Fill a Gab(1) in Cardiac Hypertrophy Signaling
Search a Missing Link Between gp130 and ERK5 in Hypertrophic Remodeling in Heart

Yibin Wang

Cardiac hypertrophy represents one of the most central issues in heart failure, involving many aspects of changes in cardiac myocyte from cellular morphology to gene expression and contractile function. Although the process is at the beginning compensatory in response to hemodynamic load or myocardial injury, cardiac hypertrophy is often followed by pathological remodeling in myocardium and a transition to overt heart failure. A large number of extracellular ligands, their cognate receptors and corresponding intracellular signal transduction pathways have been implicated in the hypertrophic process from both in vitro and in vivo studies. Among them, cardiotophin-1 (CT-1) was discovered as a potent activator of cardiac hypertrophy that shares extensive sequence and functional similarities with leukemia inhibitory factor (LIF) as members of interleukin-6 (IL-6)–related cytokine family. LIF/CT-1 bind to gp130/Ho252, a LIF cytokine receptor β heterodimer and activate downstream signaling pathways, including members of signal transducer and activator of transcription (STATs), mitogen-activated protein (MAP) kinases such as extracellular signal–regulated kinases (ERK1/2), and phosphatidylinositol 3-kinase (PI3K)/Akt. Studies have demonstrated that both LIF and CT-1 promote myocyte hypertrophy, survival, and a unique pattern of embryonic/fetal gene induction. LIF and CT-1 expression and gp130 signaling also correlated with mechanical stress in myocytes in culture and human and experimental models of heart failure. More significantly, targeted inactivation of gp130 in ventricular myocytes via Cre-loxP–mediated tissue-specific knockout resulted in rapid chamber dilation and a significant increase in myocyte apoptosis upon pressure overload. All these findings underscore the potential function of gp130 signaling in myocyte remodeling and survival in response to mechanical stress.

In addition to marker gene activation and antiapoptotic effects, gp130-mediated hypertrophy has a distinctive pattern of sarcomere organization. Unlike phenylephrine or endothelin-1 that induce hypertrophy response in cultured myocytes with enlarged cell size in all dimensions, LIF or CT-1 increases cell length by adding sarcomere units in a serial rather than parallel fashion. Such observation has prompted speculation that gp130 signaling may have a specific role in eccentric hypertrophy, a remodeling process more specifically associated with volume overload, as to concentric hypertrophy induced by pressure overload. A recent report by Nicol et al suggests that MEK5, an activator of big MAP kinase (BMK/ERK5), is capable to elicit serial assembly of sarcomere in myocytes and induces eccentric hypertrophy in transgenic hearts. They further demonstrate that MEK5/ERK5 is essential to LIF-induced myocyte elongation. However, the molecular mechanism underlying LIF/CT-1–induced MEK5/ERK5 activation via gp130 signal complex remains unclear. In this issue of Circulation Research, Nakaoka et al provide some interesting new evidence to suggest that a missing puzzle linking gp130 to MEK5/ERK5 pathway may have been found.

It should not be a surprise that Grb2-associated binder-1 (Gab-1) is a prime suspect in the search for a functional linker between gp130 and downstream MAP kinase activation. Gab-1 is a member of the Gab/DOS (daughter of sevenless) family of scaffolding/docking molecules and contains a pleckstrin homology (PH) domain and potential SH2/SH3 binding motifs. Tyrosine-phosphorylated Gab-1 can interact with a number of signaling molecules, including p85 PI3K, phospholipase C-γ, and a src homology (SH) 2 domain–containing protein tyrosine phosphatase (SHP-2). Genetic inactivation Gab-1 leads to embryonic lethality and loss of ERK activation in response to growth factor stimulation, thus underscoring the importance of Gab-1 in MAP kinase activation via tyrosine kinase receptors and cytokine receptors. Since SHP-2 recruitment to gp130 is important to downstream MAP kinase activation, and SHP-2 is found to be a strong binding partner of Gab-1, it does not seem to be a far-fetched hunch that Gab-1 may also play a role in gp130-mediated MAP kinase activation in heart. In the present study, Nakaoka et al combined both biochemical and cellular studies to demonstrate that Gab-1 phosphorylation and SHP-2 binding were dependent on LIF stimulation and was required for ERK5 activation, selective marker gene regulation, and most interestingly sarcomere organization associated with myocyte elongation (Figure). In contrast, STAT3 activation was not affected by Gab-1/SHP-2 interaction, and activity of AKT and ERK1/2 was only partially affected, suggesting a rather specific role for Gab-1/SHP-2 interaction in gp130 dependent signaling in myocytes. This result is somewhat surprising because SHP-2 and JAK/STAT are shown to have reciprocal function down-
stream of gp130 and may reflect a unique signaling property in cardiomyocytes versus other cell types.\(^{39}\)

Although the findings of the present report are consistent with the hypothesis that Gab-1 serves as a scaffold protein to link SHP-2 and its downstream signaling partner(s) into a functional signaling complex, it will remain speculative until all of its molecular components can be identified. Indeed, identification of the interacting partners of Gab-1 in cardiomyocytes will help to address many related questions. For example, which upstream kinase is part of the signaling complex that is responsible for ERK5 activation, whether and how SHP-2 phosphatase activity mediates downstream kinase activation, whether and how Gab-1/SHP-2 interaction affects other tyrosine kinase receptor–mediated signaling pathways and other gp130-mediated signaling. Obviously, finding Gab-1 will lead to many more puzzle pieces involved in the signaling network of cardiac hypertrophy.

Perhaps an even more intriguing question from the present study is whether Gab-1/SHP-2 functions as a differential signaling switch that turns on eccentric hypertrophy. Since no effective therapy is available to treat this specific form of cardiomyopathy, the potential impact of identifying a responsible signaling pathway cannot be understated. A recent report from Yasukawa et al.\(^{30}\) demonstrated that gp130-dependent signaling was highly induced by pressure overload along with a number of other signaling pathways, such as ERK1/2, p38, and AKT, but was negatively regulated by suppressor of cytokine signaling-3 (SOCS3), which was also induced by pressure overload and was capable of blocking almost all aspects of CT-1–induced myocyte hypertrophy. Furthermore, SOCS3 shares its preferred binding site on gp130 with the same docking site of SHP-2, suggesting that SOCS3 may compete and suppress Gab-1/SHP-2–mediated signaling from gp130 receptor.\(^{40}\) Therefore, in pressure-overloaded hearts, gp130-dependent signaling may have been suppressed by intrinsic inhibitor SOCS3 that channels the cardiac remodeling process toward a concentric form. By the same token, we can speculate that in volume-overloaded hearts, there might be a different balance between SOCS3 and Gab-1/SHP-2 signaling that favors ERK5 activation and leads to eccentric hypertrophy. Indeed, CT-1 has been found to be elevated in patients with valvular regurgitation but normal left ventricular systolic function.\(^{26}\) However, SOCS3 expression and the expression/phosphorylation/intracellular distribution of Gab-1 have not been fully characterized in an in vivo model of volume overload. Hopefully, the findings from Nakaoka et al.\(^{33}\) will provide enough incentive and guidance to look into these questions in a relevant model system.

Lastly, the study reported here represents only some preliminary investigation exclusively performed in cultured myocytes. Manipulation of Gab-1 expression and its interaction with SHP-2 in intact heart will be necessary to further establish its role in gp130-mediated cardiac remodeling. In that regard, sophisticated genetic approaches are already developed to achieve cardiac-specific and developmental stage–regulated manipulation to overcome embryonic lethality and to provide more concrete evidence for the physiological role of Gab-1 in cardiac hypertrophy.\(^{13}\) There is no doubt that future studies will lead us to more missing links in the complex signaling network of cardiac hypertrophy.

References


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