GATA4 and the Two Sides of Gene Expression Reprogramming

Cinzia Perrino, Howard A. Rockman

In this issue of Circulation Research, Oka et al address the role of GATA4 in the regulation of cardiac homeostasis in the adult heart. In a clever strategy that used a GATA4-loxP-targeted allele together with 3 different cardiac-specific overexpressing Cre transgenes (α-MHC-Cre, β-MHC-Cre, and Nkx2.5-Cre), the authors dissected the role of GATA4 in cardiac remodeling of the normal heart and in response to both pathological and physiological stressors. In contrast to previously reported Gata4-loxP alleles, in this study theloxP insertion sites did not alter basal expression levels of GATA4. Interestingly, gene-targeted mice with marked loss of GATA4 protein induced by either β-MHC or α-MHC promoter-driven Cre transgenes survived into adulthood but displayed progressive cardiac enlargement and dysfunction that was correlated to GATA4 levels. These hearts were also characterized by increased rates of cardiomyocyte apoptosis. Through a comprehensive microarray analysis the authors were able to show that GATA4 deletion significantly altered the expression patterns for a large number of genes of which at least three (PKCε, Bcl6, and caspase 12) are known to be involved in cell survival. These data nicely demonstrate the important role GATA4 plays as a regulator of gene expression to maintain normal cardiac homeostatic remodeling in the unstressed adult heart by promoting cell survival and inhibiting programmed cell death.

Role of Gene Expression Reprogramming in the Transition to Cardiac Dysfunction

In response to hypertrophic stimuli, adult cardiomyocytes reactivate the fetal gene regulatory program and downregulate various adult isoforms. Re-expression of the GATA4-regulated genes ANP, BNP, and β-MHC is considered a hallmark of pathological hypertrophy and heart failure, and has been shown to correlate with the efficacy of drug therapy in dilative cardiomyopathy. Moreover, inhibition of gene expression reprogramming through different approaches in several mouse models has been shown to reduce cardiac hypertrophy and ameliorate cardiac dysfunction. However, here Oka et al show that in response to chronic pressure overload, GATA4-deleted mice undergo rapid cardiac decompensation secondary to marked cardiomyocyte apoptosis. These important results indicate that progression of the normal cardiomyocyte toward a failure phenotype is much more complex than simple reversal of fetal gene reprogramming, and that other genes directly involved in cell survival might also be reprogrammed and activated to preserve cellular homeostasis.

GATA4 Is Involved in the Cardiac Growth Remodeling Induced by Either Physiological or Pathological Stress

Cardiac hypertrophy has been long ago recognized as an independent cardiovascular risk factor in large scale clinical
trials. 16 Experimental studies now indicate that inhibition of the hypertrophic growth usually results in the amelioration of left ventricular dysfunction, 17–20 despite increased wall stress. 17 However, it is well known that cardiac hypertrophy can also be an adaptive response of the heart to physiological overloads, in this case leading to a heart with enhanced cardiac performance. Undoubtedly, one of the most intriguing and provocative results in the article by Oka et al 8 is the blunted hypertrophic response in mice with cardiac-restricted GATA4 deletion when exposed to either pathological pressure overload or physical training, despite the fact that physiological and pathological hypertrophy significantly differ in the patterns of fetal gene expression programming. These important results suggest that the regulation of gene expression by GATA4 acts as a focal point in the regulation of growth responses of the myocardium. Whether GATA4-regulated gene expression is required to maintain cardiac function in response to chronic physical training is an intriguing question and one that will require further study.

Is GATA4 a Solo Player? Recently, a heterozygous missense mutation of GATA4 has been found in a large human pedigree with isolated cardiac septal defects. 4 This mutation results in diminished DNA-binding affinity and transcriptional activity of GATA4, and impaired physical interaction between GATA4 and TBX5, a T-box protein also involved in the development of syndromic cardiac septal defects. 21, 22 Interestingly, TBX5 mutations responsible for similar cardiac defects lose their ability to interact with GATA4. 4 These results suggest that GATA4 and TBX5 might cooperate to promote cardiogenesis and that the disruption of GATA4-TBX5 interaction might be responsible, at least in part, for the human cardiac defects. Further studies in genetically-modified mouse models will be needed to address this issue.

Perspective The study by Oka et al 8 significantly improves our understanding of the molecular mechanisms by which the transcription factor GATA4 preserves cardiac function and promotes cardiomyocyte survival in the postnatal heart. Their data suggest that the intricate network of signaling pathways culminating in GATA4-dependent gene expression reprogramming in the stressed adult cardiomyocyte also regulates the expression and activation of cardioprotective factors important to preserve normal cardiac homeostasis.

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