

Topographic patterns of vascular disease: HOX proteins as determining factors?

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Abstract

Steadily increasing evidence supports the idea that genetic diversities in the vascular bed are, in addition to hemodynamic influences, a major contributing factor in determining region-specific cardiovascular disease susceptibility. Members of the phylogenetically highly conserved *Hox* gene family of developmental regulators have to be viewed as prime candidates for determining these regional genetic differences in the vasculature. During embryonic patterning, the regionally distinct and precisely choreographed expression patterns of HOX transcription factors are essential for the correct specification of positional identities. Apparently, these topographic patterns are to some degree retained in certain adult tissues, including the circulatory system. While an understanding of the functional significance of these localized *Hox* activities in adult blood vessels is only beginning to emerge, an argument can be made for a role of *Hox* genes in the maintenance of vessel wall homeostasis and functional integrity on the one hand, and in regulating the development and progression of regionally restricted vascular pathologies, on the other. Initial functional studies in animal models, as well as data from clinical studies provide some level of support for this view. The data suggest that putative genetic regulatory networks of *Hox*-dependent cardiovascular disease processes include genes of diverse functional categories (extracellular matrix remodeling, transmembrane signaling, cell cycle control, inflammatory response, transcriptional control, *etc.*), as potential targets in both vascular smooth muscle and endothelial cells, as well as cell populations residing in the adventitia.

Key words: *Hox*; Blood vessel; Cardiovascular disease; Positional identity; Endothelial cell; Vascular smooth muscle cell

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Core tip: Accumulating evidence indicates regionally restricted HOX expression patterns in the adult arterial tree that may reflect a topographic vascular HOX code for specifying positional identities in various cell types of the circulatory system. We propose that this positional information is critical for maintaining local vessel wall homeostasis and that its disruption plays an important role in the development of vascular diseases with distinct topographic preferences. This editorial discusses emerging molecular data in support of this novel concept.

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INTRODUCTION

According to epidemiological data from the World Health Organization (WHO), diseases of the circulatory system, collectively known as cardiovascular diseases (CVDs) are the leading cause of death world-wide (<http://www.who.int/mediacentre/factsheets/fs317/en>), and a great number of resources have been committed to study the pathophysiology of CVDs with the goal of improving therapeutic interventions. The most common forms of CVD include atherosclerosis of various segments of the arterial tree (coronary, carotid, and cerebral arteries, aortic arch, abdominal artery), aneurysms of the thoracic and abdominal aorta, as well as cerebral arterial aneurysms, peripheral arterial disease (PAD), and venous insufficiency.

Although certain types of CVDs share some of the same pathogenic characteristics (e.g., neointima and atherosclerotic plaque formation as a result of chronic inflammation in atherosclerosis, medial degeneration in aortic aneurysms), they usually develop at distinct anatomic locations. As the most prevalent CVD risk factors including hypertension, diabetes, smoking, alcohol, lack of physical activity, obesity, high blood cholesterol and triglycerides, and stress are all systemic, regional genetic differences in the vascular bed are likely to be critical for these topographic disease patterns, as they cannot be attributed to hemodynamic differences alone. This view is underscored by aortic homograft transplant experiments in canines, in which atherosclerosis-susceptible segments of the abdominal aorta were transplanted into the atherosclerosis-resistant thoracic aorta and *vice versa*^[1]. Examination of transplanted vessel segments subsequent to keeping the animals on an atherogenic diet revealed that the abdominal segments readily developed atherosclerotic lesions in their thoracic host environment, whereas the thoracic aortic segments continued to be free from

lesion formation in the abdominal aorta. These results are consistent with data from a large-scale clinical study involving approximately 12000 patients that were treated surgically for atherosclerotic occlusive disease with a follow-up of over 25 years^[2]. In this study the arterial bed was divided into four anatomical categories for analysis including the coronary arterial bed, the major branches of the aortic arch, the visceral branches of the abdominal aorta and the terminal abdominal aorta with its major branches. The data showed that the response to systemic risk factors is distinctly different in each of the four categories^[2].

A search for potential determinants underlying these inherent differences in the response to systemic pathogenic triggers will have to consider the circumstance that vascular smooth muscle cells (VSMCs) residing in distinct segments of the arterial tree originate from different sources depending on their anatomic location. Lineage-mapping involving chick-quail chimera identified at least seven different sources including proepicardium, secondary heart field, neural crest, mesangioblasts, somites, splanchnic mesoderm and mesothelium that contribute to defined arterial segments, in addition to various types of progenitor cells residing primarily in either the media or adventitia with a more universal distribution^[3]. Overall, this fate map reveals a segmented pattern of the arterial tree that seems to reflect the metameric patterning of the vertebrate embryo. As segment identities, and therefore diversities, are specified by members of the phylogenetically highly conserved family of *Hox* transcriptional regulators, these genes have to be viewed as prime candidates for determining different positional identities in the vascular bed that reflect regional differences in CVD susceptibility.

HOX-SPECIFIED POSITIONAL IDENTITIES IN THE CIRCULATORY SYSTEM

The conserved *Hox* gene family constitutes a genetic system of unique properties that is utilized initially during embryonic patterning for specifying positional identities along the anterior-posterior (A-P) axis^[4,5]. The mouse and human genome harbor 39 *Hox* genes that are organized into four separate clusters designated *Hoxa*, *-b*, *-c*, and *-d*. Alignment of these transcriptionally unipolar clusters based on sequence similarities reveals 13 paralogous groups of *Hox* genes that are activated sequentially in distinct A-P embryonic domains such that genes of groups 1 and 2 are expressed first in the most anterior regions, whereas group 13 *Hox* genes are activated last by following the A-P morphogenetic progression. This modus of activation generates unique domains of combinatorial *Hox* activities at any given location of the embryo that has been referred to as the *Hox* code in analogy to the postal zip code for specifying positional identities^[6]. Data obtained by large-scale gene expression profiling

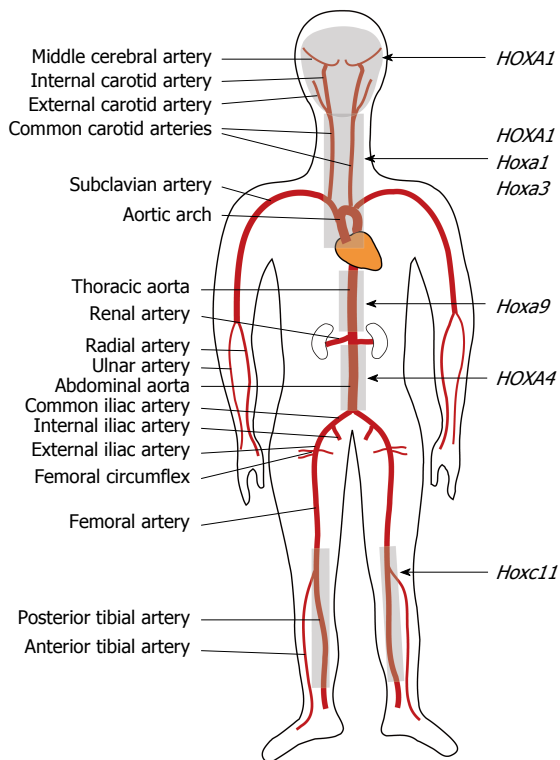


Figure 1 Map of Hox functional domains in the arterial tree. The schematic shows a rough outline of the main human arterial segments. Localization of vascular defects associated either with mutated human *HOX* or mouse *Hox* alleles as indicated at the right were used to generate a cursory map of *HOX/Hox* activity domains (grey shading) assuming that the defects observed in the mouse map to roughly equivalent anatomic positions in humans. The demarcation of the *HOXA4* activity domain is based on down-regulation of *HOXA4* expression associated with AAA. The *Hoxa9* domain in the thoracic aorta signifies an atherosclerosis-resistant segment.

of adult fibroblasts derived from different anatomic regions in humans suggest that this embryonically established topographic *Hox* code is, at least to some degree, retained in the adult^[7], where it is believed to be critical for maintaining positional identities by regulating local differentiation and signaling events.

Initial evidence for the existence of a topographic *Hox* code in the circulatory system came from *LacZ* reporter gene studies in transgenic mice that revealed remarkable regionally restricted expression patterns for *Hoxc10*, *Hoxc11*, and *Hoxa3* in subpopulations of VSMCs of the media, as well as in endothelial cells (ECs) within distinct segments of the vascular bed of young adult (6 wk), as well as 1 year old mice^[8]. Apparently, this presumptive vascular *Hox* code is instrumental in maintaining vessel wall integrity and homeostasis as indicated by the region-specific vascular remodeling events upon its interruption. Specifically, this was demonstrated by inducing changes in the vascular *Hoxc11* expression pattern that is normally restricted to the distal limb vasculature of adult mice (Figure 1). By utilizing an integrated tetracycline regulatory system and *Transgelin* (*Tagln*) promoter elements that drive expression universally in VSMCs of TetOn(*Tagln-Hoxc11*) transgenic mice upon doxycycline (dox)

induction, these mice developed severe vessel wall defects (medial thinning, elastic laminae fragmentation, intimal lesion formation) in arterial segments where *Hoxc11* is normally not expressed (carotid artery, aortic arch, thoracic aorta), whereas overexpression of *Hoxc11* in its natural vascular domain of activity, including the lower femoral artery, resulted in a drastic increase in vessel diameter but without the structural defects observed upon ectopic expression^[9]. Furthermore, human *HOX* transcriptome analysis of vascular ECs derived from different anatomic locations revealed specific *HOX* expression signatures that are believed to determine positional identities and regulate endothelial differentiation^[10].

Compared to gene expression profiling, an alternative approach to consider for mapping *Hox* activities in the circulatory system is to determine *Hox* functional domains by mutational analysis in mice and by linking human congenital vascular defects to mutant *HOX* alleles. The *Hoxa3*^{tm1Mrc} mutant is perhaps the first case in which disruption of a *Hox* gene has been linked to severe cardiovascular defects in mice that include absence of the right carotid artery and stenosis of the aortic valves, in addition to abnormalities of the cardiac chambers, as well as other developmental defects^[11]. In humans and mice, a homozygous *HOXA1/Hoxa1* mutation was linked to a complex syndrome that includes malformations of the cerebral vasculature, the internal carotid arteries, and the cardiac outflow tract in addition to neuronal defects^[12-14]. Mice homozygous for the *Hoxc11*^{tm1Mrc} targeted allele developed greatly enlarged femoral arteries that were phenotypically very similar to the enlarged vessels seen upon induced overexpression of *Hoxc11* in the distal hindlimb vasculature^[9]. Furthermore, and of potential clinical relevance is the downregulation of *HOXA4* expression associated with abdominal aortic aneurysms^[15]. Interestingly, *HOXA4* exhibits an A-P gradient in expression levels along the aorta (ibid) that might overlap with a gradient for *Hoxa9* expression, for which highest levels were found in the thoracic aorta of mice^[16] as discussed below.

HOX-REGULATED GENETIC PATHWAYS IN THE VASCULATURE - POTENTIAL CVD RELEVANCE

The vascular functions of *Hox* genes have perhaps been studied most extensively in cells of endothelial lineage within the context of angiogenesis as observed in normal physiological scenarios (e.g., wound healing) and under pathological conditions (e.g., tumorigenesis). This work has yielded useful insight into *Hox*-dependent pathways regulating EC phenotypic properties. Accordingly, all *HOX* genes of paralogous group 3 were found to stimulate angiogenesis albeit through different pathways^[17]. *HOXD3* promotes expression of *integrin* $\alpha 5$ and $\beta 3$ subunit genes in response to FGF2^[18-20];

heterodimers of these subunits with other subunits generate fibronectin receptors $\alpha 5\beta 1$ and $\alpha v\beta 3$ that facilitate adhesion and migration through fibronectin-rich granulation tissue during wound healing^[17]. Consistent with this is the *HOXD3*-regulated increase in expression of the urokinase plasminogen activator (*uPA*) gene^[18]. The human *HOXD3* paralogs *HOXA3* and *HOXB3* also promote angiogenesis although through different pathways that involve increased EC migration and expression of *Mmp14* and *uPAR* (*HOXA3*) and enhanced expression of the angiogenic ligand Ephrin A1 (*HOXB3*)^[17]. Increased EC migration in tissue culture was also observed for *HOXA9* through direct transcriptional activation of the *Ephrin receptor B4* (*EPHB4*) gene^[21]. *HOXD10*, on the other hand, was found to be inactive during angiogenesis but expressed in quiescent vascular endothelium, and pro-angiogenic factors ($\beta 4$ and $\alpha 3$ integrins, *MMP14*, *uPAR* and *cyclin D1*) were downregulated in *HOXD10*-transfected ECs^[22]. Likewise, *HOXA5* is reportedly inactive in angiogenic endothelium but expressed in quiescent ECs where *VEGFR2*, *ephrin A1*, *HIF1 α* , and *COX2* were downregulated upon transfection with *HOXA5*^[23].

As most of these *Hox* expression data and functional correlations have been obtained in cell culture systems, some of these results may not reflect the vascular patterns and functions observed *in vivo*. For example, *Hoxa3* expression is induced together with *Hoxd3* during cutaneous healing of excisional wounds in mouse^[24]. However, the same gene was found to be abundantly expressed in VSMCs of major blood vessels in addition to ECs but in a topographically restricted manner^[8].

As pointed out above, induction of ectopic *Hoxc11* expression in VSMCs of TetOn (*Tagln-Hoxc11*) transgenic mice on an FVB/NTac background resulted in severe vascular defects. Consequently, these mice offer an opportunity to start defining *Hoxc11*-regulated pathways of pathological vessel wall remodeling. Preliminary results showed induction of the apoptotic marker *CASP3*, as well as matrix protein metalloproteinase *MMP2* and *MMP9* expression in medial VSMCs of the thoracic aorta following doxycycline (dox)-induced *HOXC11* expression^[9]. Both *MMP2* and *MMP9* are involved in extracellular matrix (ECM) breakdown and restructuring of the vessel wall, as well as breakdown of the basement membrane and cell migration^[25,26], *i.e.*, events that are consistent with the formation of the type of lesion formation observed in the thoracic aorta of these mice. Interestingly, in the lower femoral artery, where *Hoxc11* overexpression resulted in an enlargement of an otherwise structurally normal vessel, only *MMP2* was induced upon dox-treatment. Accordingly, the differential histological changes observed in response to *Hoxc11* ectopic vs overexpression were mirrored by distinct differences in molecular responses, in this case *MMP9* expression, that is usually associated only with injury and inflammatory responses^[25]. Furthermore, data from

chromatin immune-precipitation (ChIP) and transient co-transfection assays suggested that *Mmp2* and *Mmp9* are transcriptionally regulated by *HOXC11*, thus linking *Hoxc11* directly to the regulation of vascular remodeling pathways involving these MMPs.

In a separate study, a search for factors that contribute to the commonly greater susceptibility to atherosclerosis in the aortic arch vs the thoracic aorta found that members of *Hox* paralogous groups 6-10 exhibit higher expression levels in the former across various mammalian species including mouse, rat, and porcine^[16]. Remarkably, essentially the same differential *Hox* expression profiles were observed in human embryonic stem cells that were differentiated *in vitro* either along the neuroectoderm pathway into aortic arch-like VSMCs or along the paraxial mesoderm pathway into thoracic aorta-like VSMCs. These data suggest that *Hox*-specified positional identities of VSMCs established during development are retained in adulthood. Apparently this positional diversity is reflected by differential responses to inflammatory stimuli that are critical for the progression of vascular diseases such as atherosclerosis. This was illustrated by the greater activity and binding to DNA of the pro-inflammatory transcription factor NF- κ B in aortic arch vs thoracic aorta VSMCs. Moreover, this NF- κ B pattern apparently is, at least in part, due to a reciprocal regulatory relationship with *Hoxa9* such that the higher levels of *HOXA9* expression in the thoracic aorta repress NF- κ B transcriptional activity, whereas the high levels of NF- κ B activity in the arch repress *Hoxa9* expression^[16,27].

As mentioned before, downregulation of already low *HOXA4* expression levels in the abdominal aorta was associated with abdominal aortic aneurysms (AAAs)^[15] that are much more prevalent than thoracic aortic aneurysms (TAAs), which themselves occur primarily in the ascending aorta, *i.e.*, the proximal region of the aortic arch^[28]. While there exist many differences in the etiology, histology, and genetics of the two diseases, it is perhaps noteworthy that both develop predominantly in vessel segments that are situated at the low ends of *Hox* expression gradients with a greater pro-inflammatory predisposition in both cases, even though the inflammatory component in TAAs is lower than in AAAs^[28]. This raises the intriguing question whether high levels of *Hoxa9* and *Hoxa4* expression may protect against the development of both aneurysms and atherosclerosis in the descending aorta, aka thoracic aorta. In that case, the further reduced *HOXA4* levels clinically associated with AAA are likely the consequence of inflammatory stimuli, a view supported by *in vitro* data showing reduced *HOXA4* expression in cultured human VSMCs and ECs treated with inflammatory cytokine IFN- γ ^[15].

Recent *in vitro* silencing experiments of *HOX* activities (*HOXB7*, *HOXC6*, *HOXC8*) in multipotent stem cells isolated from the adventitia of the human

thoracic aorta provided evidence for *Hox*-dependent differentiation into VSMCs involving epigenetic mechanisms^[29]. This raises the interesting possibility that *Hox* genes may be critical regulators of vascular cell populations that drive phenotype switching between homeostatic/regenerative vs pathological remodeling in vascular tissues in a region-specific manner.

CONCLUSION

Their persistent topographic expression patterns in post-natal vascular tissues suggest that *Hox* genes play a critical role in maintaining vessel wall homeostasis in a region-specific manner. Consequently, the idea that *Hox*-linked genetic polymorphisms affecting either their functional quality or expression levels may underlie CVD susceptibility in discrete portions of the vascular tree is a valid proposition. Albeit limited, the currently available *in vivo* data derived from analyses of *Hox* knockout and conditional *Hox* gain-of-function mutant mice, as well as from clinical studies support that view. Initial efforts of defining the genetic regulatory networks of *Hox*-dependent CVD processes implicate genes of diverse functional categories (ECM remodeling, transmembrane signaling, cell cycle control, inflammatory response, transcriptional control, etc.), as potential targets. The finding of region-specific reciprocal interactions of a *Hox* gene with a pro-inflammatory factor (NF- κ B) is intriguing and might be of universal relevance in the search for therapeutic approaches. Within this context, defining the epigenetic mechanisms controlling *Hox* activities in blood vessels will be critical as indicated by data that associate hypomethylation of CpG islands within the *HOXC11/HOXC9* genomic interval with the ectopic activation of *HOXC10* and -9 in atherosclerotic coronary arteries^[30].

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