Calcific aortic valve sclerosis (CAVS) causes profound morbidity in our increasingly dysmetabolic and aging citizenry. Two to five percent of our elderly population will require aortic valve replacement surgery to mitigate risk of death due to severe CAVS. Once considered only a passive process of dead and dying cells, arteriosclerotic calcification, including CAVS, has emerged as an actively regulated form of mineralized tissue metabolism. Preclinical and epidemiological studies reveal that aging; tobacco use; renal failure; bicuspid aortic valve; and the features of metabolic syndrome, hypertension, worsening glycemic control, hypertriglyceridemia, low high-density lipoprotein cholesterol, and obesity; are cumulative risk factors for arteriosclerotic valve calcification. Although hypercholesterolemia certainly contributes to risk of arteriosclerotic disease, targeting cholesterol via lipid-lowering statin therapy is insufficient to fully mitigate disease progression. Seminal histological studies by Otto et al indicate that although early valve lesions do exhibit intra- and extracellular lipid accumulation with inflammation, features of active matrix remodeling are present as well, including disruption of the elastic lamina with lamina fibroa protein accumulation and microcalcification. With advanced disease, remodeling woven bone can be seen in ca. 13% of specimens although the molecular fingerprints of active osteogenesis are uniformly present even when amorphous calcium phosphate deposits predominate. Currently no medical therapies exist for preventing or treating CAVS, and our capacity to identify those at greatest risk for clinical progression is limited. In the Japanese Aortic Stenosis Study (JASS), although warfarin use portended worsening disease, treatment of hypertension with angiotensin receptor blockade was associated with attenuated risk of CAVS progression. Interestingly, emerging data suggest that angiotensin receptor blockades exert beneficial actions in cardiac valve biology in part via inhibition of transforming growth factor (TGF)-β1 signaling cascades.

In culture, TGF-β1 clearly promotes aortic valve interstitial cell calcification, with responses dependent on the stiffness of the extracellular matrix. However, the contributions of TGF-β1 signaling to CAVS have not been fully examined in vivo nor have the precise cellular source of TGF-β1 important to valve pathobiology been established. In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Wang et al begin to address these important questions. Implementing the Reversa low-density lipoprotein receptor−/− mouse model of vascular disease, first validated in CAVS by Miller et al, the authors demonstrate that diet-induced hypercholesterolemia results in valve thickening, worsening aortic valve stenosis, increased wall shear stress (WSS; determined by echocardiographic measurement of valve leaflet separation and Doppler velocimetry), and elevated circulating TGF-β1 levels for a 12-month period. Reversing hypercholesterolemia after 6 months of dyslipidemia attenuates the severity of CAVS observed at 12 months, reflected in reductions in the rate of aortic stenosis and concomitant increases in transvalvular velocity, WSS, and plasma TGF-β1. In those animals with progressive valvular disease, a modest but significant positive relationship was observed between WSS and total circulating TGF-β1 levels, with a strong trend for correlation exhibited at 12 months between circulating TGF-β1 levels and the extent of aortic valve fibrosis by histological scoring (r=0.78, P=0.08). More importantly, surgical introduction of an ascending aortic constriction (AAC) in wild-type mice, an experimental mimetic of aortic valve stenosis, also increased WSS and circulating TGF-β1 levels in the absence of hypercholesterolemia. The source of TGF-β1 was firmly established to be the platelet in the AAC model; conditional deletion of TGF-β1 in the megakaryocyte lineage (PF4-Cre;TGF-β1(fl/fl) mice) markedly reduced time-dependent increases in total plasma TGF-β1 following AAC. Thus, the relationship observed between total plasma TGF-β1 levels and WSS in wild-type mice was no longer significant in PF4-Cre;TGF-β1(fl/fl) mice. Importantly, bioactive platelet-derived TGF-β1 was responsible for driving Smad2/3 and ERK phosphorylation in response to AAC in both circulating leukocytes and mesenchymal cells of the ascending aorta, and these same signaling responses were phenocopied by diet-induced aortic valve disease, WSS, and plasma TGF-β1 upregulation in the Reversa mouse model. Ex vivo, stirring-induced shear of whole blood was shown to increase leukocyte Smad2/3 and ERK phosphorylation via mechanisms inhibited by neutralizing TGF-β1 antibody. Thus, platelet-derived TGF-β1 is released and signals in response to elevated aortic shear stress, activating prosclerotic signaling cascades in the arterial vasculature.

Why is this article so intriguing? First, the storage and release of platelet-derived TGF-β1 has significant implications vis-à-vis the emerging bone–vascular axis and the endocrine regulation of arteriosclerosis. By mobilizing and recruiting mesenchymal progenitors capable of directing robust collagen deposition and matrix mineralization, TGF-β1 signaling coordinates normal bone turnover and fracture repair.
recently identified that with tissue injury, increases in circulating TGF-β mobilize and recruit bone marrow–derived mesenchymal stem cells (Sca1+CD29+CD11B–CD45−) to sites of vascular remodeling, including mechanically injured neointima formation. Therefore, by analogy, increases in WSS that promote platelet–derived TGF-β release are posited to increase circulating levels of mesenchymal stem cells capable of contributing to prosclerotic vascular responses including CAVS. Moving forward, it will be important to examine whether circulating mesenchymal stem cells are increased in response to AAC and are recruited only to that site of vascular injury or potentially populate other vascular venues with disturbed flow and dependent on platelet-derived TGF-β1. Second, this study once again points to the limitations of targeting only cholesterol in CAVS, even though lipoprotein metabolism is one critically important component of disease initiation.1 Once valve hemodynamics are perturbed in CAVS, a vicious feed-forward cycle arising from increased WSS may continue to condition hemodynamics are perturbed in CA VS, a vicious feed-forward cycle arising from increased WSS may continue to condition.

**Figure.** Shear-dependent transforming growth factor (TGF)-β release and the pathobiology of calcific aortic valve sclerosis (CAVS). In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Wang et al10 demonstrate that shear-induced release of TGF-β from platelet α granules activates prosclerotic canonical and noncanonical signals that can drive systemic arteriosclerotic disease. This portends a feed-forward vicious cycle in CAVS. Thus, in addition to providing potential biomarkers for those individuals at greatest risk for clinical progression, platelet–derived factors such as TGF-β afford novel therapeutic targets for medical treatment of CAVS. See text for details. Dkk1 indicates Dickkopf-1; PDGF, platelet-derived growth factor; and MSCs, mesenchymal stem cells.

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Disclosures

None.

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The Platelet: Sensing Shear and the Endocrine Regulation of Cardiovascular Sclerosis

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