Editorial

"Osteotropic" Wnt/LRP Signals

High-Wire Artists in a Balancing Act Regulating Aortic Structure and Function

Dwight A. Towler

Every osteotropic agent has vasculotropic actions. I have yet to see this principle violated. The reason most likely lies within the intimate relationships between bone matrix biology and the arterial vasculature in vertebrate physiology.[1] Prototypic bone anabolic hormones, such as parathyroid hormone, recruit osteoblast-derived signals to realign marrow vascular proximity to sites of bone formation.[2] These responses are shaped by parathyroid hormone–regulated mechanical cues sensed by osteocytes,[3,4] the parenchymal cells imbedded with bone matrix that regulate osteogenic Wnt actions via the release of sclerostin[5]—an inhibitor of the Wnt coreceptors low-density lipoprotein receptor–related proteins (LRP), LRP5 and LRP6.[6,7] The vasculature also provides the sustentacular niche for the osteoprogenitor throughout the skeletal lifespan.[8] Conversely, the osteoblasts and progenitors of bone marrow create the hematopoietic microenvironment[9] and are regulated gatekeepers of hematopoietic cell egress into the circulation.[10] In response to global physiological demands, the vasculature also provides the conduit for movement of calcium and phosphate in and out of the mineralized repository that is the calcified skeletal extracellular matrix.[1]

See accompanying article on page 553

Some the earliest connections between vascular health and osteotropic signaling were discovered by Boström et al.[11] In 1993, they demonstrated the expression of the powerful bone morphogenetic protein 2 in the calcifying carotid plaques of patients afflicted with atherosclerosis.[11] Many laboratories, including ours, discovered that the Wnt signaling cascades, initially identified as important in craniofacial bone and tooth formation, also participated in vascular mineralization and arteriosclerotic stiffening of conduit vessels.[12–18] In both bone[19] and aortic vasculature,[20] Wnt signaling is an important mediator of osteogenic differentiation downstream of bone morphogenetic protein stimulation. The Wnt family of polypeptide ligands signal via the frizzled family of G-protein–coupled plasma membrane receptors, shaped via coreceptors encoded by the *LRP5/6*, *ROR, RYK*, and *Celsr* gene families necessary for proper cytoplasmic membrane localization of downstream signaling platforms.[21–23] LRP5, LRP6, and ROR2 have important roles in bone development, fracture repair, and skeletal homeostasis. While classically (canonically) characterized as a coactivator of β-catenin–driven transcription in osteoblasts and vascular smooth muscle (VSM), the coreceptor LRP6 also inhibits VSM arteriosclerotic responses mediated by noncanonical Wnt signals (Figure).[15,18] Like LRP5, LRP6 can be negatively regulated by other ligands, including sclerostin and Dickkopf, to control bone formation.[4–6] As noted above, sclerostin is of particular interest because deficiency in this prototypic osteocyte product increases bone mass[25]—and is being targeted for osteoporosis pharmacotherapy.[26] Of note, within the vasculature, platelet-derived Dickkopf induces an inflammatory endothelial phenotype[27,28] and promotes prosclerotic endothelial–mesenchymal alterations.[29] However, although sclerostin is expressed in aortic tissues and upregulated with arterial mineralization,[14] the role if any for sclerostin in arterial physiology has not been robustly investigated.

In this issue of the *Arteriosclerosis, Thrombosis, and Vascular Biology*, Krishna et al[24] begin to address this latter issue by assessing impact of a sclerostin transgene and recombinant protein administration in a preclinical model of atherosclerotic aortic aneurysm formation. Using the ApoE-null mouse treated with angiotensin II, they demonstrate that either genetic or pharmacological augmentation of sclerostin tone mitigates aortic aneurysmal dilation.[24] Macrophage infiltration, matrix metalloproteinase 9 and osteopontin expression, and elastin degradation are shown to be downregulated by sclerostin, consistent with the preservation of aortic structure. Concomitant increases in canonical Wnt actions with aneurysm formation were coregistered by the upregulation of phospho-GSK3 and β-catenin,[24] 2 key components of canonical Wnt signaling.[21,30] Furthermore, they show that regional arterial (mostly medial) expression of sclerostin is downregulated in aortic segments undergoing aneurysmal dilation in both mice and humans. This arises in part because of the increased epigenomic methylation that silences the *SOST* promoter in human aortic aneurysm tissue. Thus, the authors conclude that vascular expression of sclerostin controls aortic structure and matrix remodeling in ways that might be targeted as therapeutic intervention for early aortic aneurysm management.[24]

Why is this article so important? First, it highlights yet once again the fundamental relationship between traditional osteotropic regulatory programs and the regulation of cardiovascular physiology and function. Of note, this lesson was painfully taught when a novel cathepsin K antagonist, effective in reducing fracture risk, was identified as increasing the risk for stroke in a recent and large phase III study.[31] Second,

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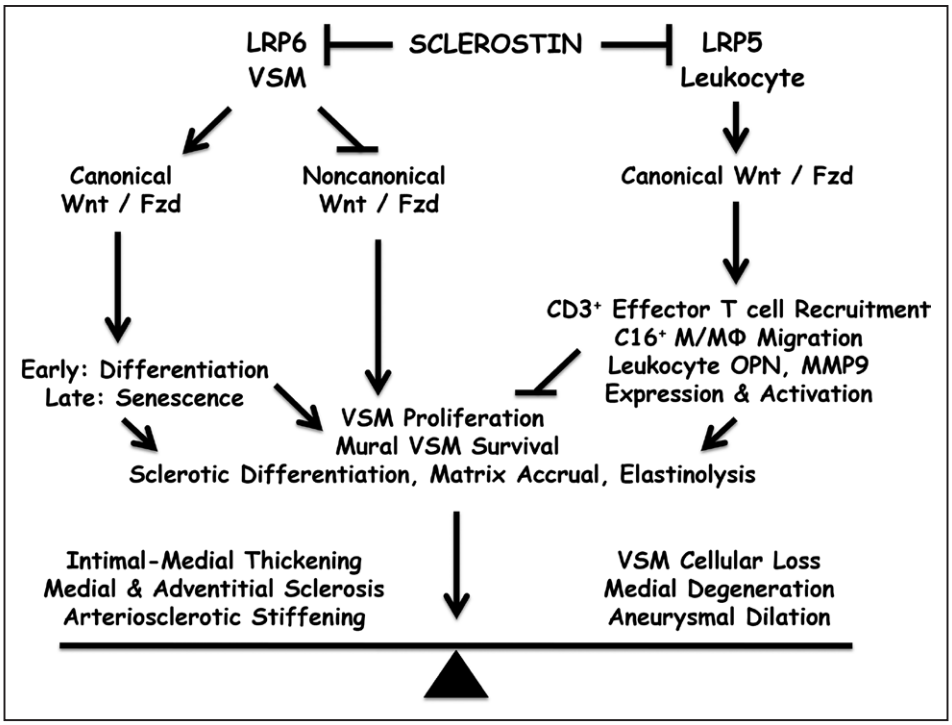

Figure. Integrating sclerostin actions with Wnt/LRP (low-density lipoprotein [LDL] receptor–related proteins) signaling programs in aortic physiology. Wnt signaling cascades continue to emerge as key regulators of conduit artery structure, function, and remodeling. In this issue, Krishna et al[24] demonstrated that sclerostin, an inhibitor of canonical Wnt signaling via LRP5 and LRP6, reduces aneurysmal dilation in the ApoE-null, angiotensin II treatment model of atherosclerotic aortic aneurysm formation. Given the role for LRP5 in leukocyte migration and matrix metalloproteinase (MMP) production, and the role for LRP6 in modulating both canonical and noncanonical pathways in vascular smooth muscle (VSM), it will be important to determine the relative cell-type–specific contributions of LRPs and their frizzled (Fzd) signaling partners to the vasculotropic actions of sclerostin modulators. The role if any for LRP4, another sclerostin binding protein, in vascular physiology is unexplored. While preventing aneurysmal dilation, excessive arterial stiffening must also be avoided given its independent contributions to the risk for stroke, cognitive impairment, and dementia (see Discussion). M/MΦ indicates monocyte/macrophage lineage; and OPN, osteopontin.

it provides additional evidence that the Wnt/LRP signaling cascade can be pharmacologically targeted to modulate arterial structure and function.[18,24] Because of the fundamental bone–vascular relationships,[1] it will be important to assess whether a pharmacokinetic–pharmacodynamic therapeutic window exists, wherein sclerostin-based strategies can be implemented to favorably impact both arterial and skeletal remodeling. Because vessel compliance is important to Windkessel physiology—the rubbery elasticity of conduit arteries that ensures smooth distal tissue perfusion throughout the cardiac cycle[32]—excessive arterial stiffening must also be avoided given its independent contributions to risk for stroke, cognitive impairment, and dementia.[33–35] Third, the discovery that the *SOST* gene encoding sclerostin is silenced in aortic regions undergoing aneurysmal dilation[24] has profound implications with respect to arterial aging.[36] The canonical Wnt signaling cascade is upregulated in the arterial vasculature with advancing age[37]; histoanatomic resolution remains to be interrogated. The extent to which altered Wnt programming is a cause or consequence of conduit artery aging[36] has yet to be fully resolved—but the observation that regional changes occur highlights that not all segments of the arterial tree physiologically or metabolically age at the same rate.[36] Elegant genetic studies by St Hilaire et al[38] also demonstrate this point, wherein extremely precocious peripheral arterial disease of the lower extremities can be inherited and distinguished from arteriosclerosis of the aorta, carotid, and coronary arteries.

Moving forward, there are numerous, important questions that remain to be explored concerning Wnt/LRP signaling in cardiovascular health and disease. The precise cellular and molecular mechanisms of sclerostin vasculotropic actions remain to be elucidated. LRP5 and LRP6—2 best characterized targets of sclerostin action[6,7]—are selectively expressed by several relevant cell types in the vessel wall. Indeed, LRP5 was identified by Austin and coworkers[39] early on as being present in the monocyte/macrophage lineage. Others subsequently discovered the vital role for LRP5 in myeloid cell migration,[40–42] foam cell formation,[41] osteopontin and bone morphogenetic protein 2 expression,[41] and regulation of cardiopulmonary fibrosis.[43] Furthermore, the effector T cell—another important player in aortic aneurysm formation[44–46]—uses canonical Wnt/LRP5 signaling to drive transendothelial migration and upregulation of matrix metalloproteinase 9 and matrix metalloproteinase 2 expression (Figure).[47] With respect to LRP6, this past year Mani and coworkers[18] and our laboratory[15] identified LRP6 as being highly expressed in the VSM lineage, where it limits neointima formation, cardiovascular sclerosis, and aortic stiffening via reciprocal control of canonical and noncanonical Wnt signaling (Figure). As of today, we do not yet understand the integrated,

cell-type–specific contributions of LRP5 and LRP6 to the regulation of aortic structure and function. However, because (1) osteopontin is suppressed by LRP6 in the VSM lineage[15] and supported by LRP5 in the macrophage lineage,[41] (2) osteopontin deficiency increases arteriosclerotic vascular stiffness[48] and conveys resistance to angiotensin II–mediated aneurysm formation,[49] and (3) sclerostin reduces both aortic osteopontin and macrophage content while mitigating aneurysmal dilation in this study,[24] it is highly probable that some of the beneficial actions of sclerostin are mediated via leukocyte LRP5 inhibition and VSM LRP6 modulation (Figure). It would be of interest to know how sclerostin impacts T-cell recruitment in this model—and the extent to which endogenous VSM *SOST* gene activity is responsible for shaping the mural inflammatory response. Of note, the larger and related protein LRP4 also binds sclerostin[50] and present it to LRP5 and LRP6;[51] the role if any for LRP4 in arterial physiology and function is unexplored. Moreover, because LRP receptors heterodimerize in response to specific Wnt ligands,[52] it is possible that sclerostin might function as a selective band pass filter for certain ligands. The downstream Wnt/Frizzled signaling complexes modulated by sclerostin in vascular physiology are unknown, and the net impact of sclerostin on canonical versus noncanonical signaling balance in VSM is of great interest (Figure).[15,18] Whether regional differences in arterial sclerostin expression might explain the differential impact of diabetes mellitus on aneurysm risk (decreased) versus peripheral arterial disease risk (increased) is also worthy of consideration.[53] Final, given bone's role as an endocrine organ,[54] a contribution of osteocyte-derived sclerostin to aortic remodeling remains a formal possibility.[55] All in all, the osteotropic Wnt/LRP signaling cascade continues to emerge as fundamentally important in arterial structure, function, and physiology. A better understanding of these vasculotropic actions holds great promise for the development of new strategies to improve cardiovascular health in our increasingly aged and dysmetabolic population.

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