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Commentary

Does Krüppel Like Factor 15 Play an Important Role in the Left Ventricular Hypertrophy of Patients with Type 2 Diabetes?

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Krüppel-like factors (KLFs) belong to the family of 17 transcription factors that contain conserved zinc finger domains involved in binding to target DNA sequences. Many of these proteins are expressed in different tissues and have distinct tissue-specific activities and functions (Pearson et al., 2008). KLFs regulate many physiological processes such as growth, development, differentiation, proliferation, and embryogenesis.

As one of KLF family members, KLF15 was discovered as kidney-enriched KLF, so called as KKLF (Uchida et al., 2000). Emerging evidence demonstrates the importance of KLF15 in various physiological and pathophysiological aspects.

The physiological functions include the important role in regulating the expression of genes for gluconeogenic and amino acid-degrading enzymes (Takashima et al., 2010). By unbiased gene expression profiling, a large number of KLF15-dependent targets were elucidated in the heart, and then its essential role in regulating a transcriptional program for efficient myocardial lipid flux was confirmed (Prosdocimo et al., 2014). In addition, circadian control of KLF15 expression controlled the expression of potassium channel-interacting protein 2 (kChIP2) that affects how potassium flows out of heart cells. Therefore, it has appreciated that too much or too little of KLF15 or kChIP2 may result in arrhythmias (Jeyaraj et al., 2012).

Pathophysiological roles of KLF15 include its novel role as transcriptional inhibitor of left ventricle hypertrophy (LVH) (Leenders et al., 2010). It was appreciated that KLF15 down-regulation is a vital step in the development of hypertrophy and possibly its progression toward heart failure. The inhibitory effect of KLF15 on LVH is probably mediated by its robust inhibition of myocardin, a potent transcriptional activator. Therefore, loss of KLF15 during pathological LVH would relieve the inhibitory effects on myocardin and stimulate the expression of serum response factor target genes, such as atrial natriuretic factor.

Reportedly that KLF15 acted as a reference to the central pressure regulator in the heart and vasculature. Under pathophysiological condition, KLF15 repressed expression of tissue growth factor-β, connective tissue growth factor, and myocardin-related transcription factor-A in cardiac fibroblasts, leading to the alleviation of cardiac fibrosis and improvement of cardiac function. Accordingly, a low expression of KLF15 could promote fibrotic remodeling during pathological LVH Yu et al., 2015; Wang et al., 2008. Therefore, the continuous low expression of KLF15 was an important determinant of cardiac remodeling. KLF15 was also able to inhibit the interaction of p/CAF with Smad3, thereby preventing the activation of fibroblastic signaling pathway in cardiac tissue Yu et al., 2015; Wang et al., 2008.

KLF15 concentrations were also markedly reduced in congestive failure heart tissues and in human aortic aneurysm tissues (Haldar et al., 2010). *KLF15* gene knock-out mice developed heart failure and aortic aneurysms in a p53-dependent and p300 acetyltransferase- dependent fashion. KLF15 activation inhibited p300-mediated acetylation of p53. Conversely, KLF15 deficiency led to hyperacetylation of p53 in the heart and aorta, a finding that was recapitulated in human tissues. These findings highlight a molecular perturbation common to the pathobiology of heart failure and aortic aneurysm formation and suggest that manipulation of KLF15 function may be a productive approach to treat these morbid diseases (Haldar et al., 2010).

The above finding that KLF15 has essential roles in the heart under physiological and pathophysiological conditions, predominantly derived from animal models, was also reflected by a recent human study (Patel et al., 2017). This clinical study investigated the association between the *KLF15* gene and LVH in the patients with type 2 diabetes. This study was composed of two parts: a discovery and confirmatory studies. A key finding in the discovery cohort was that the A allele at rs9838915 SNP in *KLF15* was associated with increased LV mass in patients with type 2 diabetes, which was confirmed in an independent cohort (Patel et al., 2017). However, limitations of this study deserved comment. Functional studies were not performed but are required to determine the exact mechanisms by which genetic variation in *KLF15* influences LV mass. The results were restricted to patients with type 2 diabetes of Caucasian ethnicity, and future studies should examine

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patients without diabetes as well as patients of different ethnic backgrounds.

In summary, analysis of the role of *KLF15* in type 2 diabetes patients with LVH has really advanced the importance of KLF15 in the physiology and pathophysiology of cardiac conditions, and also promoted us to understand the mechanism of type 2 diabetes-induced LVH. All these will lay a theoretical foundation for the potentially clinical prevention and treatment of LVH.

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