Thar’s Tendons in Them Thar Valves!

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In this issue of Circulation Research, Levay et al report an in vivo requirement for scleraxis (scx) during murine valvulogenesis and demonstrate its role in cell lineage differentiation and matrix distribution in remodeling valve structures. The scleraxis (Scx) gene encodes a basic helix–loop–helix transcription factor that is expressed in the progenitors and cells of all tendon tissues. Recent studies have identified the specific regulatory pathway in which fibroblast growth factor activates the mitogen-activated protein kinase (extracellular signal-regulated kinase 1/2) signaling cascade to promote expression of scx, which, in turn, induces expression of tenascin as being shared by developing valves and limb buds. In initial studies in chick, Lincoln et al found a restricted pattern of scx expression, suggesting that atrioventricular (AV) valve precursor cells diversify into leaflets (cartilage-like) or chordae tendineae (tendon-like) to produce both a leaflet and supporting apparatus, as opposed to semilunar valve precursor cells that exhibit both cartilage- and tendon-like characteristics and diversify into cusps with an internal supporting apparatus. However, in the present study, Lincoln and colleagues identified high levels of scx expression in remodeling AV and semilunar valve structures from embryonic day (E)15.5 through postnatal stages; the biological significance of this apparent difference between chick and mouse is not known.

Levay et al determined the in vivo function of scx using null mice (scx−/−). Scx expression is not detected during early stages of valve development, and extracellular matrix (ECM) deposition appears normal in scx−/− mice up to E16.5, suggesting that scx is not required during cushion formation. However, by E17.5, scx−/− mice display significantly thickened valve structures, and valves from mutant mice show alterations in valve precursor cell differentiation and matrix organization. This is indicated by decreased expression of the tendon-related collagen type XIV and increased expression of cartilage-associated genes including sox9, as well as persistent expression of mesenchyme cell markers including msx1 and snai1. In addition, ultrastructure analysis reveals disarray of ECM and collagen fiber organization within the valve leaflets of the scx mutants. Thickened valve structures and increased expression of matrix remodeling genes characteristic of human heart valve disease are observed in juvenile scx−/− mice. Thus, mice null for scx exhibit pathological criteria common to diseased valves from embryonic stages and, by juvenile stages, express high levels of fibrosis-associated genes and matrix proteases previously observed in human valve pathology. Taken together, these findings add to increasing evidence that valve disease associated with alterations in ECM has its origins in valve development.

The mature AV and semilunar valves are trilaminar structures composed of ECM, valvular interstitial cells (VICs), and overlying endothelial cells. The ECM is composed of 3 highly organized overlying layers with distinct mechanical properties arranged in orientation to blood flow in the AV and semilunar valves. The primary components of these layers are collagens, proteoglycans, and elastin. A hallmark of the diseased valve is the loss of the trilaminar matrix structure. Furthermore, studies of explanted, diseased valves from patients have shown cusp and leaflet thickening, collagen fiber disorganization, increased VIC density, and calcification. Although these changes are frequently thought of as resulting from degenerative or atherosclerotic processes, the observation that the diseased aortic valve is usually congenitally malformed (bicuspid) also provides support for the idea that most cases of valve disease have origins in valve development. Furthermore, similar histopathologic findings have been identified in explanted bicuspid aortic valves of pediatric patients who do not have common valve disease comorbidities such as aging, hypertension, and hypercholesterolemia seen in the adult population.

Initiation of heart valve development is signaled by formation of the endocardial cushions in the AV canal and outflow tract. Cushions form as a result of endothelial-tomesenchymal transformation (EMT) induced by myocardial-derived bone morphogenetic protein signals (Early, Figure). Two experimental approaches have been the standard tools of developmental valvologists for study of early valve formation: the explanted cushion culture system and single gene disruption studies in mice. Both techniques have contributed greatly to promoting our understanding of EMT and the molecular and cellular regulation of endocardial cushion formation. These studies of the early stages of valve development have converged on a number of signaling pathways, including Wnt/β-catenin, Notch, bone morphogenetic protein/transforming growth factor-β, vascular endothelial growth factor, NFATc1, ErbB, and NF1/Ras, that regulate endothelial proliferation and differentiation in developing valves. However, because the cushion explant studies are limited to the earliest stages of valve development and because many of the murine genetic manipulations result in embryonic lethality, these approaches have been of limited help in understanding how the highly organized ECM of the mature valve subsequently develops during post EMT remodel-
ECM organization and VIC compartmentalization, hallmarks of the mature valve structure, begin during late embryonic cusp elongation and remodeling and continue into postnatal life (Late, Figure). Cell proliferation, which is substantial during early valve development, is markedly reduced during cusp remodeling, suggesting that late embryonic and postnatal valve growth is a function of increased ECM production. The coordination of ECM organization and VIC compartmentalization during valvulogenesis suggests that developmental mechanisms regulate both processes. In diseased bicuspid aortic valves from pediatric patients, excessive ECM production, ECM disorganization, and VIC disarray without calcification are observed (Disease, Figure). The pathogenesis of aortic valve disease may be the result of dysregulation of the molecular hierarchies that control late valve development, ultimately leading to increased cusp thickness and ECM disorganization.

Human valve disease, particularly aortic valve disease, is an important clinical problem, and aortic valve replacement is the second most common cardiac operation in industrialized countries. The availability of a viable model that recapitulates the human phenotype would be a great asset to the study of valve disease. Understanding the developmental and genetic basis of valve disease promises improved assessment of valve disease risk and should provide insight into novel therapeutic strategies. The early lethality of mice lacking scx precluded the assessment of its role later during postnatal life.

Therefore, more targeted approaches will be necessary to determine all of the requirements for scx in later stages of valve development and maintenance. Work from the laboratory of Lincoln and other investigators have provided new insights into the valve remodeling in the early development and maturation of cardiac valves. These studies form the foundation for future work in the assessment of the contributions of this transcription factor to adult heart valve function and disease mechanisms.

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References

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