Cardiac hypertrophy is the natural response of myocardi- 
um to various stressors, including neurohormonal stim- uli, hemodynamic overload, and injury. In the face of con- 
tinued stress, pathological hypertrophy progresses to a loss of 
cardiomyocytes, the development of fibrosis, and, ultimately, 
heart failure. Emerging evidence has shown that glycogen 
synthase kinase-3β (GSK-3β) is an important negative reg- 
ulator of cardiomyocyte hypertrophy, yet inhibition of 
GSK-3β has been shown to reduce cell death after ischemia 
reperfusion. Therefore, it has been difficult to predict what 
the consequences of chronic inhibition of GSK-3 in the heart 
would be because it might be a balance between the potential 
for the aggravation of cardiac hypertrophy versus antiapo- 
poptotic effects. In this issue of Circulation Research, Hirotani 
and colleagues report that sustained inhibition of GSK-3β 
in postneonatal hearts results in well-compensated “physio- 
logic” cardiac hypertrophy and, most intriguingly, exerts 
protective effects against the development of “pathological” 
cardiac hypertrophy. Additionally, inhibition of GSK-3β is 
active in postischemic cardiomyocytes, and it protects from 
the consequences of chronic inhibition of GSK-3 in the heart. 

The role of GSK-3β in the heart has been extensively 
investigated both in vitro and in animal models by several 
groups (for review, see15–17). It had been demonstrated 
some years ago that hypertrophic stimuli led to 
phosphorylation and inhibition of GSK-3β in cultured 
cardiomyocytes. Among the diverse upstream 
kinases, including Akt, PKC, and PKA, GSK-3β is inactived and the 
repression is relieved (Figure, A). The other important mech- 
anism of GSK-3β inhibition is disruption of the Axin complex by Disheveled-mediated 
displacement of GSK-3β, thereby limiting the accessibility of 
GSK-3β to β-catenin.2 On the other hand, the protein inter- 
actions among PKA, GSK-3β, and AKAP 220 (A-kinase 
anchoring protein) regulate the ability of PKA to phosphor- 
ylate GSK-3β.15 Of note the PKA-mediated inhibition of 
GSK-3β may be critical to the response to β-adrenergic 
stimulation in cardiomyocytes. Among the diverse upstream 
kinases, Akt seems to be the major kinase regulating inhibi- 
tion of GSK-3β in response to various hypertrophic stimuli, 
including IGF-1, angiotensin II, endothelin-1, and α-adrenergic 
stimulation (For review, see14).

The role of GSK-3β in regulating cardiac hypertrophy has 
been extensively investigated both in vitro and in animal 
models by several groups (for review, see15–17). It had been 
demonstrated some years ago that hypertrophic stimuli led to 
phosphorylation and inhibition of GSK-3β both in vitro and 
in vivo.18,19 Overexpression of mutant GSK-3β (GSK-3β 
S9A) that is resistant to inhibitory phosphorylation has been 
shown to attenuate the development of aortic banding-induced 
hypertrophy, suggesting that the inhibition of GSK-3β is 
necessary for the development of pathologic stress-induced 
cardiomyocyte hypertrophy.18,19 Furthermore, inhibition of 
GSK-3β is also necessary for normal cardiomyocyte

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**Editorials**

See related article, pages 1164–1174

**Not All Hypertrophy Is Created Equal**

Ronglih Liao, Thomas Force

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The opinions expressed in this editorial are not necessarily those of the 
editors or of the American Heart Association.

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growth. Using a transgenic mouse model of cardiac-specific overexpression of kinase inactive GSK-3β (Tg-GSK-3β-KI), Hirotani et al show that at baseline, inactivation of GSK-3β in cardiomyocytes indeed results in cardiac hypertrophy, consistent with the notion that GSK-3β is a negative regulator of cardiac hypertrophy. Interestingly, this cardiac hypertrophy appears to be well-compensated because it is accompanied by enhanced ventricular function, as well as increased fibrosis and apoptosis relative to wild-type counterparts, at least over the 8-month observation period. Of note, Tg-GSK-3β-KI hearts develop additional hypertrophy with pressure overload, but the magnitude of hypertrophy is similar to that of wild-type hearts, suggesting the primary role of GSK-3 is in physiological, as opposed to pathological, hypertrophy. Of note, this appears to be a different conclusion than that reached by others. Strikingly, Tg-GSK-3β-KI hearts exhibit preserved function, with a lesser degree of apoptosis and fibrosis, suggesting that the sustained inhibition of GSK-3β exerts protective effects against the progression of “pathologic” hypertrophy to heart failure. Conversely, using conditional overexpression of wild-type GSK-3β, Hirotani et al show that further activation of GSK-3β leads to increased apoptosis in vivo. Based on their data, the authors conclude that the downregulation of GSK-3β observed in patients with heart failure may be compensatory.

Not all cardiac hypertrophy is equal, with two distinct recognized flavors: physiologic and pathologic hypertrophy. The classical examples of physiologic hypertrophy are normal cardiac growth and the athletic heart, the latter exhibiting normal to enhanced cardiac function, albeit with chamber dilatation. Regulation of physiologic hypertrophy is not fully understood but clearly involves IGF-1 and the PI3-K/Akt pathway. Pathologic hypertrophy, in contrast, is regulated by both neurohormonal stimuli and biomechanical stress (eg, cell stretch in vitro and pressure overload in vivo), and involves signaling through the heterotrimetric G protein, Gq/11, and Ca2+-dependent signaling with downstream factors being protein kinase C and calcineurin. PI3-K also plays a role in pathologic stress-induced hypertrophy, but it is a different isoform with critical differences in upstream activators and downstream targets. For decades, pathologic stress-induced cardiac hypertrophy has been thought to be an adaptive response to compensate for elevated ventricular pressures, designed to normalize wall stress. Recently, however, several studies using genetically altered transgenic mouse models have demonstrated that the development of hypertrophy is not required as a compensatory mechanism after pressure overload (For review, see14-27). In fact, these studies have suggested that inhibition of hypertrophy protects against the development of heart failure, despite ongoing hemodynamic stress. It has been suggested that the cardiac hypertrophy resulting from stimulation of the phosphoinositol-3-kinase (PI3K)/Akt axis, which lies downstream of insulin-like growth factor receptor and other growth factor receptor tyrosine kinases, is “physiologic.” However, this can transition to pathologic hypertrophy when Akt activity is either very marked or sustained for long periods of time. Interestingly, using a nuclear-targeted Akt construct, Sussman and coworkers have demonstrated a unique role for nuclear Akt that is antihypertrophic, yet prosurvival, when stimulated by several known hypertrophic stimuli. Hirotani et al may support this concept, suggesting that not all cardiac hypertrophy is created equal, with different signaling events occurring during the development of physiologic versus pathologic hypertrophy. Therefore, it is likely that what drives the development of heart failure is not merely the presence of hypertrophy, but rather, the underlying signaling events induced by particular hypertrophic stimuli. This notion is further supported by a recent paper from the same group of investigators showing that overexpression of GSK-3α results in less cardiac hypertrophy, but more apoptosis, fibrosis, and cardiac dysfunction after pressure overload. Taken together, these reports may implicate GSK-3 family members in the development of physiologic hypertrophy, with pathologic hypertrophy mediated via GSK-3-independent pathways.

The major caveat with the work of Hirotani et al and essentially all work done examining the role of GSK-3s in the heart is the lack of loss of function studies using gene
deletion. The reasons for the misleading conclusions that can be reached when transgenesis/overexpression is the sole approach, particularly overexpression of dominant inhibitory mutants, do not need to be repeated here. True loss-of-function studies are required to discern the role of GSks, and this is even more true for identifying isoform-specific effects. That said, the current report does provide invaluable insight into understanding the role of GSK-3β in vivo and provides guidance in the possible future application of GSK-3 inhibition in the heart. Identification of the true and diverse roles of GSK-3s will aid immensely in targeting GSK selectively in the appropriate cell types or tissues.

In summary, inhibition of GSK-3β has been suggested as a therapeutic strategy for the treatment of Alzheimer disease, diabetes, and ischemia-reperfusion injury, and an array of small molecule inhibitors targeting GSK-3s (there is no evidence that any of these are selective for one versus the other isoform) have been developed. As with many kinases or signaling molecules, whether inhibition has beneficial or detrimental effects depends on the cell type and the conditions and timing of the inhibition. Accumulating evidence suggests that Wnt or Notch pathways regulate the function of cardiac stem/progenitor cells.32−37 Manipulating GSK-3s may also directly affect the existence, survival, and function of recently identified cardiac stem/progenitor cells and cardiomyocytes.38 The notion of targeting GSK-3β for the treatment of heart failure is appealing, but given the involvement of GSK-3α and GSK-3β mutants, do not need to be repeated here. True loss-of-the-function studies are required to discern the role of GSKs, and inhibition of GSK-3β is a negative regulator of cardiomyocyte hypertrophy. J Cell Biol. 2000;151:117–130.

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