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Serial killer: angiotensin drives cardiac hypertrophy via TGF-β1

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Commentary

Fie! what an indirect and peevish course.... —Shakespeare, Richard III How a seemingly simple signal — work load — becomes transduced into long-term structural, functional, and molecular responses that sustain or impair the performance of the heart is the defining enigma in cardiac hypertrophy (1, 2). Much is now known of this ensemble of responses, which encompass dozens if not hundreds of changes in cardiac gene expression, including sarcomeric proteins, ion pumps and channels, enzymes, and peptide growth factors and cytokines. These last, soluble, factors provide opportunity for both feedback and feed-forward relationships and are attractive, conceptually, as at least a partial explanation of the hypertrophic phenotype. First, growth factor signaling cascades are better understood in fundamental terms than is mechanical signal transduction, especially given the present lack of clarity as to how and where load is sensed in the heart. Second, secreted signals provide an intuitively plausible explanation for the cross-talk among cardiac myocytes, fibroblasts, and the vasculature. Third, secreted signals provide a readily exploited site for therapeutic intervention: interfering with ligand-receptor interaction. TGF-β couples angiotensin II to cardiac hypertrophy An initial clue that peptide growth factors could be important mediators of cardiac hypertrophy was the simple correspondence of expression and effect. TGF-β1, founding member of a large superfamily, is upregulated in myocardium by increased work load and suffices […]

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—Shakespeare, *Richard III*

How a seemingly simple signal — work load — becomes transduced into long-term structural, functional, and molecular responses that sustain or impair the performance of the heart is the defining enigma in cardiac hypertrophy (1, 2). Much is now known of this ensemble of responses, which encompass dozens if not hundreds of changes in cardiac gene expression, including sarcomeric proteins, ion pumps and channels, enzymes, and peptide growth factors and cytokines. These last, soluble, factors provide opportunity for both feedback and feed-forward relationships and are attractive, conceptually, as at least a partial explanation of the hypertrophic phenotype. First, growth factor signaling cascades are better understood in fundamental terms than is mechanical signal transduction, especially given the present lack of clarity as to how and where load is sensed in the heart. Second, secreted signals provide an intuitively plausible explanation for the cross-talk among cardiac myocytes, fibroblasts, and the vasculature. Third, secreted signals provide a readily exploited site for therapeutic intervention: interfering with ligand-receptor interaction.

TGF-β couples angiotensin II to cardiac hypertrophy

An initial clue that peptide growth factors could be important mediators of cardiac hypertrophy was the simple correspondence of expression and effect. TGF-β1, founding member of a large superfamily, is upregulated in myocardium by increased work load and suffices to provoke the hypertrophic program of cardiac gene expression (3). Angiotensin II (Ang II), which is best known for its role as a vasoconstrictor, is also produced locally within the heart, is released by mechanical stress, and can trigger hypertrophy in cultured cardiac muscle cells (1). Analogous suggestive findings have accrued for other locally produced factors including FGF-2, IGF-I, TNF-α, cardiotrophin-1, and endothelin (2). Because of the sheer number of candidates, researchers have made it a priority to ascertain which are functionally akin but redundant, which are inextricable, and which operate, tellingly, in the whole-animal context. Among these, the case for Ang II is especially strong, as is highlighted by the finding that pressure-overload hypertrophy is blocked in mice lacking the AT_2 receptor (4), and by the improvement in survival in animals treated with angiotensin inhibitors (5).

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Several but not all of Koch's postulates toward proving causality have been satisfied with regard to TGF-β's role in cardiac hypertrophy. Consistent with the model that Ang II and TGF-β are linked functionally, Ang II blockade reverses myocardial fibrosis and expression of TGF-β in tandem (6), whereas blocking antibodies to TGF-β inhibit hypertrophy caused by the conditioned medium of Ang II–treated cells (7). Conversely, increased signaling by TGF-β–activated kinase-1 at pathophysiological levels suffices to provoke heart failure in mouse myocardium (8). Evidence also has come from testing antibodies to TGF-β in hypertrophy (6), but this approach has proved intractable, in part because TGF-β comprises three isoforms and is related to dozens of structurally similar proteins with overlapping specificity for certain inhibitors.

What has been missing, until now, is a bona fide genetic test, using mice lacking TGF-β1 to pinpoint whether or how well Ang II functions without it. Although knockout mice lacking a protein are especially useful for such tests, this approach is complicated when lethality, or even morbidity, occurs at earlier stages than those to be studied, or when the mutation affects extraneous organs and causes global or systemic effects. In the case of TGF-β1, absence of the protein unleashes a devastating multiorgan autoimmune disorder (9). Doetschman and colleagues' ingenuity in crossing the null genotype for TGF-β1 with the severe combined immunodeficiency (scid) mutation provides proof that the inflammation in these animals is lymphocyte-dependent and creates the first disease-free mice in which nonimmune functions of TGF-β1 might be explored (9).

Doetschman and colleagues have now used an analogous genetic background — *Rag1*$^{-/-}$, rather than scid — to test whether TGF-β1 is necessary for cardiac hypertrophy provoked by sub-pressor doses of Ang II (10). Their present report shows that the lack of TGF-β1 blocks the increase in left ventricular mass, the increase in myocyte size, the deterioration in fractional shortening, and the induction of atrial natriuretic factor, a generalizable molecular marker in cardiac hypertrophy. One admires the authors' painstaking precautions in excluding alternative events that might impinge on their results, such as fibrosis, proliferation, infiltration, blood pressure, and volume overload.

A third secreted factor couples angiotensin II to TGF-β induction

This essential role for TGF-β1 in hypertrophy parallels a similar requirement for FGF-2, as recently shown by Pellieux et al. in the *JCI* (11). Both studies vividly confirm an autocrine/paracrine circuit for hypertrophy predicted on the basis of cell culture phenotypes (3). As a result, it is opportune to pursue the logic of inhibiting these factors, their receptors, and their mediators, as targets for drug development in heart failure.

Ironically, still another secreted factor, downstream from Ang II, may be essential for angiotensin to induce TGF-β in the first place. G protein–coupled receptors activate signaling by the EGF-R, too, by metalloprotease-dependent cleavage of heparin-binding EGF (12). This novel circuit seemingly mediates cardiac hypertrophy induced by Ang II, phenylephrine, and even mechanical load (13) and connects the Ang II receptor to TGF-β expression (14). Hence, a nominal inhibitor of hypertrophy might act on one, two, or three stages in this odyssey.

1. Sadoshima, J., and Izumo, S. 1997. The cellular and molecular response of cardiac myocytes to mechanical stress. *Annu. Rev. Physiol.* **59**:551–571.
2. MacLellan, W.R., and Schneider, M.D. 2000. Genetic dissection of cardiac growth control pathways. *Annu. Rev. Physiol.* **62**:289–320.
3. Parker, T.G., Packer, S.E., and Schneider, M.D. 1990. Peptide growth factors can provoke "fetal" contractile protein gene expression in rat cardiac myocytes. *J. Clin. Invest.* **85**:507–514.
4. Senbonmatsu, T., Ichihara, S., Price, E., Gaffney, F.A., and Inagami, T. 2000. Evidence for angiotensin II type 2 receptor-mediated cardiac myocyte enlargement during in vivo pressure overload. *J. Clin. Invest.* **106**:R25–R29.
5. Cohn, J.N., and Tognoni, G. 2001. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N. Engl. J. Med.* **345**:1667–1675.
6. Tomita, H., et al. 1998. Early induction of transforming growth factor-beta via angiotensin II type 1 receptors contributes to cardiac fibrosis induced by long-term blockade of nitric oxide synthesis in rats. *Hypertension.* **32**:273–279.
7. Gray, M.O., Long, C.S., Kalinyak, J.E., Li, H.T., and Karliner, J.S. 1998. Angiotensin II stimulates cardiac myocyte hypertrophy via paracrine release of TGF-beta 1 and endothelin-1 from fibroblasts. *Cardiovasc. Res.* **40**:352–363.
8. Zhang, D., et al. 2000. TAK1 is activated in the myocardium after pressure overload and is sufficient to provoke heart failure in transgenic mice. *Nat. Med.* **6**:556–563.
9. Diebold, R.J., et al. 1995. Early-onset multifocal inflammation in the transforming growth factor beta 1-null mouse is lymphocyte mediated. *Proc. Natl. Acad. Sci. USA.* **92**:12215–12219.
10. Schultz, J.E.J., et al. 2002. TGF-β1 mediates the hypertrophic cardiomyocyte growth induced by angiotensin II. *J. Clin. Invest.* **109**:787–796. DOI:10.1172/JCI200214190.
11. Pellieux, C., et al. 2001. Dilated cardiomyopathy and impaired cardiac hypertrophic response to angiotensin II in mice lacking FGF-2. *J. Clin. Invest.* **108**:1843–1851. DOI:10.1172/JCI200113627.
12. Prenzel, N. 1999. EGF receptor transactivation by G-protein-coupled receptors requires metalloproteinase cleavage of proHB-EGF. *Nature.* **402**:884–888.
13. Asakura, M., et al. 2002. Cardiac hypertrophy is inhibited by antagonism of ADAM12 processing of HB-EGF: metalloproteinase inhibitors as a new therapy. *Nat. Med.* **8**:35–40.
14. Uchiyama-Tanaka, Y., et al. 2001. Angiotensin II signaling and HB-EGF shedding via metalloproteinase in glomerular mesangial cells. *Kidney Int.* **60**:2153–2163.