surviving infarction one gene at a time
decreased remodeling and mortality in engineered mice lacking the angiotensin ii type 1a receptor
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angiotensin ii (ang ii), named for its first-discovered physiological role as a potent vasoconstrictor, is perhaps the most widely studied paradigm of a pleiotropic agent in cardiovascular biology and medicine, with diverse targets and effects far beyond those first envisioned.1 notably, ang ii has received scrutiny as an intramyocardial growth factor (one, among others) that is produced locally within the myocardium, is released from cardiac cells after mechanical load, and is subsequently expressed at higher levels as part of the “hypertrophic phenotype.”2 both cardiac myocytes and fibroblasts are responsive to ang ii,3 which suffices in tissue culture experiments not only to trigger most of the molecular features of hypertrophy but also to drive fibroblast proliferation. in clinical heart failure, this gives credence to the beneficial effects of treatments that decrease ang ii production (ace inhibitors) or that decrease binding to its type i receptors, thereby preserving ventricular function at doses that do not lower blood pressure and consequently are thought to be mediated by blocking of local actions of this peptide.4 a second clinical setting, related but distinct, in which blockers of ang ii production or function in the heart have proven to be especially valuable is the more acute context of adverse ventricular remodeling after myocardial infarction.5,6 in the instance of ang ii, the universal caveat that a pharmacological intervention might actually work through unanticipated mechanisms has given rise to perennial controversy, because ace inhibitors, apart from their nominal role, also impair the degradation of bradykinin.4

given the foreseeable, recurrent, and vexing limitations of reliance on drug studies alone to decipher protein function in vivo, in recent years it has become a conventional wisdom that the “gold standard” for such insights is to be found in animal models that have been genetically engineered to lack the protein in question (so-called knockout mutations). as

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in contrast to the failure of this seemingly straightforward test to substantiate an essential role for ang ii signaling through at1a in load-induced hypertrophy, harada et al15 report in this issue of circulation that survival, heart failure, remodeling, and fibrosis after myocardial infarction were markedly improved in mice lacking the at1a receptor. no significant difference was seen in infarct size between control and at1a receptor-deficient
mice, in agreement with an earlier investigation by this group using a murine model of ischemia-reperfusion injury\(^{16}\); a decreased prevalence of reperfusion arrhythmias was the one positive finding in that report. In the present study, after permanent occlusion, the cumulative 4-week mortality rate was reduced from 22.7% to 5.9% in AT\(_{1A}\) knockout mice; left ventricular (LV) wall thickness, fractional shortening, and end-diastolic pressure were preserved; LV dilatation was minimized; and fibrosis was prevented. Although several early responses 1 week after infarction were equivalent in wild-type and receptor-deficient mice (with regard to mRNA levels for atrial natriuretic peptide, \(\beta\)-myosin heavy chains, and collagen III), others were attenuated (transforming growth factor \(\beta\)-1 and collagen I). Even more striking effects on the normalization of gene expression were seen at 4 weeks, including return of both collagen genes to sham-operated control levels.

In short, the lack of AT\(_{1A}\) receptors was associated with improved survival after infarction, despite an infarct size similar to controls, and with improvements in myocardial structure, myocardial function, and myocardial gene expression. These findings are remarkably congruent with the clear-cut protective effect of ACE inhibitors after infarction in humans, and this genetic evidence thus attests to Ang II as the responsible agent in the clinical setting. The present study, deleting the gene for only 1 of 3 Ang II receptor genes, also demonstrates a complex range of cardiac responses contingent on AT\(_{1A}\), although some of these responses may reflect the favorable effects of this knockout on LV geometry and, hence, wall stress.

Arguably, the single largest effect of the deletion of AT\(_{1A}\) was on the extent of interstitial fibrosis, which in turn may account for some, much, or all of the other improvements observed. Recent evidence demonstrates the existence of complex cross talk between cardiac myocytes and cardiac fibroblasts that could underlie the cardiac fibrosis induced by Ang II.\(^{17}\) One cannot conclude from the present work the extent to which these improved outcomes might be due to absence of AT\(_{1A}\) in cardiac fibroblasts versus its absence from cardiac myocytes themselves. Refinements in gene-targeting technology in mice ("conditional" knockouts that use a DNA recombinase to excise critical segments of suitably tagged genes) now permit gene deletion to be confined to any lineage or region for which an appropriate, specific promoter or gene is available.\(^{18}\) The feasibility and utility of cardiac-specific knockouts have been established,\(^{19,20}\) an approach that clearly is suited to resolving the relative importance of myocytes versus other cell types as Ang II targets in the myocardium. Another, subtle issue raised by previous work on AT\(_{1A}\) receptor-deficient mice is the basis for abnormal activation that was seen for several growth-promoting protein kinases in cardiac cells, even under basal conditions.\(^{12}\) In these circumstances, hypertrophic growth induced by mechanical load might conceivably be dependent on a chronic secondary response to the absence of the protein. This biochemical anomaly serves as an eloquent reminder that knockout mutations, as a sine qua non for protein function, are themselves susceptible to ambiguities. Many of these questions (indirect effects via extra-normal cell types, systemic effects via other organs, and confounding effects of long-term compensatory adaptations) can be answered, at least in part, by confining gene deletion to a predetermined time and place.

References

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