Deleting Vascular ADAM17 Sheds New Light on Hypertensive Cardiac Hypertrophy

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A disintegrin and metalloprotease (ADAM) 17 has sheddase activity for cleaving the ectodomain of several precursor molecules, including heparin-binding epidermal growth factor (EGF)--like growth factor. Over the past decade, Dr Eguchi and his colleagues have meticulously presented evidence that ADAM17 couples the angiotensin II (Ang II) type-1 (AT1) receptor to activation of the EGF receptor (EGFR) in vascular smooth muscle cells. Studies on cultured cells have shown that EGFR transactivation is responsible for vascular smooth muscle cell hypertrophy in response to Ang II, but not contractility. Moreover, EGF was found to be capable of inducing endoplasmic reticulum stress, which serves to enhance the coupling of Ang II to EGFR signaling by upregulating the expression of ADAM17. In a study that appeared last year in Hypertension, Eguchi’s group reported that inhibiting EGFR or endoplasmic reticulum stress attenuated vascular remodeling and cardiac hypertrophy in mice infused with Ang II, without affecting the increase in blood pressure. In the current issue, these investigators extend these observations further by showing that knockout of ADAM17 specifically in vascular smooth muscle cells prevents cardiac hypertrophy, vascular medial hypertrophy, and perivascular fibrosis in mice treated with Ang II, again without affecting the induced hypertension. ADAM17 deficiency also diminished EGFR activation and endoplasmic reticulum stress in the vasculature, and a similar outcome was achieved by treatment of Ang II--infused mice with a human cross-reactive ADAM17 inhibitory antibody (Figure). These new findings are remarkable for several reasons. First, they provide additional support for the contention that increased blood pressure and adverse cardiovascular remodeling, which contributes to end-organ damage, are independent phenomena that can be targeted separately. This conclusion has profound clinical significance given that hypertension for many individuals is difficult to control with current drugs and strategies. Moreover, as mentioned by Takayanagi et al, optimally treated hypertensive patients are at an increased risk of a cardiovascular event compared with untreated normotensive subjects. Thus, there is a great need to identify druggable targets to prevent the complications of hypertension, and ADAM17 may represent such a target.

Left ventricular hypertrophy represents a stronger risk factor than increased blood pressure for adverse cardiovascular events, and accumulating evidence indicates that elevated blood pressure and cardiac hypertrophy can be targeted independently. Odenbach et al reported evidence that it is possible to block hypertension and still observe cardiac hypertrophy and fibrosis in the Ang II–infused mouse by targeting matrix metalloproteinase 2 (MMP-2), which was placed downstream of MMP-7 and ADAM17 activation. MMP-7 and ADAM17 were linked to both hypertension and cardiac remodeling by independent mechanisms. Simultaneously knocking down MMP-7 and ADAM17 with siRNA attenuated both Ang II–induced cardiac remodeling and hypertension. This finding may indicate a critical role for nonvascular ADAM17 in hypertension in light of the somewhat conflicting findings of Takayanagi et al.

In their study, Takayanagi et al demonstrate that it is possible to block cardiac hypertrophy while still observing increased blood pressure, which gives the present study perhaps more translational weight given the abovementioned clinical issues. Their observation is consistent with the findings made with other models of hypertension–induced cardiac hypertrophy. For instance, Ang II type-1 receptor blockade attenuated cardiac hypertrophy in response to transverse aortic constriction, and knockdown of ADAM17 with siRNA attenuated cardiac hypertrophy in the spontaneously hypertensive rat without diminishing blood pressure. These findings, however, are at odds with those of a seminal study involving a murine renal cross-transplantation model, which reported a critical role for increased blood pressure resulting from activation of the kidney Ang II type-1 receptor in cardiac remodeling in response to Ang II treatment. Graft-driven inflammation does not occur in this model, but given recent evidence that the immune system is important in cardiovascular remodeling, one may speculate that immunotolerance may have been induced and affected the outcome.

The study by Takayanagi et al is also remarkable because it raises the possibility that vascular remodeling may actually drive or at least make a substantial contribution to cardiac remodeling. Although vascular smooth muscle cell–dominant deletion of ADAM17 was achieved by sm22α promoter-driven Cre expression, the possibility that ADAM17 was effectively deleted in cardiac myocytes as well, because of their moderate and transient embryonic expression of sm22α, precludes a definitive conclusion in this regard. Nonetheless, there is evidence that vascular cells affect cardiac hypertrophy and fibrosis.
Figure. Cardiac hypertrophy occurs independently of increased blood pressure (BP) in response to angiotensin II (Ang II). Previous models placed hypertension upstream of cardiac hypertrophy as a causative factor. The study by Eguchi and colleagues described in this issue reveals that Ang II–induced cardiac remodeling occurs downstream of vascular a disintegrin and metalloprotease 17 (ADAM17) activation by the ang II type-1 (AT1) receptor and independent of the increase in blood pressure. ADAM17 engagement transactivates epidermal growth factor receptor (EGFR) via increased extracellular heparin-binding growth factor-like growth factor (HB-EGF), leading to a hypertrophic synthetic phenotype of vascular smooth muscle cells (VSMC). HB-EGF or other paracrine factor produced by vascular ADAM17 may lead to cardiac fibrosis and hypertrophy. Vessel image is from Servier Medical Art with modifications. ER indicates endoplasmic reticulum.

in a paracrine manner. For instance, endothelial-specific deletion of interleukin-33 was recently reported to worsen transverse aortic constriction–induced cardiac hypertrophy. Finally, the study by Takayanagi et al does not definitively establish the causative factor in hypertension-induced cardiac remodeling, which is assumed to be heparin-binding EGF-like growth factor. This possibility is consistent with the observation that mice lacking EGFR transactivation specifically in cardiac myocytes because of a mutation in the Ang II type-1 receptor exhibit no cardiac hypertrophy and reduced cardiac fibrosis with Ang II infusion. However, ADAM17 is also involved in the generation of other prohypertrophic factors, including tumor necrosis factor–α, which is also implicated in Ang II–induced cardiac remodeling. Angiotensin I converting enzyme 2 is also cleaved by ADAM17. It is worth noting that in response to Ang II infusion, a negative correlation was reported in the mouse heart for the levels of ADAM17 and angiotensin I converting enzyme in the liver and overall to protect against acute hepatotoxic stress. Notably, the clinical use of ADAM17 inhibitors to treat patients with rheumatoid arthritis was associated with hepatotoxicity, although the basis for this hepatotoxicity is undefined. Thus, as supported by the study of Takayanagi et al, a tissue-targeted approach for inhibiting ADAM17 in hypertension may be both necessary and efficacious.

Disclosures

None.

References


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