Cardiac hypertrophy is the natural response of myocardi-um to various stressors, including neurohormonal stimu-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 antiapto-potic 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” hypertrophy and heart failure with pressure overload.1 Although there are a number of concerns that need to be addressed before targeting GSK-3 for the treatment of heart failure, this “best of both worlds” outcome provides an interesting and favorable rationale for such intervention.

The GSK-3 family of protein kinases is encoded by 2 genes, α and β. They are highly conserved throughout evolution and are critical to the regulation of diverse biological processes ranging from organ development to cell death, including cell growth, cell cycling, cytoskeletal organization, and metabo-lism.2,3 Furthermore, dysregulation of GSK-3β has been implicated in the pathogenesis of many human diseases including Alzheimer disease, diabetes, and tumorgenesis.4–8 GSK-3α (51 kDa) is the larger of the two and has a glycine-rich N terminus of unknown function. GSK-3β (47 kDa) and α share significant sequence homology (97%) in their kinase domains, however the homology between the last 76 C-terminal residues is rather low (36%).9 Both isoforms are widely expressed, but the majority of prior investigations have focused on the role of GSK-3β. This bias likely arose from studies in Drosophila that may have erroneously identi-fied GSK-3β as the dominant isoform.9 Although these two isoforms typically share substrates, the pattern of their expres-sion, substrate preference, and biological function are not always the same.9,10 For example, embryonic lethality, attrib-utable to marked hepatic apoptosis, occurred in mice lacking GSK-3β, suggesting that GSK-3β plays a dominant role during liver development.11 In contrast, α and β appear to be completely redundant in the regulation of β-catenin, the down-stream effector of the canonical Wnt pathway, because deletion of both α alleles or both β alleles had no effect on β-catenin expression or function.9

Unlike most kinases, under unstimulated conditions, GSK-3s are active and phosphorylate downstream targets, including β-catenin, NF-AT family members, c-Jun, cyclin D1, c-myc, and the protein translation factor, eIF2Be, with subsequent repression of activity of these targets. On phosphorylation (at serine 21 for α and serine 9 for β) by its upstream kinases including Akt, PKC, and PKA, GSK-3 is inactivated and the repression is relieved (Figure, A). The other important mecha-nism of GSK-3β regulation, recruited by Wnt signaling, likely does not involve phosphorylation of Ser 9/21 because mice with knock-ins of GSK-3 with mutations at Ser 9 and 21, preventing phosphorylation, demonstrated normal inhibition of GSK-3 as evidenced by normal activation of β-catenin signaling. This mechanism is not well-defined but involves modulation of GSK-3 activity by the scaffolding protein Axin and by Disheveled (Figure, B). In brief, this mechanism leads to disruption of the Axin complex by Disheveled-mediated displacement of GSK-3, thereby limiting the accessibility of GSK-3 to β-catenin.12 On the other hand, the protein interactions among PKA, GSK-3β, and AKAP 220 (A-kinase anchoring protein) regulate the ability of PKA to phosphorylate GSK-3β.13 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-3 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.18–20 Furthermore, inhibition of GSK-3β is also necessary for normal cardiomyocyte...
...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 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 heterotrimeric G protein, Gq/11, and Ca2+-dependent signaling with downstream effectors 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 hypertension, 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 pathological hypertrophy mediated via GSK-3β-independent pathways.

The major caveat with the work of Hirotani et al and essentially all work done examining the role of GSK-3 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-the-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-3β 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-3 (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 GSKs, and mediates protein kinase AAKAP220 binds to glycogen synthase kinase-3beta (GSK-3beta) and mediates protein kinase A-dependent inhibition of GSK-3β. J Biol Chem. 2002;277:36955–36961.


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REFERENCES


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Not All Hypertrophy Is Created Equal
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