Interferon Regulatory Factors in Heart Stress Response Beyond Inflammation

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Cardiac hypertrophy and pathological remodeling are hallmarks of cardiomyopathy associated with many pathological stressors, such as mechanic overload, oxidative injury, hormonal stimulation, or viral infection. Transcriptional regulation is key to this process, involving well-established transcription factors, such as NFAT, GATA, MEF2, and NF-κB among others. They function as the downstream effectors for upstream signaling to alter the cardiac transcriptome that ultimately leads to pathological changes in cardiomyocyte morphology and function. Therefore, uncovering the molecular basis of the regulatory circuit for cardiac gene expression has been a major focus of intense research efforts. In this issue, a study from the laboratory of Dr Hongliang Li expands the complexity of the transcriptional network in the heart by uncovering yet another new player from an unexpected family.

Interferon regulatory factors (IRFs) are a group of transcription factors that were first identified for their inducible expression in response to interferon signaling. Members of the IRF family play critical roles in antiviral responses, inflammatory regulation, cytokine signaling, cell death, growth, and differentiation. Interferon exerts potent antipathogenic responses in the host immune system and have been used as therapeutic agents against viral infections, such as hepatitis C. The link between interferon function and heart disease was first observed in interferon-based antiviral therapies where interferon-α treatment was reported to cause transient or irreversible cardiomyopathies. In contrast, conflicting effects of interferon γ were observed in both clinical and animal studies, whereas interferon γ treatment was beneficial for viral-induced myocarditis; it was also reported to cause cardiomyopathy and dysfunction in transgenic mice. Genetic knockout of interferon γ receptor reduced angiotensin II–induced hypertrophy and remodeling. In contrast, genetic ablation of interferon γ enhanced pathological hypertrophy and diastolic heart failure. These functional effects of interferon on cardiac hypertrophy and pathological remodeling raise important questions about the role of downstream IRFs in cardiac pathology. Do they affect cardiomyocytes indirectly via infiltrating inflammatory cells or do they function directly to regulate cardiac hypertrophy and remodeling in cardiomyocyte in a cell-autonomous fashion? More importantly, are IRFs involved specifically in interferon-triggered cardiomyopathy or broadly in other pathological stress responses in the heart? A series of recent reports from the laboratory of Dr. Hongliang Li began to address these questions on the basis of sophisticated genetic analysis both in cultured myocytes and in intact mouse hearts.

In the study published in the current issue of Hypertension, Jiang et al found that the IRF7 expression in heart was downregulated on pressure overload induced by aortic banding. Similar downregulation of IRF7 expression was observed in cultured cardiomyocytes after angiotensin II or phenylephrine treatment, indicating that IRF7 expression in cardiomyocytes can be regulated in response to a broad spectrum of pathological stressors, perhaps in an interferon-independent manner. By both genetic ablation and cardiac-specific overexpression in mice, the authors further revealed an inhibitory effect of IRF7 on the cardiac hypertrophy and associated pathological changes in response to pressure overload. By demonstrating a similar effect in cultured myocytes, Jiang et al established a cell-autonomous effect for IRF7 in regulating cardiac hypertrophy under different pathological stressors. After similar experimental approaches, the same group has also implicated other IRF members, including the role of IRF4, IRF9, and IRF3 in cardiac hypertrophy regulation. In particular, IRF9 and IRF3 share similar antihypertrophic effects as IRF7, whereas IRF4 seems to possess opposite functions in the heart. Altogether, these findings clearly indicate that the IRF family members are potentially important new players in cardiac gene regulation in the onset of pathological hypertrophy and remodeling.

Despite their shared effect on cardiac hypertrophy and remodeling, the underlying mechanisms involved in each IRF family members seem to be significantly different. Whereas IRF4 promotes cardiac hypertrophy at least in part via transcriptional induction of cAMP response element–binding protein (CREB), IRF9 and IRF3 inhibit cardiac hypertrophy via targeted manipulation of myocardin and mitogen-activated protein (MAP) kinase (extracellular-signal regulated kinase) activities, respectively. In contrast, Jiang et al report here that IRF7 directly interacts with inhibitor of kappa B kinase beta (IKKβ) and inhibits hypertrophy via negative regulation of the NF-κB pathway. Clearly, although originally discovered as transcription...
factors, IRF members also possess diverse function as signaling modulators for transcription factors and protein kinases. This is also in line with their established diverse functions in antipathogen responses and inflammatory regulation. Therefore, it is tempting to speculate that the IRF members (IRF7, IRF9, and IRF3) with inhibitory effects on cardiac hypertrophy may be mobilized as a coordinated compensatory response to pathological stresses in the heart by targeting different but complementary pathways in hypertrophy, involving NF-xB, myocardin, and extracellular-signal regulated kinase (Figure).

These findings on IRFs function in heart highlight the complexity of cardiac regulatory network and raise more interesting questions for future investigation. Although these reports from the laboratory of Dr Li focus mainly on cardiac hypertrophy and remodeling induced by mechanical overload, the role of IRFs in physiological hypertrophy in response to exercise or pregnancy remains untested. On the basis of this observation of largely normal cardiac phenotypes in genetic ablation of IRFs in physiological hypertrophy in response to exercise or pregnancy remains untested. Rather, IRF-mediated signaling may be specifically related to pathological stress responses in the heart, a speculation that needs to be investigated further experimentally. Furthermore, considering the importance of downstream pathways implicated in IRF function, the functional effect of IRFs in acute stress response, such as myocardial infarction, would be an interesting question to pursue. Finally, beyond the heart, CREB, extracellular-signal regulated kinase, and IKKβ are widely expressed in different tissues. It is not clear whether these interactions are common mechanisms for each IRF across different tissues or a unique mechanism only manifested in the specific context of the cardiomyocyte. If similar mechanisms exist in other tissues, IRFs may function beyond their originally defined interferon regulation in inflammatory cells but rather as a family of universal stress–response genes implicated in different tissues and pathological conditions. The creation of genetic models with tissue-specific manipulation of the IRF members, such as in the current report, will be powerful tools to investigate the expanding universe of IRF function in different tissue and diseases.

With insights learned from IRF function in the pathologically stressed heart, we can now explore the potential therapies by targeted manipulation of IRFs. In the report by Jiang et al., manipulation IRF7 expression or downstream NF-kB pathway achieved significant effect on disease progression in pressure-overloaded hearts. Similar efforts targeted to other IRF members, by either augmenting the function of IRF3 and IRF9 or inhibiting that of IRF4, also exerted protective effect in heart. However, it is still unstated whether such manipulations can reverse established cardiac hypertrophy or pathological remodeling. Clearly, with the finding of IRFs as new regulators of pathological hypertrophy and remodeling in heart, we can anticipate more research in this area to advance our current understanding on the pathological stress response in the diseased heart.

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References