More than a decade ago, DeBakey and Glaser reported that human atherosclerotic lesions form and progress in distinct regional patterns in spite of uniform systemic risk factors, such as smoking, high blood pressure, and serum cholesterol. The authors proposed that this might be because of unknown position-specific genetic differences within the arterial system itself. The Hox gene family is a prime candidate for determining these postulated genetic differences, because these conserved developmental control genes are known to specify positional identities and regional diversities along the longitudinal body axis during embryonic patterning in bilateral animals. The mammalian Hox system includes 39 genes that are organized in 4 separate clusters designated Hox through –d, whose sequence alignment reveals the existence of 13 paralogous Hox groups. The successive activation of these tandemly arranged genes in each cluster mirrors the rostro-caudal morphogenetic progression such that the genes located at the 3’end (groups 1 and 2) are activated first and exhibit the most anterior expression boundaries, and the genes located at the 5’end (group 13) are activated last and occupy the most posteriorly restricted expression domain. This results in distinct domains of unique combinatorial Hox activities, the so-called Hox code that specifies positional identity at a given location, and is believed to function analogous to a postal ZIP code. Importantly, this topographical Hox code is retained in certain cell populations of adult tissues, such as dermal fibroblasts, where it is believed to be critical for regulating local differentiation and signaling events.

Evidence for a Vascular Hox Code

Although many Hox genes are expressed in endothelial cells and vascular smooth muscle cells (SMCs), surprisingly little information is available about their in vivo functional roles in the cardiovascular system with respect to both development and disease. Among the few cases that document regional vascular patterning defects linked to mutations in mammalian Hox genes is mouse Hoxa3, whose disruption by gene targeting resulted in a range of cardiovascular defects, including malformations of the carotid artery system, aortic valve stenosis, and abnormalities of the cardiac chambers. In humans, a homozygous mutation of Hoxa1 was linked to a complex congenital syndrome whose cardiovascular manifestations include malformations of the cerebral vasculature, the internal carotid arteries, and the cardiac outflow tract. Furthermore, Hoxc11 gene–targeted mice that seemed overtly normal developed greatly enlarged femoral arteries compared with wild-type mice. These localized mutational defects are consistent with regionally restricted Hox expression patterns in the formation of specific arterial segments during development.

Positional Identity for Aortic Smooth Muscle

In an article appearing in this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Trigueros-Motos et al report evidence that links positional identity of aortic SMCs with differential responses to inflammatory cytokines thought to play important roles in the initiation and progression of atherosclerosis. The authors first performed genome-wide transcript profiling comparing atherosclerosis-prone aortic arch (AAo) with atherosclerosis-resistant thoracic aorta (TAo) in wild-type and apoE-null (apoE-knockout) mice. This analysis identified various members of Hox paralogous groups 6 to 10 as more abundantly expressed in TAo than AAo segments in both wild-type and apoE-KO mice. Although these 2 aortic segments experience substantially different blood flow characteristics in vivo, this segment-specific Hox expression signature was also found in primary SMC cultures in the complete absence of blood flow considerations. Thus, differential Hox gene expression profiles in AAo versus TAo probably reflect stable differences in SMC epigenomes that establish a positional identity during development, which is maintained in adult mice. This concept is supported by the striking finding that essentially the same Hox expression profile is generated during in vitro differentiation of human pluripotent stem cells along a neural ectoderm pathway versus a paraxial mesoderm pathway, a process that produces 2 types of in vitro–derived SMCs that faithfully exhibit the unique phenotypes of neural crest–derived and somite-derived aortic SMCs described by others.

Interpreting Inflammation

Smooth Muscle Positional Identity and Nuclear Factor-κB Signaling

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Smooth Muscle Positional Identity and Nuclear Factor-κB–Dependent Responses to Tumor Necrosis Factor α

The critical departure from previous studies comes when Trigueros-Motos et al. address the question of whether differences in SMC identity conferred by origin and position in development translate into aortic segment–specific differences in responses to proinflammatory stimuli involved in the progression of vascular disease in adults. Here, the key findings are that both basal and tumor necrosis factor α–stimulated nuclear factor (NF)-κB activation and binding to DNA were significantly greater in SMCs from atherosclerosis-prone AAo segments compared with SMCs from atherosclerosis-resistant TAO segments. Moreover, when one particular member of the Hox groups 6 to 9, that is, HOXA9, was examined in detail, it was found that high levels of NF-κB activity strongly repress HOXA9 expression and, in reciprocal fashion, HOXA9 expression can repress NF-κB transcriptional activity (Figure). These data have exciting implications for a better understanding of the segment-specific distribution of atherosclerosis in the arterial system reported by DeBakey and Glaeser. They raise the possibility that atherosclerosis-prone versus atherosclerosis-resistant aortic segments exhibit differential responses to a common level of inflammatory cytokines, in part, as a consequence of stable differences in SMC identity conferred by differences in the topographical position of their progenitors during development. Although the molecular mechanisms that write these stable differences to the SMC epigenome during development are not yet understood, the consequences of these mechanisms may be to produce a mosaic pattern of susceptibility on which the more familiar stimuli of arterial injury, inflammation, and thrombosis act to produce overt vascular disease.

Summary and Future Directions

The evidence from studies of vascular development suggests that arterial smooth muscle is a mosaic tissue in which both lineage-dependent and position-dependent imprints prepattern these cells to be capable of responding differently to identical stimuli. Available data point to a topographical vascular Hox code, specifying positional identity that is not necessarily restricted to embryonic lineage, as exemplified by the expression patterns of Hoxa3 and Hoxa4 in vascular SMCs of different lineages as well as in endothelial cells. A better understanding of how these topographical Hox activities intersect with vascular disease pathways will require determination of Hox-dependent targets in the artery wall and analyses of how those targets are linked to regulators of inflammation, proliferation, cell death, and vascular remodeling. The apparent reciprocal regulatory relationship between HOXA9 and NF-κB in AAo- and TAO-derived vascular SMCs as shown by Trigueros-Motos et al. (Figure) is an important step in this direction. The next experiments to obtain definitive data for this kind of functional relationship will require the use of conditional Hox knockout alleles in mice in conjunction with more detailed analyses of in vivo expression patterns of Hox genes, identification of their potential downstream targets, and characterization of the molecular mechanisms for crosstalk with key mediators in the pathogenesis of vascular disease.

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Disclosures

None.

References


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