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Review

SOXF transcription factors in cardiovascular development

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ABSTRACT

Cardiovascular development during embryogenesis involves complex changes in gene regulatory networks regulated by a variety of transcription factors. In this review we discuss the various reported roles of the SOXF factors: SOX7, SOX17 and SOX18 in cardiac, vascular and lymphatic development. SOXF factors have pleiotropic roles during these processes, and there is significant redundancy and functional compensation between SOXF family members. Despite this, evidence suggests that there is some specificity in the transcriptional programs they regulate which is necessary to control the differentiation and behaviour of endothelial subpopulations. Furthermore, SOXF factors appear to have an indirect role in regulating cardiac mesoderm specification and differentiation. Understanding how SOXF factors are regulated, as well as their downstream transcriptional target genes, will be important for unravelling their roles in cardiovascular development and related diseases.

Contents

1. Introduction

The adult cardiovascular system is an extremely complex interconnected network made up of the heart, vasculature and blood. These key components are derived from a common mesodermal pool of progenitors that arises early in development: from E6.5 in the mouse embryo. Differentiation along cardiac, vascular and lymphatic endothelial lineages involve regulation of cell fate decisions as well as intricate changes in cell type specific behaviour, which are controlled by dynamic adjustments in transcriptional networks. A growing body of evidence indicates that SOXF transcription factors are crucial regulators of endothelial cell differentiation and behaviour in distinct subpopulations. These include: endothelial precursors (EPCs), arterial and venous vascular endothelial cells, lymphatic endothelial cells as well as endocardial cells. Furthermore, studies in xenopus and mouse embryos indicate an indirect role for SOXF factors in cardiogenic mesoderm specification and differentiation.

Despite the issue of redundancy and compensation between SOXF family members, it is clear that each member has some specificity in terms of the transcriptional program it regulates. In this

Abbreviations: EPC, endothelial precursor cells; HMG, high mobility group; TAD, transactivation domain; BRY, brachyury; ESC, embryonic stem cell; LECs, lymphatic endothelial cells; Ra, ragged; Ra^{op}, ragged opossum; ISV, intersomitic vessels; EHT, endothelial to hematopoietic transition; CDH, congenital diaphragmatic hernia.

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review, we consider the various reported roles of the SOXF family members in regulating cardiovascular development during mouse, zebrafish and xenopus embryonic development.

2. Structure and function of SOXF factors

In most vertebrates, the SOXF subgroup of the SOX family transcription factors is comprised of SOX7, SOX17 and SOX18 [1,2]. Teleosts also possess a divergent SOXF factor called Sox32, which is thought to have arisen through tandem gene duplication of sox17 [3]. Mammals have two isoforms of SOX17, with the short isoform missing the N-terminal region and half of the high mobility group (HMG) domain [4]. However, the function of the short SOX17 isoform is currently unknown [5]. Like other SOX factors, SOXF factors possess a highly conserved HMG DNA binding domain which recognises the core DNA consensus sequence of AACAAT (see Fig. 1) [6]. The HMG domain of SOX factors interacts with the minor groove of the DNA helix causing bending of the DNA towards the major groove thus resulting in localised changes in DNA structure [7,8]. However, the role of the DNA bending in relation to the biological function of SOX factors is poorly understood. All of the murine, human and xenopus SOXF factors possess a conserved c-terminal β-catenin binding domain; whereas zebrafish Sox17 does not [3,9–11]. Interactions between SOX7, SOX17 or SOX18 with β-catenin inhibits the activity of β-catenin/TCF transcriptional complexes, and therefore repress Wnt signalling [11]. SOXF factors also have a transactivation domain (TAD), required for mediating transcriptional activation (see Fig. 1).

A hallmark of the SOX family of transcription factors is the ability to interact with different DNA binding partner proteins to regulate specific transcriptional programs, which is important due to the degenerate nature of the core SOX DNA consensus sequence [12]. The HMG domain of SOX factors is often key in mediating the interaction with other transcription factors, which is surprising given the similarity of the HMG domain across the SOX family [13]. In terms of the SOXF subgroup, SOX18 has been shown to physically interact with the transcription factor MEF2C in endothelial cells via their respective HMG and MADS-box DNA binding domains, and act synergistically to activate transcription [14]. It is well characterised that SOX17 physically interacts with OCT4 via their respective HMG and POU DNA binding domains, which mediates cooperative DNA binding to specify endoderm development [15–17]. However, generally speaking, the interacting partners of SOXF factors controlling various cardiovascular transcriptional programs have not been well characterised.

3. SOXF factors in cardiogenesis

Cardiogenesis initiates when cardiogenic mesoderm cells, specified during gastrulation, migrate through the primitive streak where they form the cardiac crescent at around E7.5 in the mouse embryo [18,19]. Cardiogenic mesoderm cells subsequently differentiate along specific cardiac lineages including: myocardial, endocardial, and smooth muscle cell lineages [20,21]. During this period of cardiac specification, endoderm derived growth factors such as BMPs are key in mediating the formation and differentiation of myocardial and endocardial cells [22,23]. At around E8.0 the cardiac crescent fuses, forming a heart tube which grows and undergoes looping forming the embryonic heart which starts to beat from E8.25 [24].

In the mouse embryo, *Sox7* and *Sox18* are expressed in vascular endothelial cells located in the precardial region at E8.25, whereas *Sox17* expression levels in this region are low [25]. From E8.5 *Sox7* and *Sox18* are expressed in the heart tube and from E12.5 in the endocardium and vascular endothelium of the heart [25,26]. *Sox17*$^{-/-}$ mouse embryos display aberrant looping of the developing heart tube [25], and SOX17 is essential for the specification of cardiac mesoderm in vitro [27]. Given that SOX17 is highly expressed in developing endoderm [25,28], together with the importance of endoderm derived signals in regulating cardiac development, it is likely that SOX17 regulates cardiac development in a non-autonomous fashion. In agreement with this idea, *Sox17* knockdown in differentiating embryonic stem cell (ESC) cultures decreased *Hex* expression: an endoderm gene known to be important in regulating paracrine signals important for cardiac development [27,29].

Studies in xenopus also indicate a non-autonomous role of SOXF factors in regulating cardiogenesis. Sox7, Sox17 and Sox18 are important regulators of endoderm development, and animal cap experiments have demonstrated that Sox7 and Sox18 are cardiogenic but Sox17 is not [30–32]. Inhibition of endodermal Wnt signalling plays an important role in paracrine mediated regulation of cardiogenesis [29]. However, whilst Sox7 and Sox18 inhibit Wnt signalling via interacting with β-catenin, mutational analyses demonstrated that the induction of cardiogenesis by SOXF factors is reliant on the TAD rather than β-catenin inhibition [30].

In vitro ESC differentiation has demonstrated that cardiac progenitors and hemangioblasts are derived from mesodermal precursors expressing the transcription factor Brachyury (BRY), which are specified in two distinct FLK1 expressing waves [21,33]. The first BRY/FLK1^{+} hemangioblast population differentiates along vas-

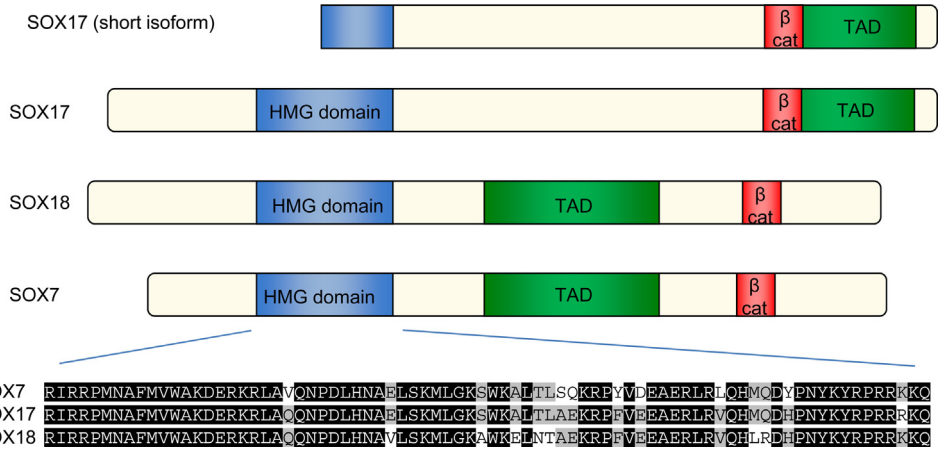

Fig. 1. The structure of murine SOXF factors. SOXF factors possess an N-terminal HMG DNA binding domain, a transactivational domain (TAD) and a c-terminal β-catenin binding domain. There are two isoforms of SOX17, the short isoform is missing the N-terminal region and half the HMG domain, but its function is unknown. The amino acids of the HMG domain show a high level of similarity between the SOXF factors. The amino acids highlighted in black and grey are common to three and two SOXF factors respectively.