Cardiac transcription factor biologists have spent many years identifying transcription factors that function as critical regulators of important cellular processes; however, the challenges in understanding cardiac transcriptional regulatory networks have been formidable. The cardiovascular system is a complex organ system in which component muscle cells must interact with other cells in a coordinated fashion to generate and maintain the heart and vasculature. Within the heart, muscle cells contract to circulate the blood, while specialized muscle cells are required for generation of the heartbeat and electrical propagation of coordinated contractile signals. In the vasculature, vascular smooth muscle cells (VSMCs) maintain vascular tone but also undergo phenotypic changes including proliferation, migration, and conversion from a contractile, differentiated state to a more synthetic, dedifferentiated state in response to injury. At the molecular level, various transcription factors within these cells coordinate gene expression patterns to enable them to perform these various roles. Linking transcription factors to the complex and varied behaviors of cardiac and smooth muscle cells has challenged transcription factor biologists for many years. Disruptions within these transcriptional networks can lead to extensive functional deficits. Studies on the Kruppel-like factors (KLFs) provide many instructive examples.

The KLFs comprise a family of zinc finger transcription factors whose members play important roles in cardiovascular tissues, as highlighted in this issue of the Journal [1]. In this review, the authors provide a concise and timely update on the biology of KLFs in cardiac, smooth, and skeletal muscle. These factors are numerous, comprising 18 members to date, and are functionally diverse, serving as either ubiquitous or tissue-restricted transcriptional repressors or activators that interact with numerous protein partners.

In the heart, KLFs play critical roles in cardiac development, hypertrophy, metabolism, and arrhythmogenesis. During development, KLF13, a transcriptional repressor, is essential for heart morphogenesis and functions through an interaction with GATA4 to regulate cardiac-specific genes [2]. Similarly, KLF3, also a transcriptional repressor, is also required for normal heart morphogenesis, although the mechanism remains to be elucidated [3]. In cardiac hypertrophy, a response to stress that often is a precursor to heart failure, KLF5, a transcriptional activator, plays an important cardio-protective role by induction of IGF-1 in cardiac fibroblasts [4]. Within cardiomyocytes, KLF15 functions as a negative regulator of pathological hypertrophy, through transcriptional inhibition of MEF2 and GATA4 [5]. KLF15 also interacts with p300 to dampen p53 acetylation and may maintain normal heart function through repressing p300-dependent acetylation of other important transcriptional regulators such as GATA4, MEF2, and histones [6]. KLF15 is essential for preferential substrate utilization of fatty acids over glucose in the heart and regulates genes involved in lipid flux [7]. KLF15 expression also exhibits circadian variation and regulates QT-interval duration through regulation of the potassium channel regulator KChIP2 [8], thereby affecting repolarization and susceptibility to arrhythmias. Deletion of KLF10 in mice leads to a gender-specific male cardiac phenotype reminiscent of human hypertrophic cardiomyopathy (HCM), associated with increased expression of Pttg1 [9]. Mutations in KLF10 have also been identified in human HCM patients, further validating the findings in mice [10]. Loss of KLF4 in cardiac myocytes is associated with reduced cardiac contractile function and increased sensitivity to hemodynamic stress, through a mechanism involving myocardin induction and activation of fetal genes [11–13].
In VSMCs, KLFs function as critical regulators of differentiation and response to injury. KLF2 is essential for vascular maturation, and its absence is associated with embryonic vascular hemorrhage and lethality. At the tissue level, the arteries demonstrate reduced numbers of differentiated VSMCs and poorly formed medial layers, which are likely due to defects in VSMC differentiation and migration [14,15]. KLF4 functions as a negative regulator of VSMC differentiation and promotes the synthetic, proliferative phenotype by a mechanism involving inhibition of the binding of Serum Response Factor to CArG elements in SMC contractile protein genes [16,17]. KLF4 has also been implicated in the pathogenesis of aortic aneurysms in mice [18]. KLF5 also functions as a negative regulator of VSMC differentiation and promotes the synthetic phenotype, through an interaction with RARs and p300 [19]. KLF15 is involved in the pathogenesis of aortic aneurysm and suppresses neointimal formation after vascular injury, mediated by effects on p53 acetylation and p300 activity as described above [6,20].

From these studies, several important questions emerge. For example, KLF15 plays multiple roles in the heart and vasculature by regulating hypertrophy, proliferation, metabolism, electrical activity, and aortic aneurysm formation, and one must wonder if there is an intrinsic fundamental mechanism by which it exerts these specific effects. Published mechanisms include interaction with cardiac-specific transcription factors, interaction with transcriptional coactivators, regulation of genes involved in lipid flux, and circularization of potassium channel function. Given the fundamental role of metabolism in cellular function, it is possible that the metabolic effects may underlie the effects on hypertrophy, proliferation, electrical activity, and vascular integrity. Further studies to examine the links between KLF15-dependent metabolism and these processes are warranted. Further elucidation of the interaction between KLF15 and other regulators of metabolism such as the PPAR family of nuclear receptor transcription factors will also be informative. Identification of additional KLF15 target genes by ChIP-seq in cardiomyocytes and VSMCs will likely provide further insight into the global KLF15 transcriptional program. Similarly, for KLF4, there may be a fundamental role in maintaining organ integrity, as loss of function leads to both cardiomyopathy and aortic aneurysm under stress conditions. Additional studies that examine the role of KLF4 in muscle homeostasis are eagerly anticipated.

Given the plethora of findings caused by alterations in KLF gene expression in cardiovascular tissues, one also is left to wonder about the hierarchical nature of these effects. KLF15 and KLF4 are both expressed in myocytes and regulate the development of pathological hypertrophy, but whether their effects are cooperative or independent is unknown. Similarly, both KLF4 and KLF5 function as negative regulators of smooth muscle differentiation and affect the response to vascular injury, and both KLF4 and KLF15 affect the development of aortic aneurysms. Future compound heterozygote studies examining the interactions between these factors will also provide additional insight.

While the importance of KLFs in rodent cardiovascular biology is firmly established, their roles in human cardiovascular disease are emerging. As described above, KLF10 mutations have been identified in patients with hypertrophic cardiomyopathy [10], but roles for KLFs in heart failure and vascular disease remain under investigation. A single nucleotide polymorphism in the promoter for KLF5 has been linked to human hypertension [21], suggesting that identification of upstream regulatory influences that control KLF expression will likely aid in the development of new therapies. The identification of small molecule inhibitors of KLF5 expression [22], for example, may foreshadow the development of new drugs for hypertension and to suppress pathological cardiac and vascular remodeling. Further elucidation of the roles of KLFs in human cardiovascular disease will be essential for the continued ascension of KLFs in cardiovascular medicine.

References


