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Sox7 in vascular development: review, insights and potential mechanisms

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ABSTRACT Cardiovascular development is crucial to the survival of higher organisms, integrally transporting oxygen and nutrients and in later life, facilitating immune function. Only in recent years has the molecular basis of the formation of this ancient conduit system been explored. While transcription factors are essential to specify and differentiate core cellular and structural components of the developing heart and vessels, only a subset of these essential factors are currently known. A transcription factor of emerging importance in the cardiovascular system is *Sox7,* a member of the F group of *Sox* genes, as *Sox7* removal in recent animal and cellular studies has resulted in disruptions of cardiovascular development. However, the molecular mechanisms of *Sox7* action have largely remained obscure. In this paper, we first review the highly conserved and robust cardiovascular expression pattern of *Sox7* across multiple species. We then provide evidence of a compelling role for *Sox7* in vascular development, elucidating major pathways in which *Sox7* functions, including VEGF/Flk1 signaling, Wnt signaling, and Notch pathway. Furthermore, we propose mechanisms connecting all of these important developmental pathways through *Sox7,* in a way not previously postulated in the developing vascular system. The emerging picture reveals *Sox7* as an important developmental gene that connects other vascular regulators and that has significance in human disease.

KEY WORDS: *Sox7, Wnt signaling, vascular development, Notch pathway, expression pattern*

Introduction

Proper development of the cardiovascular system is vital to higher organisms. Perturbations in this system can lead to devastating diseases, including congenital heart disease, the number one cause of infant morbidity, and vessel abnormalities that contribute to disorders ranging from tumor formation to retinal diseases. While the anatomy and physiology of many cardiovascular malformations have been well-characterized, only in the past decade have the genetic underpinnings of these abnormalities begun to be explored using vertebrate and invertebrate model organisms. Thoroughly characterizing these molecular pathways has important implications in understanding normal heart and vessel development as well as in facilitating therapies for cardiovascular disease.

Thus far, the majority of genes identified in congenital heart diseases encode transcription factors such as *Gata4* and *Nkx2.5*. Many of these cardiac- and vascular- relevant transcription factors function in major developmental pathways. Emerging evidence suggests that the *Sox* family—in particular the *SoxF* subfamily of *Sox7*, *Sox17*, and *Sox18*—directs normal cardiovascular development.

The *Sox* gene family (Sry-related HMG box gene family) encodes transcription factors containing a common ~80 amino acid HMG DNA binding domain, which is closely related to the HMG box in the founding member SRY (Gubbay *et al.,* 1990). There are ten subgroups of SOX proteins (A-J) (Bowles *et al.,* 2000). SOX proteins are important in embryonic development and in cell fate determination (Pevny and Lovell-Badge, 1997; Avilion *et al.,* 2003). *Sox7* belongs to the subgroup F, along with *Sox17* and *Sox18*. *Sox17* has been shown to be involved in cardiac and hematopoietic development in addition to definitive endoderm development (Liu *et al.,* 2007; Kanai-Azuma *et al.,* 2002; Sakamoto *et al.,* 2007). *Sox18* is important in blood vessel and lymphatic development in mice.

There is evidence of conservation of sequence, expression, and function among SoxF family genes. SoxF proteins share a very similar primary structure with greater than 80% amino acid

Abbreviations used in this paper: BMP, bone morphogenetic protein; CXCR4, chemokine (C-X-C motif) receptor 4; GATA4, GATA Binding Protein 4; Nkx2.5, NK2 homeobox 5; SDF1, stromal cell-derived factor; Sox, *S*ry-related HMG b*ox;* SRY, sex determining region Y; VEGF, vascular endothelial growth factor.

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identity within the HMG domain (Bowles *et al.,* 2000). SoxF subgroup members in *Drosophila* and vertebrates also share highly conserved intronic positions, which represent ancient introns present before vertebrate lineage divergence (Bowles *et al.,* 2000; Kanai *et al.,* 1996; Taniguchi *et al.,* 1999). Expression of mouse *Sox18* across embryonic and adult tissue Northern blot analyses occurs in a very similar pattern to that of *Sox7*; furthermore, *Sox7*, *Sox17*, and *Sox18* each colocalize to the developing mouse embryonic vasculature (Takash *et al.,* 2001; Young *et al.,* 2006). Functionally, *Sox7* and *Sox17* can also activate *Sox18* targets and modify the *Sox18* mutant mouse phenotype (Hosking *et al.,* 2009).

Sox17$^{-/-}$ mouse mutants have defects in heart looping, cardiac bifida, and impaired cardiac mesoderm differentiation (Liu *et al.,* 2007; Pfister *et al.,* 2011; Sakamoto *et al.,* 2007). Mutations in *SOXF* genes have also been reported in human diseases: *SOX18* mutations cause hypotrichosis-lymphedema-telangiectasia syndrome, a congenital condition characterized by dilated veins, varicosities, and capillaries underneath transparent skin, and *SOX17* mutations have been found in some cases of primary lymphedema (Francois *et al.,* 2008; Irrthum *et al.,* 2003). These findings indicate that SOXF proteins are critical for normal cardiovascular development.

Here, we review *Sox7* in the developing cardiovascular system by its expression pattern, detailed across mouse, human, zebrafish, and *Xenopus* species, and tumor tissues in Table 1, and animal

TABLE 1

***SOX7* EXPRESSION IN MOUSE, HUMAN, ZEBRAFISH, AND *XENOPUS* DURING DEVELOPMENTAL AND ADULT STAGES**

Developmental stage	Structure/location of Sox7 expression	Reference
Mouse		
E7.5	parietal endoderm; visceral endoderm; extraembryonic endoderm	Kanai-Azuma *et al.* 2002; Murakami *et al.* 2004
	embryonic mesoderm	Murakami *et al.* 2004
	endoderm proximal to the amnion	Tam *et al.* 2004
	yolk sac region; mesodermal masses that give rise to blood islands	Gandillet *et al.* 2009
E8	somites; head regions	Takash *et al.* 2001
E8.25	presumptive vascular endothelial cells in precardial region, dorsal aorta, and allantois; sinus venosus	Sakamoto *et al.* 2007
E8.5	endothelial cells of dorsal aorta; blood vessels around hindgut	Matsui *et al.* 2006
	heart tube; cardinal veins; pericardial region; endocardial tube; posterior dorsal aorta; allantoic vasculatures	Sakamoto *et al.* 2007
	vascular endothelium	Tam *et al.* 2004
E8.75	heart tube; cardinal veins; endocardial tubes; ventricle; posterior dorsal aorta; allantoic vasculatures	Sakamoto *et al.* 2007
E9.5	whole embryo; intersomitic vessels; small branching vessels; throughout embryo vasculature; atria	Takash *et al.* 2001
	endothelial cells lining posterior dorsal aorta; anterior neural axial artery	Young *et al.* 2006
E10.5	blood vascular endothelial cells of dorsal aorta	Hosking *et al.* 2009
E11.5	intersomitic vessels	Takash *et al.* 2001
	endothelial cells lining posterior dorsal aorta; anterior neural axial artery	Young *et al.* 2006
E12.5	pancreas	Lioubinski *et al.* 2003
	endocardium of heart;	Wat *et al.* 2012
	endothelial cells of surrounding blood vessels of the diaphragmatic pleuroperitoneal fold	
E14.5	whole embryo; head; tail	Takash *et al.* 2001
	teeth: molar and incisor tooth germs	Stock *et al.* 1996
	vascular endothelium of anterior diaphragm;	Wat *et al.* 2012
	heart	
E15.5	pancreas	Lioubinski *et al.* 2003; Wilson *et al.* 2005
	vascular endothelium of heart; vascular endothelium of anterior diaphragm	Wat *et al.* 2012
E16.5	endocardium; heart vascular endothelium; vascular endothelial cells of anterior diaphragm	Wat *et al.* 2012
E17.5	heart (strong expression); lung (strong expression); whole embryo; head; tail; gut; brain; cochlea; tongue; cartilage; liver; vertebrae	Takash *et al.* 2001
E18.5	pancreas	Lioubinski *et al.* 2003
P1	strong nuclear staining in vascular endothelium in muscular anterior and posterior diaphragm; nuclei of diaphragmatic muscle cells in anterior and posterior diaphragm;	Wat *et al.* 2012
	endocardium; vascular endothelial cells of heart and lungs	
P7	cortex and glomeruli of kidney (weak expression); heart; lung	Matsui *et al.* 2006
Adult	heart (strong expression)	Taniguchi *et al.* 1999; Takash *et al.* 2001; Matsui *et al.* 2006
	ovary; at the protein level, localized in oocytes	Taniguchi *et al.* 1999
	lung; mesenchyme and epithelial layers of ear	Takash *et al.* 2001
Human		
8-week embryo	heart; lung; brain; tongue; liver; vertebrae	Takash *et al.* 2001
Fetus	lung	Takash *et al.* 2001; Katoh, 2002
	heart	Katoh, 2002
Adult	heart, especially in ventricles, interventricular septum, and apex; lung	Takash *et al.* 2001; Katoh, 2002
	mesenchyme and epithelial layers of colon	Takash *et al.* 2001
	trachea; lymph node; placenta; prostate	Katoh, 2002
Tumor	upregulated in pancreatic, gastric, and esophageal cancer cell lines; downregulated[a] in primary kidney, lung, prostate, breast, and colorectal tumors	Katoh, 2002; Guo *et al.* 2008; Yamamoto and Yamamoto, 2008; Wiech *et al.* 2009; Zhang *et al.* 2009

TABLE 1 (CONTINUATION)

***SOX7* EXPRESSION IN MOUSE, HUMAN, ZEBRAFISH, AND *XENOPUS* DURING DEVELOPMENTAL AND ADULT STAGES**

Developmental stage	Structure/location of Sox7 expression	Reference
Zebrafish		
Bud stage	bistripes corresponding to the posterior lateral plate mesoderm (PLM)	Pendeville *et al.* 2008
4-somite stage	PLM	Cermenati *et al.* 2008
5-somite stage	extends along PLM; anterior lateral plate mesoderm (ALM)	Pendeville *et al.* 2008
8-somite stage	PLM; innermost fli1-positive cells in the PLM; ALM	Cermenati *et al.* 2008
18-somite stage	head; presumptive axial vessels	Pendeville *et al.* 2008
22-somite stage	developing dorsal aorta; posterior cardinal vein; intermediate cell mass (ICM)	Cermenati *et al.* 2008
12 hpf	localized to lateral mesoderm	Herpers *et al.* 2008
18 hpf	cord-like structure (future dorsal aorta and posterior cardinal vein); presumptive migrating angioblasts	Herpers *et al.* 2008
24 hpf	dorsal aorta; posterior cardinal vein; ICM; intersomitic vessels; otic vessels; vasculature of head, trunk, and tail; dorsal aorta; two stripes in hindbrain	Cermenati *et al.* 2008; Pendeville *et al.* 2008
26 hpf	endothelial cells of main axial vessels, head vessels, and intersegmental vessels; two rhombomeres	Herpers *et al.* 2008
Xenopus (*Xenopus laevis* unless otherwise noted)		
Early stage embryos (blastula)	generalized; eggs; oocytes	Fawcett and Klymkowsky, 2004
Stage 8/9 embryos	localized to vegetal hemisphere	Zhang *et al.* 2005 a
Stage 10/11 embryos	dorsal marginal zone/Spemann Organizer; lateral marginal zones	Zhang *et al.* 2005 b
Stage 14 embryos	ciliated cells of epidermis	Fawcett and Klymkowsky, 2004
Stage 16/17 embryos	anterior dorsal region; anterior ventral region	Zhang *et al.* 2005 b
Stage 24-27 embryos	endocardium; procardiac tube; posterior cardinal veins; aortic arch; vitelline veins; embryonic vasculature; hindbrain; epidermal ciliated cells; dorsal aspect of neural tube	Fawcett and Klymkowsky, 2004
Stage 33/34 larvae	posterior cardinal veins; aortic arches; branching intersomitic arteries; hindbrain; stomodeal depression; epithelial straps; olfactory pit; notochord; ciliated cells; posterior rhombomeres; outer edges of rhombencephalon	Fawcett and Klymkowsky, 2004
Stage 33/34 (*X. Tropicalis*)	posterior cardinal veins; pronephric sinus; ciliated cells; central nervous system; olfactory pit; pharyngeal arches	Kyuno *et al.* 2008
Stage 40 larvae (3 dpf)	aortic arch; hindbrain; lateral edges of rhombomere 5	Fawcett and Klymkowsky, 2004
Adult	lung; ovary; testis; kidney; brain; spleen	Shiozawa *et al.* 1996

[a] In some tumors, such as colorectal and prostate, *Sox7* down-regulation was partly due to hypermethylation at its promoter (Guo *et al.,* 2008; Zhang *et al.,* 2009).

studies and molecular mechanisms. Furthermore, we connect *Sox7* to important developmental networks of genes in putative mechanisms of *Sox7* action (Fig. 1).

A conserved role for *Sox7* in cardiovascular tissues: *Sox7* expression in tissues of developing & adult mouse, human, zebrafish, & *Xenopus*

Throughout the developing cardiovascular system across species, *Sox7* has a specific and prominent role as evidenced by expression studies showing its high expression level and restriction to early precursor tissues and progenitors of the vasculature and heart (Table 1).

In mouse embryos at 7.5 days post coitum (dpc), *Sox7* is expressed in the parietal and visceral endoderm, the extraembryonic endoderm, the endoderm proximal to the amnion, and the embryonic mesoderm, though not in the definitive endoderm (Kanai-Azuma *et al.,* 2002; Murakami *et al.,* 2004; Tam *et al.,* 2004; Table 1).

Interestingly, at 7.5 dpc, SOX7 is also expressed in the yolk sac region and the mesodermal masses that give rise to blood islands (Gandillet *et al.,* 2009). Around this stage (7.0-7.5 dpc), the cardiac mesoderm and foregut endoderm also migrate anteriorly and condense into the cardiac crescent. At around 7.5 to 8.0 dpc in mouse development, yolk sac blood islands appear, and the yolk sac vasculature and paired dorsal aortae form from the lateral mesoderm. Also at this stage, groups of hemangioblasts formed from embryonic mesodermal cells are found distributed throughout the embryo and will become incorporated into the developing embryonic vasculature.

Sox7 is found expressed in the somites and head regions at 8 dpc (Takash *et al.,* 2001). At 8.25 dpc, *Sox7* expression is found in the presumptive vascular endothelial cells in the precardial region, the dorsal aorta, the sinus venosus, which would become the future atria, and the allantois (Sakamoto *et al.,* 2007). At this point in mouse development, the linear heart tube has been formed after the left and right cardiac primordia have fused.

By 8.5 dpc, *Sox7* is highly expressed in the heart tube, posterior dorsal aorta, vascular endothelium, cardinal veins, pericardial region, endocardial tube, endothelial cells of the dorsal aorta and blood vessels around the hindgut, though not in the hindgut endoderm (Tam *et al.,* 2004; Matsui *et al.,* 2006; Sakamoto *et al.,* 2007). At this stage, the linear heart tube begins looping morphogenesis, and the interventricular sulcus is present. Also at this stage, angioblasts aggregate and the primitive vascular network is formed, circulation begins, intraembryonic vitelline vessels link to yolk sac vessels, and umbilical vessels link to placenta. *Sox7* is also expressed in the allantoic vasculatures at 8.5 dpc (Sakamoto *et al.,* 2007), when the allantois extends from the embryo's posterior end and contacts the chorion. *Sox7* expression continues in the heart tube, cardinal veins, posterior dorsal aorta, allantoic vasculatures, and developing ventricle at 8.75 dpc (Sakamoto *et al.,* 2007).

At 9.5 dpc and 11.5 dpc, *Sox7* is expressed in the intersomitic vessels and endothelial cells lining the posterior dorsal aorta and in the anterior neural medial axial artery (Young *et al.,* 2006; Takash *et al.,* 2001). At 9.5 dpc, *Sox7* expression is also found in small branching vessels, throughout the embryonic vasculature,

and in the atria (Takash *et al.,* 2001). Around this time, the mouse heart approaches the adult form. At 10.5 dpc, SOX7 is robustly expressed in the blood vascular endothelial cells of the dorsal aorta, but not in lymphatic endothelial precursors, indicating that SOX7 is not normally involved in establishing the early lymphatic vasculature (Hosking *et al.,* 2009). *Sox7* expression is found in the mouse pancreas at 12.5, 15.5, and 18.5 dpc (Lioubinski *et al.,* 2003; Wilson *et al.,* 2005).

In later stages of mouse development, *Sox7* can be found in other organs derived from the mesoderm and endoderm, with the strongest expression in the heart and the lungs persisting to postnatal stages. From 12.5 to 17.5 dpc, *Sox7* is expressed in a variety of organs, with strongest expression in the vascular endothelium, endocardium, heart, and lung (Wat *et al.,* 2012; Takash *et al.,* 2001; Stock *et al.,* 1996). At postnatal stages, *Sox7* is highly expressed in heart, lung, and vascular endothelium of diaphragm, lung, and heart, while barely expressed in the postnatal liver (Wat *et al.,* 2012; Matsui *et al.,* 2006; Takash *et al.,* 2001); the high endothelial expression indicates possible involvement in regulating transcription of other vascular-relevant genes. In the adult mouse, *Sox7* also has high expression in mesenchyme and epithelial layers of the ear and oocytes (Taniguchi *et al.,* 1999; Takash *et al.,* 2001).

In humans, expression begins in heart and lung during the embryo and persists in the adult. *SOX7* is expressed in the heart, lung, brain, tongue, vertebrae, and liver of the 8-week human embryo (Takash *et al.,* 2001). *SOX7* expression in the heart and lung continued in the fetus (Katoh, 2002; Takash *et al.,* 2001), and in the adult SOX7 is present in the heart, lung, trachea, lymph node, placenta, prostate, and the mesenchyme and epithelial layers of the colon (Takash *et al.,* 2001; Katoh, 2002). Importantly, in the adult heart, *SOX7* is more highly expressed in the ventricles, interventricular septum, and apex than in the atria (Katoh, 2002).

In zebrafish, no *sox7* expression is detected prior to the end of gastrulation (Pendeville *et al.,* 2008; Cermenati *et al.,* 2008), but becomes expressed in the posterior lateral plate mesoderm by bud and 4-somite stages. As development continued, *sox7* is expressed in the anterior lateral plate mesoderm, and then in the presumptive axial vessels coalescing into the dorsal aorta, axial vein, and posterior cardinal vein (Cermenati *et al.,* 2008; Pendeville *et al.,* 2008; Herpers *et al.,* 2008). At the time circulation begins, *sox7* is expressed in the head, trunk and tail vasculature, dorsal aorta, intersomitic vessels, intermediate cell mass containing endothelial and blood cell precursors (Pendeville *et al.,* 2008). By 1.5 days post-fertilization (dpf), *sox7* expression peaks at the time the vascular tree undergoes active remodeling.

In *Xenopus laevis* early stage blastula embryos, *sox7* is expressed in the eggs and oocytes, and in stage 8/9 embryos, *sox7* is localized to the vegetal hemisphere (Fawcett and Klymkowsky, 2004; Zhang *et al.,* 2005a). In gastrula stage 10/11 embryos, *sox7* is expressed in the dorsal marginal zone/Spemann Organizer and lateral marginal zones (Zhang *et al.,* 2005 b). Stage 24-27 embryos shows strong *sox7* expression in the endocardium, procardiac tube, aortic arch, posterior cardinal veins, vitelline veins, embryonic vasculature, hindbrain, epidermal ciliated cells, and dorsal aspect of neural tube (Fawcett and Klymkowsky, 2004). At stage 33/34 larvae, *sox7* expression continues in the posterior cardinal veins, aortic arches, branching intersomitic arteries, hindbrain, and ciliated cells, and is also found in the stomodeal depression, epithelial straps, olfactory pit, notochord, posterior rhomomeres, and outer edges of rhombencephalon (Fawcett and Klymkowsky, 2004). In *Xenopus tropicalis* stage 33/34, *sox7* is expressed in the posterior cardinal veins, the pronephric sinus, ciliated cells, central nervous system, olfactory pit, and pharyngeal arches (Kyuno *et al.,* 2008). By stage 40 larvae, or 3 dpf, *sox7* expression in most of the vascular endothelia, particularly the posterior cardinal veins, has disappeared; however, *sox7* is still expressed in the aortic arch, hindbrain, and lateral edges of rhombomere 5 (Fawcett and Klymkowsky, 2004). In adult *Xenopus laevis*, *sox7* expression is found in the lung, ovary, testis, kidney, brain, and spleen.

Detailed expression of *Sox7* over developmental time in mouse, human, zebrafish, *Xenopus*, and tumor tissues, is presented in Table 1. *Sox7* appears to be predominantly expressed in the early developing cardiovascular system across species. The expression across embryonic development points to a critical role in certain systems, such as the vasculature, which is likely conserved across different species.

SOX7 *expression in tumor tissues and cell lines*

Human *SOX7* mRNA and/or SOX7 protein is up-regulated in pancreatic, gastric, and esophageal cancer cell lines, and down-regulated in primary kidney, lung, prostate, breast, and colorectal tumors (Katoh, 2002; Guo *et al.,* 2008; Yamamoto and Yamamoto, 2008; Wiech *et al.,* 2009; Zhang *et al.,* 2009; Table 1). In some tumors, such as colorectal and prostate, *SOX7* down-regulation is partly due to hypermethylation at its promoter (Guo *et al.,* 2008; Zhang *et al.,* 2009). *Sox7* expression and activity changes may modulate Wnt-β-catenin-stimulated transcription and β-catenin activity *in vivo* and in cancers. Mouse *Sox7* has been shown to repress β-catenin-mediated activation of a Tcf reporter (Takash *et al.,* 2001). SOX7 has been shown to physically interact with and deplete active β-catenin to suppress β-catenin-mediated transcription, and restoring SOX7 antagonizes Wnt signaling and induces colorectal cancer cell apoptosis (Guo *et al.,* 2008; Zhang *et al.,* 2009).

SOX7 in vascular development and integration of Vegf signaling, Wnt signaling, VE cadherin, and Notch pathways

The expression pattern of *Sox7* in the major and branching arteries and veins—including vascular endothelial cells, intersomitic vessels, axial vessels, vitelline veins, aortic arches, and posterior cardinal veins—of developing mouse, zebrafish, and *Xenopus* (Table 1, and discussed above) indicates a specific role for *Sox7* in vascular development. The lateral plate mesoderm, in which *Sox7* is expressed, gives rise to both the blood vessels and heart. Moreover, the visceral endoderm and yolk sac, which also have *Sox7* expression (Table 1), have an active role in inducing and organizing the underlying vasculature development through production of vascular endothelial growth factor (VEGF), a key ligand for vessel development.

Blocking *Sox7* and *Sox18* by morpholinos leads to notable vascular defects in arteriovenous morphogenesis and multiple fusions between the major axial vessels (Pendeville *et al.,* 2008; Cermenati *et al.,* 2008). Proximal aorta dysmorphogenesis and arteriovenous shunts result in lack of circulation in the trunk and tail of double-knockdown *Sox7* and *Sox18* morphants, which leads to pericardial edema and subsequent embryo death (Herpers *et al.,*

2008; Pendeville *et al.,* 2008; Cermenati *et al.,* 2008). Anomalous intersomitic branching is also observed (Cermenati *et al.,* 2008). These studies utilized zebrafish, a good model for *in vivo* developmental studies due to availability of molecular markers (Lo *et al.,* 2011).

In addition to animal models, molecular studies show connections of *Sox7* to important vascular markers. The proposed mechanisms of *Sox7*'s function in the vasculature are summarized in Fig. 1. Another important vascular marker is Flk-1, the major receptor for VEGF, which is critical for vasculogenesis and early hematopoiesis, and is a marker of hemangioblasts, the common precursors of endothelial and hematopoietic cells. *Flk1* expression in mouse embryos has been observed in the dorsal aorta, intersomitic vessels, endocardium, yolk-sac vasculature, and base of the allantois (Shalaby *et al.,* 1995), locations also of *Sox7* expression (see Table, and discussed above). In fact, *Sox7* shows perfect colocalization with *Flk1* in endothelial precursors of the presumptive dorsal aorta and in those that later contribute to axial vein formation (Pendeville *et al.,* 2008). *Flk1*$^{-/-}$ embryos die in utero between 8.5 and 9.5 dpc; interestingly, *Flk1*-null homozygotes phenotypically resemble to the *Sox7*-null homozygotes, with complete absence of yolk-sac blood islands and of organized blood vessels in yolk sacs and embryos (Shalaby *et al.,* 1995); *Sox7*$^{-/-}$ embryos fail to remodel yolk sac vasculature and exhibit abnormal intersomitic vessel remodeling (Wat *et al.,* 2011, 2012).

SOX7 has been proposed as a potent activator in the endothelial differentiation of Flk-1$^+$ cells (Yamauchi *et al.,* 2007). Importantly, in the Flk1$^+$ population, the vasculogenic *Sox7* transcription factor is significantly up-regulated, overlapping with the emergence of the cardiac transcription factors *Nkx2.5* and *Gata4* (Nelson *et al.,* 2009). Notably, sorting the parental Flk-1$^+$ pool using the CXCR4/Flk-1 biomarker pair, which is a predictor of the beginning of heart cell specification among pluripotent stem cells, reveals a divergent *Sox7* expression, with significantly lower *Sox7* expression in the cardiogenic subpopulation compared with the subpopulation enriched for endothelial and smooth muscle markers of vasculogenesis (Nelson *et al.,* 2009). Thus, differential *Sox7* expression may be a potential regulatory switch in deciding between cardiac and vascular pathways in Flk1$^+$ multi-lineage precursors (Nelson *et al.,* 2009).

Wnt/β-catenin appears to be a key signaling cascade that integrates the *SoxF* family, including *Sox7*, with the cardiovascular VEGF/Flk-1 and SDF1/CXCR4 pathways (Nelson *et al.,* 2009). Wnt/β-catenin signaling displays biphasic and opposite effects on vascular and cardiac fate selection depending on developmental stage (Naito *et al.,* 2006). Activation of the pathway early in embryoid body formation promotes cardiomyocyte differentiation but late activation inhibits cardiomyogenesis and rather promotes hematopoietic/vascular marker expression (Naito *et al.,* 2006). Ueno *et al.,* (2007) also describe biphasic effect of Wnt/β-catenin signaling in zebrafish embryos and mouse ES cells, with cardiogenic promotion if expressed early but inhibition if expressed later. Wnt/β-catenin clearly influenced cardiogenesis, with opposing effects depending on developmental timing (Naito *et al.,* 2006; Ueno *et al.,* 2007).

In addition, *Wnt* and *Frizzled* genes are differentially expressed in Flk1$^+$ cells from mouse ES cells: non-canonical *Wnt-5a* and *Wnt-11* has significantly higher expression in Flk1$^+$ cells compared to Flk1$^-$ cells, while expression of canonical *Wnt-3a* is reduced in Flk1$^+$ cells (Kim *et al.,* 2008). *Fzd5*, believed to be the non-canonical Wnt-5a receptor and essential for yolk sac and placental angiogenesis, is strongly detected in Flk1$^+$ cells but not in Flk1$^-$ cells; *Fzd7*, involved in non-canonical Wnt signaling, also has robust expression in Flk1$^+$ cells but not in Flk1$^-$ cells (Kim *et al.,* 2008). Such differential expression may be related to the differential roles of canonical and non-canonical Wnt signaling in vascular development and

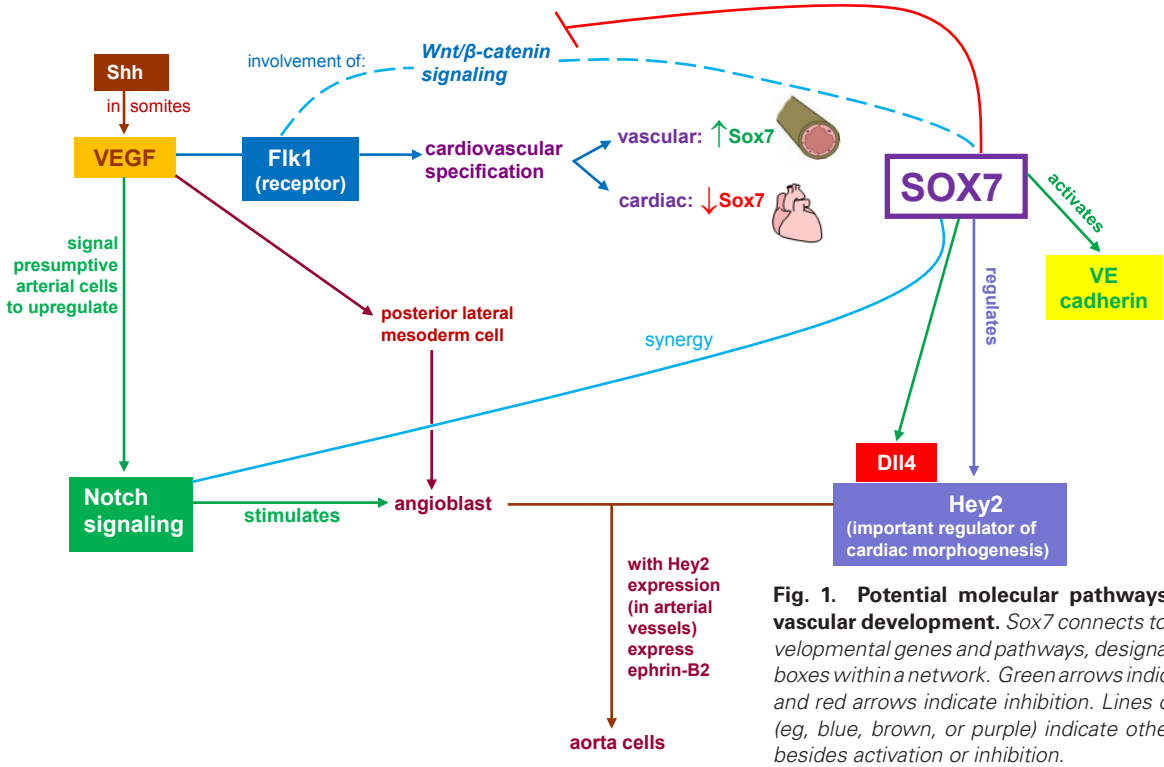

Fig. 1. Potential molecular pathways for Sox7 in vascular development. *Sox7 connects to important developmental genes and pathways, designated as colored boxes within a network. Green arrows indicate activation, and red arrows indicate inhibition. Lines of other colors (eg, blue, brown, or purple) indicate other connections besides activation or inhibition.*

cardiogenesis. The available evidence indicates noncanonical Wnt signaling plays a key role in vasculature development.

While non-canonical Wnt signaling seems to have a role in vascular endothelial fate determination, canonical Wnt/β-catenin signaling appears to be particularly down-regulated in the vascular system (Nacher *et al.,* 2005; Kim *et al.,* 2008). *Xenopus* sox7 has been shown to induce non-canonical *wnt-11* by acting indirectly through Nodal-related *xnr2* (Zhang *et al.,* 2005 b). Wnt-11 induces cardiogenesis through activating non-canonical Wnt signaling; non-canonical Wnt signaling, similar to SOX7, has been shown to repress the canonical Wnt signaling pathway (Maye *et al.,* 2004; Takash *et al.,* 2001). Inhibition of Wnt/β-catenin signaling plays a role in inducing cardiogenic mesoderm (Marvin *et al.,* 2001). Moreover, in *Xenopus*, the sox7 C-terminal domain that physically interacts with β-catenin is necessary to modulate *nkx2.5* and other cardiac gene transcription (Zhang *et al.,* 2005 b). These findings suggest that *Sox7* control of multi-lineage cardiovascular differentiation may potentially be through the Wnt/β-catenin axis.

sox7 is also important in establishing proper arteriovenous identity (Herpers *et al.,* 2008; Pendeville *et al.,* 2008; Cermenati *et al.,* 2008). In double-knockdown *sox7* and *sox18* morphants, the only endothelial cell marker affected is *flk1*, which has a slight reduction in expression (Pendeville *et al.,* 2008). However, expression of *gridlock*/*hey2*, an artery marker, is totally abolished in the aorta of double morphants, with higher doses of *sox7* morpholino significantly expanding the vein at the artery's expense (Pendeville *et al.,* 2008). Furthermore, *hey2* and *sox7/sox18* morphants have strikingly similar phenotypes (Pendeville *et al.,* 2008). These findings indicated that the *sox7/sox18* morphant phenotype likely result from inhibition of *hey2* expression (Pendeville *et al.,* 2008). Sox7 has been suggested to act upstream of and activate *hey2*, possibly synergizing with a factor specific in the dorsal aorta, or with a component of the Notch signaling pathway (Pendeville *et al.,* 2008). Indeed, *hey2* has been shown to be important in arteriovenous specification and dependent on Notch signaling (Zhong *et al.,* 2001). During arterial-venous differentiation, Sonic hedgehog (Shh) induces expression of Vegf in somites, which signal presumptive arterial cells to upregulate Notch signaling. Notch signaling controls specification of angioblasts to either arteries or veins: Notch activation in angioblast membranes leads to activation of Gridlock, which activates ephrin-B2 and other arterial markers, while low Gridlock levels in angioblasts leads to EphB4 expression and vein formation (Zhong *et al.,* 2001; Lawson *et al.,* 2002; Fig. 1). Arterial *Dll4* expression is also decreased with the ablation of the Sox motif in the *Dll4* enhancer-transgene expression in mice (Sacilotto *et al.,* 2013). Knockdown of *sox7*, *sox18*, and *rbpj* in zebrafish leads to loss of endogenous *dll4* expression and disappearance of both arterial markers and a dorsal aorta (Sacilotto *et al.,* 2013).

Hey2 mediates *Notch* signaling in the developing cardiovascular system. Hey proteins have been shown to depend on, and be downstream targets of, Notch signaling. Nakagawa *et al.,* has demonstrated that the intracellular domain of the Notch-1 receptor upregulates *Hey2* in fibroblasts (Nakagawa *et al.,* 2000). In cultured arterial smooth muscle cells, *Hey2* has been found to be a direct target of Notch signaling (Iso *et al.,* 2002), suggesting a role for HEY2 in the cardiovascular system as a transcriptional repressor downstream of Notch signaling. In zebrafish, a Notch-Hey2 pathway appears to control the first embryonic artery assembly in arteriovenous specification (Zhong *et al.,* 2001). In addition, HEY proteins appear to repress their own expression through interference with Notch signaling (Nakagawa *et al.,* 2000). In somites, *Hey* genes exhibit a periodic expression (Nakagawa *et al.,* 1999), similar to Notch signaling-related molecules.

Hey genes are expressed in vascular precursors from the earliest developmental stages. In addition to its connection to *Sox7* in zebrafish as described above, *Hey2*—an important artery marker—is strongly expressed in allantois (which harbors large numbers of vascular precursor cells), dorsal aorta, aortic arch arteries, vasculature (including the smooth muscle layer), and developing kidney vasculature in the mouse (Nakagawa *et al.,* 1999), having an expression pattern similar to that of *Sox7* (Table 1). Moreover, *Hey2* vascular expression is lower at 15.5 dpc than at 10.5 dpc (Nakagawa *et al.,* 1999). As discussed earlier, *Sox7* vascular expression in the mouse is also primarily in earlier stages, such as prior to 12.5 dpc; indeed, *Sox7* expression in most of the vascular endothelia, particularly the posterior cardinal veins, had disappeared by stage 40 larvae of *Xenopus* (Table 1). In the developing vasculature at around 8.5 and 9.5 dpc in the mouse, SOX7 expression is limited to the endothelial cells of the vasculature and the heart endocardial cells (Wat *et al.,* 2011).

Hey2 mutant mice exhibit disrupted vascular development. Combined loss of *Hey2* and *Hey1* results in embryonic death after 9.5 dpc with a global lack of vascular remodeling and massive hemorrhage (Fischer *et al.,* 2004). In addition, yolk sac vasculature is disorganized and embryonic developing major vessels are small or absent, similar to the *Sox7* mutants which lack blood vessel remodeling in the yolk sac (Wat *et al.,* 2012). Also, both *Hey2* and *Hey1* expression in yolk sacs of *Notch1* knockouts are strongly reduced (Fischer *et al.,* 2004). Decreased vascular flow in the $Sox7^{-/-}$ mutants is observed between E8.5 and E9.5, and $Sox7^{-/-}$ embryos have abnormal angiogenesis and vascular remodeling, with the vasculature appearing disordered and supernumerary (Wat *et al.,* 2011).

Another role for *Sox7* in endothelial development comes from results showing that enforced SOX7 expression in mouse hemangioblast colonies sustains the expression of endothelial markers (Costa *et al.,* 2012). SOX7 binds and activates the promoter of VE-cadherin, demonstrating that VE-cadherin is a downstream transcriptional target of SOX7 (Costa *et al.,* 2012). These results indicate that SOX7 transcriptionally regulates genes expressed in the hemogenic endothelium (Costa *et al.,* 2012). Furthermore, *Sox7* knockdown results in a strong reduction in embryonic stem (ES) cell ability to form endothelial colonies (Gandillet *et al.,* 2009).

Sox7's connection to the Flk1/VEGF pathway and Wnt and Notch signaling as discussed above, implicate it as a key regulator in this process. Taken together, all these findings point to a role of *Sox7* in a VEGF-Flk1-Notch-Hey2 pathway, potentially through involvement with Wnt/β-catenin signaling, for vascular development. The connections between these pathways are displayed in Fig. 1.

Mesoderm to endoderm connections: implications of *Sox7*'s role in the vasculature on development of other organs

Signaling between mesoderm and the anterior visceral endoderm is necessary for proper cardiac induction. Mesoderm-endoderm signaling is also important in the development of several other structures: for example, in addition to endodermal specification

of cardiogenic mesoderm, mesodermal derivatives can induce the endodermal tube to produce the rudiments of some digestive organs. This, along with the *Sox7* expression patterns discussed earlier, yields an interesting connection. Specification and formation of the liver particularly requires the gut endoderm to be exposed to both cardiogenic mesoderm and blood vessel endothelial cells; meanwhile, pancreas formation needs activation by the notochord and blood vessels (Lammert *et al.,* 2003; Deutsch *et al.,* 2001). Mouse aortic endothelium recombined with isolated dorsal endoderm leads to endocrine pancreatic differentiation; conversely, removal of dorsal aortic endothelial precursors in frog embryos abolishes endocrine pancreas gene expression, demonstrating the critical role of endothelium in pancreatic development (Lammert *et al.,* 2001). Similarly, hepatic epithelium from mice lacking endothelial cells fails to undergo proper morphogenesis (Matsumoto *et al.,* 2001). Interestingly, as seen in the Table, *Sox7* is expressed in both the cardiac and vascular endothelial structures, and also in all three of the above structures: pancreas, liver, and notochord, as well as the gut. It has been proposed that signaling molecules, such as certain BMP, Wnt, TGF-beta, and PDGF family members from endothelial cells, play an important role in organ formation (Lammert *et al.,* 2003). *Sox7* may control the transcription of signaling molecules which control development of these organs.

Conclusions

In this review, we have presented a comprehensive overview of *Sox7*, revealing its role as a key regulator of significant transcription factors, signaling molecules, and pathways involved in vascular and cardiac development, with connections to other organs as well. The expression patterns observed across species demonstrate a very early and specific role for *Sox7* in cardiovascular development. Indeed, this role has been confirmed in both invertebrate and vertebrate animal models, with zebrafish morphants exhibiting features of cardiovascular failure strikingly similar to those observed in *Sox7* mutant mice. Moreover, *Sox7*'s expression in cardiogenic mesoderm and blood vessel endothelium also suggests involvement in mesoderm to endoderm signaling and organ development. The major pathways discussed in the vasculature include VEGF-Flk1, Wnt, and Notch. Mechanistically, *Sox7*'s role in arterial differentiation and endothelial development, and its molecular interactions with the Wnt/β-catenin, VEGF-Flk1, and Notch pathways, situates it as a key regulator within a network of important vasculature development genes. As there are clearly similarities within the *SoxF* group, it would be interesting to further elucidate how *Sox7* interfaces with its highly homologous family members, *Sox17* and *Sox18*. Clearly, understanding more of *Sox7* promises to expand our knowledge of the complex workings underlying cardiovascular development across species. Collectively, these connections reveal that *Sox7* stands at the intersection of vital biological pathways and processes, which crosstalk in mediating vascular formation and organogenesis.

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