindopril, reduced plaque accumulation in ApoE/ACE2 double KO mice is evidence for the involvement of Ang II in the atherogenic response observed in this model.12 The degree of conferred protection was less than that observed following ACE inhibitor administration to ApoE KO mice. ACE2 activity in the vasculature was decreased following the administration of perindopril,12 which is surprising considering that others have shown increases in ACE2 activity following the administration of either ACE inhibitors or Ang II type 1 receptor blockers.17,18 Nevertheless, the improvement in atherogenesis with the ACE inhibitor implies Ang II dependency and is consistent with the expected impairment in the degradation of this peptide in the face of ACE2 deficiency. It is possible, however, that peptides other than Ang II could also be altered in mice with genetic ACE2 ablation and may contribute to the amplification of vascular inflammation and atherogenesis. For instance, ACE2 removes the C-terminal residue from apelin and des-Arg9-bradykinin, as well as other vasoactive peptides, such as neurotensin and kinetensin. The status of these peptides in the ACE2 KO is currently unknown.

Atherosclerotic lesions express matrix metalloproteinases (MMP), which possess proteolytic activity. For instance,
MMP-8 has been shown to convert Ang I to Ang II. This may provide a mechanism of activation of the RAS locally within the plaque. Along with this concept, Thomas et al now show that ACE2 KO mice have increased aortic expression of MMP-2 and MMP-9, as well as increased MMP-9 production in macrophages. It is therefore likely that the deficiency of ACE2 leads to excessive Ang II accumulation particularly in the face of MMP-driven Ang II formation. In this way, it would be difficult to escape from Ang II overactivity, which becomes a perpetuating mechanism leading to atherogenesis as a result of both increased formation and decreased degradation of Ang II (Figure).

It would have been of interest to know ACE2 expression in the vasculature of ApoE KO mice early on and as the disease progresses. ACE2 is present in atherosclerotic arteries in humans and levels of its activity seem to vary in vessel wall in the course of the lesions progression. Although it is still unclear whether its presence reflects a compensatory response to enhanced Ang II activity within the diseased vasculature, increasing ACE2 activity may be therapeutically relevant. A gain of ACE2 activity by adeno viral overexpression exerted beneficial effects in ApoE KO mice fed a lipid-reach diet by reducing atherosclerotic aortic lesions. Adeno viral ACE2 overexpression has also been shown to stabilize existing atherosclerotic plaques and attenuate the progression of lesions early on but not the progression of plaque size at more advanced stages.

As mentioned above, ACE2 cleavage of Ang II results in the formation of Ang-(1-7), a peptide that is believed to have anti-inflammatory properties. The 2 effects of ACE2, degrading the proinflammatory Ang II and promoting formation of antiinflammatory Ang-(1-7), may be synergistic from the perspective of inflammation (Figure). This raises the question of what causes the observed proinflammatory effect of ACE2 deficiency. Is it increased Ang II or decreased Ang-(1-7) or both? The levels of Ang-(1-7) were not reported by Thomas et al in the ACE2 KO, but one would expect them to be decreased as a result of diminished ACE2-driven Ang II degradation. Ang-(1-7) infusion has been shown to be atheroprotective in ApoE KO mice, suggesting a role for this peptide on atherogenesis. At present, however, the relative contribution of Ang II versus Ang-(1-7) regarding atherogenesis is unknown. We have previously shown that Ang II rather than Ang-(1-7) mediates the antihypertensive effect of recombinant ACE2 protein in the hypertension associated with Ang II infusion. It will be important to elucidate the relative contribution of these 2 peptides on atherogenesis, particularly because Ang-(1-7) agonists are now available.

There could also be other mechanisms involved in the action of ACE2 in addition to its effect on the degradation of Ang II to Ang-(1-7) (Figure). A noncatalytic role for ACE2 has been postulated and cannot be ruled out as being involved in its vascular protective actions. Another question is what happens to ACE activity when ACE2 activity decreases? The administration of MLN-4760, a specific ACE2 inhibitor, has been shown to increase ACE expression in the kidney vasculature and glomeruli. It is possible that over-activity of Ang II may originate not only from impaired degradation as a result of ACE2 deficiency but also by enhanced formation resulting from increased ACE activity (Figure). This combination of increased ACE but decreased ACE2 expression has been described in glomeruli from mice.

Figure. Impact of ACE2 deficiency on the balance between Ang II and Ang-(1-7) is tilted toward Ang II accumulation as a result of impaired Ang II degradation (top). ACE surplus also shifts the balance toward Ang II accumulation via increased formation from Ang I (bottom). Some of the known detrimental actions of Ang II are opposed by Ang-(1-7), whereas Ang I has no known biological actions.
models of diabetic kidney disease. A state of ACE2 deficiency and ACE excess would potentiate Ang II accumulation by further shifting the balance away from Ang II degradation and in favor of Ang II formation (Figure).

In the future, it will be important to evaluate the antiatherosclerotic and antiinflammatory response to interventions aimed at amplifying ACE2 activity directly, such as the administration of recombinant ACE2 protein. Moreover, a combination of approaches, blocking Ang II formation and increasing Ang II degradation via ACE2 administration, should have an additive effect on reducing plaque formation. Because the effect of blockade of RAS in clinical studies has been relatively modest in terms of plaque reduction, it would seem that a more effective approach may involve amplification of ACE2 activity alone or perhaps in combination with RAS blockade to protect the vascular ring.

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Disclosures
D.B. has a pending patent application entitled “Methods for Achieving a Protective ACE2 Expression Level to Treat Kidney Disease and Hypertension.”

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