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EDITORIAL COMMENT

GDF-11 as a Potential Cardiac Pro-Angiogenic Factor*

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The cardiovascular role of growth differentiation factor (GDF)-11, a member of the transforming growth factor (TGF)-β superfamily, is controversial. In 2013, we reported that heterochronic parabiosis, whereby 2 mice of different ages ("heterochronic") are joined together to share a common circulation, reduced cardiac hypertrophy in the old mouse without a concomitant increase in heart size of the young mouse. By taking a proteomic approach, GDF-11 was identified as one potential circulating factor mediating this effect, and exogeneous GDF-11 reduced cardiac hypertrophy.[1] Although our initial study misidentified GDF-11 on a Western analysis due to a monoclonal antibody that recognized both GDF-11 and GDF-8 (a closely related ligand also known as myostatin), exogenous administration of GDF-11 has clear biological effects. The role of different circulating forms of these ligands and heart disease is an area of active investigation, but thus far it appears that total GDF-11 blood levels do not decrease with aging in mice or humans.

Because GDF-11 and GDF-8 share 90% identity at the protein level in their mature domains and can activate similar receptors, they have been logically considered to serve similar biochemical roles. However, landmark studies by the Se-Jin Lee laboratory have shown that GDF-11 and GDF-8 have distinct functions in vivo.[2] GDF-8 deficiency leads to a hypermuscular phenotype, whereas complete absence of GDF-11 is incompatible with life. GDF-11-null mice have perinatal lethality due to developing defect. Homozygous loss of GDF-11 results in skeletal abnormalities, including anterior homeotic transformation of the axial skeleton due to altered Hox gene expression with additional ribs as well as kidney defects. A recent exciting discovery is that in humans heterozygous loss-of-function mutations lead to a multisystem disease including neurodevelopmental, skeletal, and cardiac disorders.[3] GDF-11 is a substantially more potent ligand compared with GDF-8, and we have shown that specific amino acid differences between the ligands mediate this effect both in vitro and in vivo.[4]

Exogenous GDF-11 may be beneficial in some disease models. The Houser laboratory reported that exogenous GDF-11 can attenuate cardiac hypertrophy and fibrosis under pressure overload in mice in a dose-dependent manner.[5] Although GDF-11 up-regulated profibrotic genes in fibroblasts in vitro, exogenous GDF-11 reduced fibrosis under pressure overload but was toxic at high doses. These results suggest that under pathologic conditions, GDF-11 may be cardioprotective. As with many potent signaling factors, sustained high levels of GDF-11 signaling are likely detrimental.

In this issue of *JACC: Basic to Translational Science*, Zhu et al[6] provide new insights into the potential protective role of endogenous GDF-11 under pathologic stress, building on the Houser laboratory findings.[5] First, the authors showed that GDF-11 protein and messenger RNA levels were elevated in the hearts of the patients with dilated cardiomyopathy as well as in mouse hearts after transverse aortic constriction (TAC).They separated cardiomyocytes (CMs) from hearts, and the cardiac source of GDF-11 was mainly from CMs, not non-CMs. Conditional CM-specific GDF-11 deletion in mice revealed normal cardiac

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function, revealing that endogenous CM-produced GDF-11 is not essential in normal physiology. However, these mice showed worse cardiac function after TAC in terms of cardiac hypertrophy, systolic function, angiogenesis, and fibrosis. The authors also showed that GDF-11 may participate in paracrine/autocrine signaling in the myocardium. CM-deletion of GDF-11 in vivo led to reduced capillary density at 56 days, with a reduction in vascular endothelial growth factor (VEGF) protein and messenger RNA compared with control mice. Studies in vitro suggested that conditioned medium of CMs with GDF-11, but not GDF-11, improved tube formation in endothelial cells, possibly through GDF-11-mediated activation of the Akt/mTOR pathway through TGF-β receptor 1.

The molecular mechanisms of GDF-11 in postnatal mammals are unclear. It is likely that endogenous GDF-11 functions only locally within specific tissues, given multiple known inhibitors that bind the mature ligands after signaling. However, exogenous systemic mature GDF-11 ligand may bypass inhibitors to reach tissues and signal before inhibitors bind and inactive the mature GDF-11 ligand. This study by Zhu et al[6] provides evidence that CM-produced GDF-11 can induce VEGF release and can thus promote angiogenesis in a paracrine manner under pathologic stress. This is consistent with the concept that GDF-11 may regulate angiogenesis in other tissues.[2] Given that the TGF-β family can mediate diverse effects, often dependent on biological context, it is likely that additional molecular mechanisms beyond VEGF will emerge. It is also important to note that the TAC model is an important experimental model for its reproducibility and relevant myocardial pathophysiological effects, such as hypertrophy and fibrosis, but TAC is not directly representative of a specific human disease. Thus, studies in other models will be important to study the pathways proposed by Zhu et al.[6]

At the current time, the role of endogenous GDF-11 in postnatal human biology is an exciting area, particularly with the recent report of multisystem human disease in the setting of heterozygous loss of function of GDF-11.[3] A potential therapeutic approach using exogenous GDF-11 is under active investigation, and there could possibly be a future role for exogenous GDF-11 in human genetic disease. The study by Zhu et al[6] provides useful mechanistic information that can be addressed in other cardiac disease models. Thus, this study is likely one piece of a complex emerging puzzle regarding the role of GDF-11 in human biology.

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