Cardiomyopathies are primary disorders of cardiac muscle associated with abnormalities of cardiac wall thickness, chamber size, contraction, relaxation, conduction, and rhythm. They are a major cause of morbidity and mortality at all ages and, like acquired forms of cardiovascular disease, frequently progress into heart failure. In contrast to dilated cardiomyopathy (DCM), which is characterized by left or biventricular dilatation in association with depressed myocardial contractility, familial hypertrophic cardiomyopathy (FHC) is characterized by increased cardiac mass with myocyte and myofibrillar disarray. The disease is associated with electrical instability (ie, atrial and ventricular arrhythmias), which makes it the leading cause of death in young athletes. There is marked diversity in the morphological features and clinical manifestations of both DCM and FHC.

Family studies have demonstrated that hypertrophic cardiomyopathy is a heritable disorder that is transmitted as an autosomal-dominant trait or as a sporadic disease. There is neither a racial nor an ethnic predisposition to this condition. Hypertrophic cardiomyopathy is not a rare condition; several noninvasive studies have demonstrated echocardiographic criteria for this disease in 0.2% of young adults (reviewed by Maron). Genetic linkage studies in FHC have found disease loci on at least 14 different genes, most of them encoding sarcomeric genes; hence, FHC has been called a disease of the sarcomere. Thus far, however, most of the clinical heterogeneity of FHC and in cardiomyopathy in general.

Reports pointed to the presence of compound-heterozygous and double-heterozygous mutations in at least 5% of all affected individuals, the study by Tsoutsman et al in this issue of Circulation provides the first in vivo experimental evidence for the role of double-heterozygous missense mutations in FHC and in cardiomyopathy in general.

In an elegant series of experiments, Tsoutsman et al generated and analyzed the first double-mutant mouse model with heterozygous mutations in the cardiac myh7 gene together with a missense mutation in the troponin I (tni) gene. Both mutations are known to be associated with FHC in humans, and experimental evidence for each mutation in mouse models recreated most of the features of FHC. In fact, a recent publication reported that missense mutations in tni were present in 3% of a test population of 100 black subjects.

Strikingly, the resulting double-mutant mouse model is associated with a stunningly severe early onset (postnatal day 14) dilated cardiomyopathy without a prolonged hypertrophic phase but with significant cardiac fibrosis, conduction system abnormalities, severe heart failure, and death by age 21 days.

The fact that the combination of both mutations results not in massive hypertrophy but rather in a severe DCM-like phenotype is unexpected and provides novel experimental insights. Although FHC and DCM phenotypes can be clinically distinguished in affected patients, a variety of genes, such as myh7 or mybpc3, can harbor mutations leading to both diseases. The presence of 2 or more mutations, either double- or compound-heterozygous and/or homozygous, might help to explain why up to 10% of all FHC patients develop a DCM-like phenotype later in life. Moreover, it complicates genotype–phenotype relationships, because gene dosage effects are likely to affect the clinical phenotype. A few examples have been published recently, among them the k207q myh7 mutation, in which heterozygous individuals develop a hypertrophic phenotype but those with the homozygous variant (only 1 individual) develop a DCM-like phenotype. Thus, the tni-203/mhc-403 mouse model supports the clinical observation that ~5% of all individuals affected by FHC carry compound- and/or double-heterozygous mutations and exhibit a more severe phenotype.

In searching for the underlying mechanisms responsible for the rapid progression into dilation and heart failure in tni-203/mhc-403 double-mutant mice, Tsoutsman et al performed a detailed functional and molecular analysis. They observed an increase in malignant tachycardias, which may be explained by the massive fibrosis, a possible substrate for electrical instability. However, changes in calcium metabolism, such as cardiac ryanodine receptor instability, have also

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Circulation is available at http://circ.ahajournals.org
DOI: 10.1161/CIRCULATIONAHA.108.767657
been shown to cause severe arrhythmias. In fact, Tsoutsman et al. reported a significant reduction in the mRNA expression of the cardiac L-type calcium channel, cardiac ryanodine receptor (ryr2), sarcoplasmic/endoplasmic reticulum calcium ATPase (serca2a) and phospholamban (plb) genes. Because brain natriuretic peptide has also been found to be significantly upregulated in tni-203/mhc-403 mice and because it has been shown to downregulate serca2a expression, brain natriuretic peptide induction might be, at least in part, responsible for serca2a downregulation. Brain natriuretic peptide gene expression itself depends on activity of the transcription factor nuclear factor of activated T cells. However, Tsoutsman et al. did not find evidence of the activated upstream signaling mechanisms of the nuclear factor of activated T cells, mainly mitogen activated protein kinases, in tni-203/mhc-403 mice. In fact, the only signaling molecule that was substantially activated with onset of disease symptoms in tni-203/mhc-403 mice was signal transducer and activator of transcription-3 (STAT3), a molecule that acts as a signaling mediator and transcription factor within the janus kinase/STAT signaling pathway.

This observation raises the question of how and why STAT3 is activated in this double-mutant model of FHC. The correlation of increased STAT3 tyrosine phosphorylation with the onset of disease suggests that STAT3 activation may not be a direct consequence of either mutation or even the combination of both mutations, but may rather result from a secondary stress response. In this regard, experimental studies showed that STAT3 is rapidly and transiently activated under various stress conditions, such as pressure overload and hypoxia and in acute myocardial infarction. Most notably, STAT3 is activated by the interleukin-6 cytokine family, which signals through the shared receptor gp130. Recent studies reported that STAT3 is also activated by angiotensin II via the AT1 receptor in isolated cardiomyocytes and in the heart. Interestingly, a link between STAT3 and the angiotensin II autocrine loop has been suggested, as a strong binding activity of STAT3 to the angiotensinogen gene promoter has been described in cardiomyocytes. STAT3 thereby drives angiotensinogen expression, from which angiotensin II is generated through proteolysis. Such an autocrine loop could explain the constitutively strong activation of STAT3 in tni-203/mhc-403 mice and raises the question of an activated renin-angiotensin system in these mice.

Tsoutsman et al. emphasize that the observed STAT3 activation at the onset of cardiac disease symptoms in tni-203/mhc-403 double-mutant mice is indicative of the start of endogenous protection systems. Indeed, STAT3 signaling holds important roles in promoting cardiomyocyte survival and adaptive hypertrophy. For instance, STAT3 protects the heart from ischemic injury and age-related failure and plays an important role in protecting the heart from oxidative damage in response to cytotoxic agents and to the physiological stress of pregnancy.

Although these experimental data on STAT3 signaling point to a largely beneficial role in the protection of the heart against physiological and pathophysiological stress, reports also exist on potential adverse effects of STAT3 activation in the heart. For example, it has been reported that the janus kinase/STAT axis is involved in unfavorable changes after infarction, such as alteration of gene activity that may underlie early diastolic dysfunction (ie, upregulation of phosphatase 1 and downregulation of p16-phospholamban), as well as downregulation of Kv4.2 gene expression that may underlie increased arrhythmogenicity of the postinfarction heart. In agreement with such an effect, Tsoutsman et al. observed enhanced induction of ventricular arrhythmias in tni-203/mhc-403 mice with onset of disease symptoms. Along the same lines, it is known that interleukin-6, the classic cytokine known to activate STAT3, reduces cardiomyocyte contractility in vitro, partly by decreasing intracellular Ca2+ transients, most probably due to the downregulation of serca2a in cardiomyocytes, another feature that Tsoutsman et al. describe in tni-203/mhc-403 mice. Furthermore, a recent article in Circulation emphasizes that angiotensin II–mediated activation of STAT3 in cardiomyocytes may contribute to adverse remodeling caused by an activated renin-angiotensin system.

In conclusion, the tni-203/mhc-403 double-mutant mouse model used by Tsoutsman et al. uncovered numerous interesting novel features in the pathophysiology of FHC, of which only a few were mentioned in this editorial. Specifically interesting to us is the observation that although each mutation by itself is linked to a hypertrophic phenotype, the combination of both rapidly progresses to dilatation. This finding suggests that DCM and FHC, even though clinically distinct, might under certain conditions represent different stages of the same disease. Further exploration of the underlying molecular mechanisms, that is, the modality and the precise role of signaling pathways (ie, STAT3) in the tni-203/mhc-403 double-mutant mouse model, may provide important novel information that in the long run may help to optimize the pharmacological management of FHC.

Disclosures

None.

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KEY WORDS: Editorials  cardiomyopathy  genetics
Disease-Modifying Mutations in Familial Hypertrophic Cardiomyopathy: Complexity From Simplicity
Denise Hilfiker-Kleiner and Ralph Knöll

Circulation. 2008;117:1775-1777
doi: 10.1161/CIRCULATIONAHA.108.767657
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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