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Kruppel-like factors in muscle health and disease

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ABSTRACT

Kruppel-like factors (KLF) are zinc-finger DNA-binding transcription factors that are critical regulators of tissue homeostasis. Emerging evidence suggests that KLFs are critical regulators of muscle biology in the context of cardiovascular health and disease. The focus of this review is to provide an overview of the current state of knowledge regarding the physiologic and pathologic roles of KLFs in the three lineages of muscle: cardiac, smooth, and skeletal.

Introduction

Cardiovascular disease remains the leading cause of morbidity and mortality in the world [1]. Although recent advances in clinical modalities and pharmacotherapeutics lessen disease burden, a more detailed understanding of molecular mechanisms that drive disease initiation and progression is required for further therapeutic impact. The two predominant cell types in the heart and blood vessels are cardiomyocytes and vascular smooth muscle cells (VSMC), respectively. The primary function of these cell types is contraction, thus enabling sufficient blood flow and oxygenation to peripheral tissues. Dysfunction of muscle leads to a broad spectrum of cardiac and vascular states that can impair their physiologic role. As such, understanding the molecular mechanisms governing cellular function in health and disease is critical for the development of novel therapies.

Kruppel-like factors: General considerations

Kruppel-like factors are members of the zinc-finger class of DNA-binding transcription factors whose name was derived from the German word kruppel (meaning "cripple") [2]. The original Kruppel gene was identified in Drosophila as a developmental gene critical in early-stage body patterning and segmentation [3]. The first mammalian KLF was identified in 1993, and to date, 18 family members have been identified and numbered chronologically based on their order of discovery [2]. The KLFs share sequence homology in their C-terminal zinc-finger domains characterized by three Cys_2/His_2 zinc-finger regions connected by a conserved TGEKP(Y/F)X amino acid sequence. DNA binding and specificity are mediated through this zinc-finger region via consensus sequences including CACCC- GC- or GT- box elements located in proximal promoters and enhancers. Structural and functional divergence of the KLF family is determined by the non-DNA-binding N-terminal domains that regulate protein-protein interaction and informs transcriptional activation or repression. Moreover, phylogenetic analysis of the mammalian KLF family reveals structural homologies within the N-terminal domain that correlate with functional similarities. As such, these structure/function characteristics allow for the classification of KLF family members into three distinct groups: Group 1 (KLFs 3, 8, and 12) are transcriptional

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repressors that interact with carboxy-terminal binding protein, Group 2 (KLFs 1, 2, 4, 5, and 6) are predominately transcriptional activators, and Group 3 (KLFs 9, 10, 11, 13, 14, and 16) act to repress transcriptional activity (via interaction with the co-repressor Sin3A) while KLF15 and 17 are more distantly related [2]. While some KLFs are expressed ubiquitously, others display tissue restriction allowing for redundant and non-redundant roles in response to various physiological stimuli. Expressed predominately in the nucleus, KLFs are subject to various post-transcriptional modifications and responsible for recruitment of transcriptional co-activator/co-repressor complexes, which modifies their DNA-binding and functional activity, respectively, to exert their cellular effects. Since their identification, these factors have been implicated as critical regulators of diverse cellular processes, including metabolism, growth, proliferation, hematopoiesis, immunity, determination of pluripotency, and, importantly for this review, muscle remodeling and cellular differentiation/plasticity [2]. This review will thus focus on the role of KLFs in the physiology and pathophysiology of muscle function.

KLFs and cardiac muscle

Despite the appreciation that transcriptional inputs guide cardiac function in health and disease, the role of KLFs is only beginning to burgeon. This topic was last reviewed seven years ago, and since then, additional evidence has provided mechanistic insights and expanded previously known roles of KLFs in cardiac function while new biologic themes have emerged [4]. As will be discussed below, seminal observations have broadly implicated KLFs as critical mediators of cardiac development, hypertrophy/remodeling, metabolism, and electrical activity.

Cardiac development

Congenital heart disease (CHD) is the leading cause of mortality in infants under the age of 1 year [5]. Inherited forms of CHD have been linked to mutations in transcription factors that are critical in heart development [6]. Examples of such transcription factors include Tbx5 and Nkx2.5, which act in a coordinated fashion with GATA4 to drive cardiac development [7]. Until recently, however, no known role for the KLF family in mediating cardiac development has been described. Work from the Nemer laboratory first described KLF13 as essential for cardiac development in vivo [8]. Cardiac KLF13 is expressed in both the atria and the ventricles, with expression first detected at E9.5 in the developing embryo. KLF13 expression is reduced postnatally, with low levels detected in the adult valves and septum. Embryonic deletion of KLF13 in Xenopus results in septal defects with hypotrabeculation, while murine deletion results in enlarged hearts, suggesting a critical role for KLF13 in heart development and function. Mechanistically, KLF13 interacts with GATA4 to regulate critical cardiac promoters, including BNP and ANF during development [9]. In addition to KLF13, a more recent study has linked another KLF family member, KLF3, with embryonic cardiomyopathy and perinatal lethality [10]. When screening for dominant mutations that affect cardiovascular function in N-ethyl-N-nitrosourea (ENU) mutagenized mice, Kelsey and colleagues identified a missense mutation in KLF3, with homozygocity resulting in embryonic lethality. Heterozygotes for the histidine to arginine mutation in the zinc-finger DNA-binding region that died were characterized by biventricular cardiac hypertrophy while adult survivors exhibited reduced blood pressure along with enlarged cardiac chambers and valvular stenosis. Taken together, these data suggest that KLF13 and KLF3 are critical in the developing heart and could serve as novel gene targets for therapeutic gain in congenital heart disease.

Cardiac hypertrophy/remodeling

Hypertrophy is one of the strongest predictors for the pathogenesis of heart failure, arrhythmia, and sudden cardiac death [11]. Hypertrophy is an adaptive response to hemodynamic and neurohormonal stress wherein the heart enlarges to increase its primary function of contraction and maintain circulatory function while reducing myocardial wall tension. In addition to myocyte enlargement, myocyte disarray, fibrosis, and alterations in myocardial fuel utilization are linked to the pathogenesis of cardiac hypertrophy. This pathologic response occurs through the activation of molecular and genetic pathways, and over the past several years, multiple KLFs have emerged as critical regulators of cardiomyocyte remodeling.

Work largely derived from the laboratory of Dr. Ryozo Nagai, one of the first KLFs identified as critical in regulating cardiac function was KLF5 [12,13]. Early studies indicated that cardiac KLF5 expression is restricted to fibroblasts, with limited detection in cardiomyocytes. KLF5 expression is upregulated in response to pro-hypertrophic stimuli such as angiotensin II, while heterozygous deletion of KLF5 blunts the angiotensin II hypertrophic response. More recently, Takeda et al. [14] showed that fibroblast KLF5 serves as a cardioprotective factor by modulating cardiomyocyte hypertrophy through a paracrine mechanism involving IGF-1. These studies thus establish KLF5 as central to the interplay between cardiac myocytes and fibroblasts in response to the pathogenesis of cardiac hypertrophy and remodeling.

While KLF5 expression is restricted to cardiac fibroblasts, KLF15 expression is robust in cardiac myocytes. Initial studies by the Jain laboratory demonstrated that cardiac KLF15 expression is induced postnatally, a time at which canonical hypertrophic gene makers (e.g., ANF and BNP) are downregulated [15]. Moreover, KLF15 expression is downregulated in both rodent and human biopsies of heart failure as well as in vitro in response to hypertrophic stimuli including angiotensin II, phenylephrine, and endothelin-1 [16]. Germ-line deletion of KLF15 results in mice that are viable and do not display a cardiac phenotype at baseline. However, in response to pressure overload, these mice develop severe eccentric hypertrophy characterized by systolic dysfunction through a molecular mechanism involving transcriptional inhibition of MEF2 and GATA4, thus establishing KLF15 as a negative regulator of pathologic hypertrophy [15].

This molecular mechanism and the role for KLF15 in regulating cardiac hypertrophy/remodeling has been recently