The temporal link between cardiac hypertrophy and progressive myocardial failure has been recognized for some time, although mechanistic connections have been elusive. More than 100 years ago, Sir William Osler described three classic stages of cardiac hypertrophy, which culminate in “broken compensation.” Much research in recent years has focused on identifying specific hypertrophic stimuli and dissecting the corresponding signaling pathways to elucidate the events responsible for this maladaptive transition. The development and widespread adoption of molecular techniques to modify the genome, chiefly in small mammals, have fueled this search and have provided investigators a means to test the physiological consequences of single gene defects, engineered in vivo. Toward this end, both gain- and loss-of-function mutations have been used in efforts to understand the biochemical pathways and molecular mechanisms underlying the transition from cardiac hypertrophy to failure, at least in mice, culminating in a robust and still-growing array of transgenic models with a cardiomyopathic phenotype similar in many respects to the human disease state.

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In this issue of Circulation, Sakata et al report the progressive decompensation of cardiac function after experimental pressure overload in transgenic mice that overexpress the GTP-binding protein, Gq, selectively in cardiac muscle. Gq-coupled receptors mediate signaling by α-adrenergic agonists, angiotensin II, and endothelin, among other molecules with trophic or functional effects on the myocardium. Previous studies amply demonstrate the ability of Gq-coupled receptors and Gq itself to stimulate hypertrophy in neonatal cardiac myocytes grown in cell culture; however, their respective role in vivo requires more direct substantiation. Agonist binding to this family of receptors increases the proportion of Gq that is active (GTP-bound), activating phospholipase C and ultimately protein kinase C. A previous report by these investigators, directing the α-subunit of Gq to the myocardium in transgenic mice, established the presence of hypertrophy and measurable contractile dysfunction in the line used for the present study as well (Gq-25), but not overt congestive heart failure in the time frame reported; by contrast, lines that express higher levels of Gq led to cardiac decompensation and early death. In their present study, these authors sought to determine the effects of Gq on ventricular adaptation to pressure overload by subjecting their Gq-25 transgenic mice to transverse aortic banding. At baseline, Gq ventricular myocytes exhibited contractile dysfunction (intrinsic to the myocytes, shown by decreased +d/dt and −d/dt). Impaired mechanical performance was accompanied by the reexpression of a panel of fetal genes, characteristic of plasticity seen in the pressure-overloaded ventricle.5 After banding, however, the transgenic ventricles developed pulmonary congestion, with eccentric hypertrophy and a depressed ejection fraction, unlike the compensated, concentric hypertrophy provoked in normal mice. Whereas nontransgenic mice developed the characteristic myocardial pattern of fetal gene expression, gene expression in the Gq mice did not change further after banding. Thus the key conclusion of the present study is that a single gene, Gq, can modify the susceptibility to failure after a pathophysiological intervention.

The findings in this report raise several important questions for our understanding of mechanisms mediating cardiac hypertrophy and its transition to myocardial dysfunction. Are the detrimental effects of Gq overexpression unique to this G protein or true for this signaling pathway more generally? Do distinct programs for G protein–dependent hypertrophy exist, as suggested by differences among transgenic phenotypes? Are differences in phenotype, among particular transgenes, reconcilable with merely technical differences such as the resulting levels of protein expression achieved or with differences in the respective downstream intermediaries? From a clinical perspective, when can cardiac hypertrophy be considered truly compensatory, if hypertrophy itself predisposes to failure? What inferences into human disease, mechanisms for congestive heart failure, and potential countermeasures are suggested from the analysis of genetically engineered mice? This editorial will attempt, briefly, to address these issues and provide insight into the current status of the use of transgenic mice as a tool for exploring the pathophysiology of congestive heart failure.

Sakata and colleagues anticipated an increased growth response to load in Gq mice after aortic banding: rather than augmentation of concentric hypertrophy, they found that hemodynamic stress caused eccentric hypertrophy and rapid progression to heart failure when superimposed on the background of growth due to the Gq transgene. From the fact that...
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the net effect of $G_{\text{q}}$ plus aortic banding was a maladaptive form of hypertrophy, with cardiac decompensation, one might extrapolate a role for $G_{\text{q}}$ in the development of left ventricular failure induced by hemodynamic stress more generally. If true, this supposition would encourage a focus on $G_{\text{q}}$ and $G_{\text{b}}$-dependent proteins as potential targets for drug development. One limitation of the present report is that there remains a margin of uncertainty whether decompensation in $G_{\text{q}}$ mice after banding is necessarily due to the specific signaling cascade activated by this G protein or, alternatively, is related to the effects of hemodynamic load superimposed on myocytes that are already compromised. Other transgenic mice, with lower intramyocardial levels of $G_{\text{q}}$, had normal function before banding, did not display a propensity for decompensation, and were indistinguishable from nontransgenic animals. This suggests that a threshold of expression must be exceeded to develop the phenotype.

Cardiac hypertrophy and adverse effects on ventricular function also can be elicited by directed expression of other G proteins—$G_{\text{b}}$, the mediator of $\beta$-adrenergic signaling, and RAS, a mediator for various polypeptide growth factors and other trophic signals—but the susceptibility to failure after imposition of a load is not yet known in these models. Neither overexpression of a constitutively active $\alpha_{1\text{B}}$-adrenergic receptor (which signals through $G_{\text{q}}$) nor overexpression of RAS was sufficient for overt heart failure despite similar or greater degrees of cardiac hypertrophy than in $G_{\text{q}}$ mice. By contrast, marked impairment of left ventricular fractional shortening resulted from directed expression of protein kinase C $\beta_2$, a known target for $G_{\text{q}}$, through activation of phospholipase C. Differing outcomes also have been reported for fibrosis: present in the case of the transgenes encoding $G_{\text{q}}$, RAS, or protein kinase C $\beta_2$ and absent when hypertrophy was induced by $G_{\text{q}}$ or the activated $\alpha_{1\text{B}}$-receptor. These distinctions lend credence to the notion that activation of specific signaling molecules might plausibly result in selective hypertrophic phenotypes, with differing degrees of dysfunction, fibrotic replacement, and failure. However logical, this conclusion may be premature, because phenotypic differences are obvious even between mouse lines expressing different amounts of $G_{\text{q}}$ or echo-selected sublines of RAS transgenic mice. Moreover, the intrinsic function of isolated ventricular myocytes was not analyzed in most studies, nor have other transgensics been subjected to pressure overload, the trigger for heart failure here, so a definitive comparison of other genes’ consequences versus $G_{\text{q}}$ is not feasible. Thus despite the theoretical attractiveness of mouse genetics for identifying selective mediators of adaptive versus maladaptive hypertrophy, the graded phenotypes of $G_{\text{q}}$ mice, depending on gene dosage, may indicate instead that hypertrophy and failure might be better viewed as a falling along a continuum (at least for this mode of signal transduction). One inherent ambiguity, common to these studies both of RAS and heterotrimeric G proteins, is the existence of multiple agonists that might signal through the proteins: in the case of $G_{\text{q}}$, forced expression might emulgate the signal of $\alpha_{1\text{B}}$-adrenergic agonists, endothelin, or angiotensin II. Thus such experiments attest to a biological role for the transducer but do not distinguish which upstream signal is involved. A second issue is the potential for subtle or overt differences between forced expression of the transducer versus signaling by the ligand itself.

The number of transgenic mouse models that develop a phenotype resembling human cardiomyopathy, to differing degrees, has expanded dramatically in recent years. The impetus to create such models can arise from the need to test the functional significance of molecules whose expression or activity is known to be altered in diseased hearts, including myosin heavy chain mutations that can cause familial hypertrophic cardiomyopathy, or the need to provide in vivo validation for conclusions drawn from studies of cultured cells. Importantly, advances in “microphysiology” have dramatically extended the diagnostic armamentarium that is available for mice. In many cases, a role for these proteins in mediating left ventricular dysfunction has been strengthened by observations of genetically altered mice. Despite this potential for substantial informative results, transgenic models (like all models) are imperfect. Although the extent to which single gene defects can emulate acquired forms of cardiomyopathy is both useful and gratifying, such models may diverge at some level from the pathophysiological response to chronic hemodynamic stress or to load superimposed on the substrate of ischemia or prior infarction. Thus it will be intriguing to learn to what extent each model can successfully mimic the human counterpart with respect to components of clinical heart failure such as humoral factors or $\beta$-adrenergic desensitization.

A second inherent limitation of protein overexpression in the heart is the genetic equivalent of “pharmacological versus physiological” dosing in drug studies: what is the exact relevance of a maneuver that expresses a protein many fold in excess of the levels in normal or diseased myocardium or involves mutational activation of the protein? This highlights the concept that a protein may sufficient to induce the phenotype of hypertrophy or failure but not be necessary for these in conventional pathophysiological settings. Nonetheless, transgenic models are a powerful tool that can satisfy one key criterion of Koch’s postulates for causality in disease. Definitive proof that a molecule is necessary for cardiac decompensation in vivo will often require the converse approach, gene deletion, and is likely to benefit from the refinement of conditional systems to inactivate genes selectively in myocardium or at predetermined times to obviate global effects, embryonic death, or both. As illustrations, the occurrence of dilated cardiomyopathy in mice deficient for the cytoskeletal muscle LIM-family protein, MLP, or lacking Mn-superoxide dismutase, raises a significant possibility that defects in these proteins’ expression or function may contribute to human heart failure.

Perhaps the most important aspect of the present study is the authors’ integration of a genetically engineered animal with a microsurgical intervention to study the interplay of genes and pathophysiology in vivo. The present study reaffirms the link between cardiac hypertrophy and failure and heralds a new approach to the study of this disease. It is hoped that a clearer understanding of the pathways involved in cardiac hypertrophy and failure will emerge from this form of cross-disciplinary analysis, providing unique insights into
human disorders and auspicious models with which to design and test potential therapies.

References

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Success in Failure: Modeling Cardiac Decompensation in Transgenic Mice
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