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Editorial

Is Smyd1 Involved in Vasculature?

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Editorial

SMYD1 belongs to a family of SET and MYND domain-containing proteins. SET domain is an evolutionarily conserved domain responsible for protein lysine methylation [1]. MYND domain is a protein–protein interaction module involved in corepressor complex recruitment [2]. SMYD1 is important for heart and muscle development. SMYD1 knockout in mice results in early embryonic lethality due to disruption of cardiac differentiation and morphogenesis [3]. Similar results have been observed in zebrafish, in which knockdown of SMYD1 causes severe myofibrillar disorganization and malfunction of cardiac and skeletal muscles [4].

SMYD1 is involved in early cardiogenesis via the Isl1-dependent transcriptional network [5]. This network is critical for the development of the secondary heart field, contributing to the outflow tract and right ventricular myocardium, endocardium, and smooth muscle of the great vessels [6]. SMYD1 may regulate gene transcription through direct histone modification. H3K4 methylation by SMYD1 suggests its role as a transcriptional activator in epigenetic gene regulation [4,7,8]. SMYD1 also has transcriptional repressive activity and could repress its target genes via recruiting repressors or repression complexes. SMYD1 associates with multiple repression complexes such as N-CoR and Sin3 [3]. SMYD1 also binds to class I and class II histone deacetylases (HDAC) [3]. Addition of TSA, an HDAC inhibitor, inhibits SMYD1 repressive activity [3]. These data indicate that SMYD1 is an important myogenic factor involved in a highly coordinated transcriptional network that regulates cardiogenesis and myogenesis [9]. This also makes SMYD1 an interesting candidate for the control of cardiac growth and differentiation, as it could be useful in initiating or sustaining the cardiogenic program in cardiac regenerative medicine.

Current research is in favor of the role of SMYD1 in cardiac muscle development. Whether it is also involved in the vascular component of the cardiovascular system is unknown. SMYD1 is a direct transcriptional target of MEF2C, a central muscle enhancer, and regulates the expression of HAND2, a transcriptional factor specific to right ventricle [3,10]. The presence of serum responsible factor (SRF) binding sites in the SMYD1 promoter suggests that SMYD1 also functions as a downstream regulator of SRF and acts in the same regulatory cascade involving SRF [11]. SRF, the master regulator of the contractile apparatus, plays a crucial role in cellular migration and cytoskeleton biology [12]. Note that both MEF2C and SRF have a significant functional role in the vasculature. MEF2C is expressed in endothelial cells *in vivo* and *in vitro* [13,14]. Targeted deletion of MEF2C in mice leads to severe vascular defects due to the mispatterning of endothelial cells in the primitive vascular plexus [15]. SRF is required for angiogenic remodeling and vessel maintenance. Endothelial-specific ablation of SRF causes hemorrhaging, yolk sac vascular failure, and embryonic lethality [16]. In addition, SMYD1 expression is regulated by hepatoma-derived growth factor (HDGF). HDGF represses SMYD1 gene transcription through binding to the SMYD1 promoter and recruiting the transcriptional corepressor C-terminal binding protein CtBP [17,18]. HDGF is a nuclear protein with mitogenic and angiogenic activity [19]. HDGF is highly expressed in heart and vasculature and stimulates smooth muscle cell growth after vascular injury [19]. HDGF also has mitogenic and angiogenic roles in pulmonary endothelial cells and aortic endothelial cells [20,21]. Re-expression of HDGF in vascular smooth muscle cells *in vivo* correlates with human atherosclerosis [19]. These data indicate that SMYD1 may be involved in vasculogenesis and functions as a downstream effector in MEF2C, SRF, or HDGF-mediated angiogenic pathways.

We have shown that SMYD1 is expressed in bone marrow-derived endothelial progenitor cells (EPC) (unpublished data). This suggests that SMYD1 may play a role in regulating EPC function. EPCs are blood-circulating progenitor cells with the ability to differentiate into endothelial cells, the cells that form the lining of blood vessels. Growing evidence indicates that EPCs contribute to endothelial repair and neovascularization [22-24]. Impaired EPC homing and mobilization affect vascular homeostasis and also compensatory angiogenesis [25,26]. In response to tissue ischemia or endothelial damage, EPCs are mobilized from the bone marrow into the circulation and home to sites of vascular injury where they contribute to new blood vessel formation and repair endothelial damage. Patients with reduced EPC levels are at increased risk for cardiovascular events and death [27,28]. Augmentation of circulating EPCs results in improved coronary collateral development in coronary artery disease [29]. In addition, the number and function of endothelial progenitor cells correlate inversely with cardiovascular risk factors such as cigarette smoking, diabetes, hypertension, and high blood cholesterol [28,30,31]. Deterioration of endogenous EPC function with age is associated with decreased capacity for neovascularization and reduced endothelialization of vascular lesions, facilitating the development and progression of atherosclerotic disease [32]. Therefore, studying the mechanisms controlling EPC mobilization, homing, and differentiation into endothelial lineage is of therapeutic and clinical significance. Uncovering the role of SMYD1 in EPC biology could provide innovative fundamental understanding of EPC neovascularization pathways and expand the role of SMYD1 into the vasculature.

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