Vertebrates have evolved 2 types of blood vessels—arteries and veins—that function to supply oxygen and nutrients and remove cellular waste. To efficiently accomplish these specialized functions, arteries and veins have developed distinct morphological and molecular differences. As a result, the endothelial cells that compose arteries and veins are vastly different in their biochemical and cellular properties. During development, the nascent endothelial cells generated from hemangioblasts or angioblasts\textsuperscript{1,2} undergo tightly regulated specification and differentiation processes to adopt either the arterial or venous endothelial fate. Differentiated endothelial cells migrate and aggregate to form either arteries or veins according to their adopted fate.\textsuperscript{3} Dysregulation of these regulated events often results in devastating consequences. For instance, failure to segregate arterial and venous endothelial cells causes potentially fatal clinical consequences. For instance, failure to segregate arterial and venous endothelial cells causes potentially fatal clinical conditions such as arteriovenous malformation, hereditary hemorrhagic telangiectasia, and cerebral cavernous malformation.\textsuperscript{4}

Significant progress has been made in understanding how nascent endothelial cells adopt the arterial fate, resulting in identification of several key signaling molecules and their intracellular transducers involved in the specification of arterial endothelial cells.\textsuperscript{5} However, transcription factors that function downstream of these signaling cascades are largely unknown to date. Recently, hey2/Gridlock,\textsuperscript{6,7} a member of the hairy and enhancer of split-related family of bHLH transcription factors, and Foxc1 and Foxe2,\textsuperscript{8,9} which are forkhead transcription factors, have been implicated in arterial specification (Figure). A report in this issue of Circulation Research by Herpers et al elucidates the essential function of another transcription factor family, Sox, in this process.\textsuperscript{10}

Sox transcription factors are DNA binding proteins that have a high degree of sequence homology to the testis-determining gene Sry.\textsuperscript{11-13} They contain a characteristic DNA-binding motif commonly known as the high mobility group domain.\textsuperscript{14} Sox family transcription factors can be further divided into 10 subgroups: SoxA to SoxJ.\textsuperscript{15} Sox protein transcription factors appear to have important roles in various developmental process, including fate specification and organogenesis.\textsuperscript{13} For instance, Sox2 is critical for maintenance of neural stem cell fate,\textsuperscript{16} and Sox13 is essential for specification of γδ T cells.\textsuperscript{17} In zebrafish, the endodermless casanova phenotype is caused by a mutation in Sox3,\textsuperscript{18} indicating that Sox transcription factors are essential for establishing endoderm fate during development.

Sox transcription factors that belong to the SoxF subgroup, such as Sox7, Sox17, and Sox18, are highly expressed in the developing vasculature.\textsuperscript{10,19} Among these members, the functions of Sox17 and Sox18 are relatively well studied. Sox17- and Sox18-null mice have been previously generated.\textsuperscript{20,21} Despite their expression pattern, neither Sox17- nor Sox18-null mice exhibit any obvious vascular defects, although double nulls of Sox17 and Sox18 display a wide range of vascular defects including defective dorsal aorta formation.\textsuperscript{19} In contrast to what is known about Sox17 and Sox18, the function of Sox7 remains to be investigated. In their article, Herpers et al reveal a novel function for Sox transcription factors by demonstrating that Sox7 and Sox18 may serve as essential regulators in the specification of arterial fate.\textsuperscript{10} However, these 2 transcription factors do not appear to be essential regulators for vascular development individually: morpholinos targeting either one of these 2 genes does not display any discernable vascular defects. Intriguingly, when blocked simultaneously, attenuation of Sox7 and Sox18 function causes a loss of circulation in the posterior part of embryos, which eventually leads to the development of a circulatory loop in the anterior part of the affected embryos.\textsuperscript{10} To elucidate the etiology of this peculiar phenotype, the authors investigated the molecular properties and cellular architecture of endothelial cells in embryos coinjected with Sox7 and Sox18 morpholinos. In these embryos, the authors found that the specification of arterial endothelial cells is severely disrupted, which is often accompanied by failure of segregation of arteries from veins.\textsuperscript{10} Based on their observation, the authors concluded that Sox7 and Sox18, although dispensable for vascular development individually, synergistically function to promote the specification of arterial endothelial cells.

The biochemical nature of how Sox7 and Sox18 interact remains to be discovered. Nevertheless, the article by Herpers et al clearly demonstrates that these Sox proteins together regulate the specification of arterial fate.\textsuperscript{10} Sox7 has been implicated as a potential modulator of many developmentally essential signaling pathways, such as fibroblast growth factor,\textsuperscript{22} Wnt/β-catenin,\textsuperscript{23} and Nodal.\textsuperscript{24} It will therefore be extremely interesting to see how the interaction between
The studies by Herpers et al.10,11,12 open up new critical signaling pathways to promote the specification of arterial endothelial cells. In addition, open questions remain about the direct transcriptional targets of these transcription factors within angioblasts and how the Sox7/Sox18-dependent gene expression program culminates in artery-vein segregation. The studies by Herpers et al10,11,12 the authors demonstrate the indispensable function of Delta-like 4 (Dll4) also appears to be critical in arterial specification. To date, relatively few transcription factors have been identified that regulate this process (ie, FoxC1/FoxC2, Hes-related protein, and FoxH1). In the article by Herpers et al,10 the authors demonstrate the indispensable function of Sox7/Sox18 modifies Sox7-mediated activation of these transcription factors, Foxc1 and Foxc2, are required for arterial specification and lymphatic sprouting during vascular development. Dev Biol. 2006;294:458–470.

Sox7 and Sox18 modifies Sox7-mediated activation of these critical signaling pathways to promote the specification of arterial endothelial cells. In addition, open questions remain about the direct transcriptional targets of these transcription factors within angioblasts and how the Sox7/Sox18-dependent gene expression program culminates in artery-vein segregation. The studies by Herpers et al open up new opportunities to understand the molecular and cellular mechanisms of vascular development and of vascular diseases associated with arteriovenous shunt formation.

Disclosures

None.

References


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