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Review

Mechanisms of aortic stenosis

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ABSTRACT

The pathobiology of degenerative aortic valve stenosis (AS) is complex and involves multiple features such as fibrosis, inflammation, oxidative stress, angiogenesis, hemorrhage, and osteogenic differentiation. We summarize the mechanism of valve calcification and angiogenesis which is necessary for calcifying processes. A promising therapeutic target is nuclear factor (NF)-κB which activates bone morphogenetic protein (BMP)2 via interleukin-6. BMP2 activates Wnt signaling via msh homeobox 2 causing osteogenic differentiation. BMP2 also activates Runx2/Cbfa1 which is an osteoblast-specific transcription factor. Signals in the hypoxia-inducible factor-2 axis activated by the NF-κB signaling pathway also play important role in calcifying processes including angiogenesis. The reason why angiogenesis takes place in avascular valves is still unknown, but it is likely angiogenesis and angiogenesis-related hemorrhage play critical roles in the progression of AS.

Contents

Introduction

Degenerative aortic valve stenosis (AS) is common among the elderly and the most frequent cause of heart valve replacement in industrialized countries [1–3]. The incidence of degenerative AS has been increasing, and AS is associated with high morbidity and mortality [4,5]. Recently, the management of degenerative AS has changed dramatically. Transcatheter valve therapy has emerged as an alternative to surgical aortic valve replacement (AVR). On the

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other hand, no pharmacotherapy has proved to inhibit the progression of AS. Thus, surgical or transcatheter AVR is still the only effective treatment of AS [6,7]. It is necessary to know the mechanism of AS progression to prove new pharmacotherapy for AS. In this review, we discuss the mechanism of calcific AS.

Epidemiology

Degenerative disease is the most common etiology of AS, although AS can also be caused by congenital valve defects, systemic inflammatory diseases, endocarditis, and many other conditions. Bicuspid aortic valve is thought to be the most common congenital valve defect causing AS, and the prevalence of bicuspid aortic valve is about 0.5–1% in children. It is also known that patients with bicuspid valve develop degenerative AS earlier than those with tricuspid AS [8–11]. The most frequent systemic inflammatory disease causing AS is rheumatic heart disease. However, there has been a significant decrease in the prevalence of rheumatic heart disease. On the other hand, there has been a significant increase in the prevalence of degenerative AS in elderly people [12–14]. The overall incidence of degenerative AS is expected to increase over the next decades because of population aging.

Treatment

In cohort studies, the progression of AS was associated with many traditional atherosclerotic risk factors [15–20]. In histological studies, stenotic aortic valve and atherosclerotic arterial wall share several common features, including lipid accumulation, calcification, infiltration of inflammatory cells, and neoangiogenesis [21–26]. Although there are some types of pharmacotherapy which prove to inhibit the progression of atherosclerotic disease, no pharmacotherapy has been proved to inhibit the progression of AS. According to the results of clinical trials, the effects of statins and cholesterol absorption inhibitor have been examined but gave negative results in preventing the progression of AS [27–29]. Thus, the only treatment for patients with severe AS is AVR either surgically or percutaneously.

The first successful surgical AVR was performed in 1960 [30]. Over the past half century, the mortality associated with AVR has decreased dramatically because of marked progress in operative techniques and valve design [31,32]. However, increasing age and comorbidities increase operative mortality after AVR [33,34]. In fact, approximately one-third of patients with indications for AVR are not treated owing to age, multiple comorbidities, and other factors [35,36]. Transcatheter aortic valve replacement (TAVR) is a procedure in which a bioprosthetic valve is inserted through a catheter and implanted within the diseased native aortic valve. Since 2002, when the procedure was first performed, there has been a rapid growth in its use throughout the world for the treatment of severe AS in patients at a high risk of operative mortality. For patients who are not candidates for surgical AVR, TAVR has been a transformative innovation providing a life-saving treatment [37–42]. The PARTNER Trial clearly showed the superiority of TAVR compared to standard therapy [37]. Other randomized trials of balloon-expandable and self-expanding valves have also demonstrated superiority of TAVR compared to surgery in patients at high risk for AVR [38,39].

Mechanisms

Fibro-calcific remodeling

The aortic valve is typically composed of three leaflets which are constructed mainly from valve interstitial cells (VICs), smooth muscle cells (SMCs), and endothelial cells (ECs). ECs cover the aortic and ventricular surface and provide an interface between blood and valve [43]. SMCs reside only at the base of the ventricularis. VICs are the predominant population of cells in the aortic valves, and are found in three layers of the valve—the fibrosa, the spongiosa, and the ventricularis [44]. These three layers have different matrix compositions: lamina ventricularis is richer in elastin, lamina spongiosa in proteoglycans, and lamina fibrosa in collagen. Fibrosis is one of the most important features for AS progression. Fibrosis is defined by the overgrowth, hardening, and scarring of various tissues and is attributed to excess deposition of extracellular matrix components including collagen. Collagen produced by VICs serves as a scaffold, but excess production and disorganization of collagen is an important feature of AS. A potentially involved peptide in the pathogenesis of aortic valve fibrosis is transforming growth factor-β (TGF-β). It stimulates the formation and deposition of extracellular matrix [45]. The level of TGF-β is high in the fibrotic organs, and tissue specific overexpression of TGF-β in transgenic mice results in fibrosis and deposition of extracellular matrix in those organs [46,47]. The presence of TGF-β has been shown in the stenotic aortic valves, and expression of TGF-β in the stenotic aortic valves has suggested that TGF-β plays an important role in progressive deposition of matrix (Fig. 1). Another feature involved in the pathogenesis of aortic valve fibrosis is an increased production of extracellular matrix including tenascin-C and proteoglycans (Fig. 1). Tenascin-C is a modular and multifunctional hexameric extracellular matrix glycoprotein implicated in cell proliferation and differentiation [48]. Proteoglycans are overexpressed in stenotic aortic valves, and biglycan, a proteoglycan, has been thought to induce the expression of osteogenic factors in VICs.

Osteogenic differentiation

Osteogenic differentiation of VICs is likely to be implicated in aortic valve calcification. Previous studies have demonstrated the presence of specific bone cell phenotypes in calcifying valves, which in turn suggested that VICs might have the potential to differentiate into calcifying phenotypes. Possible triggers for VICs differentiation include hemodynamic shear stress, reactive oxygen species, inflammatory cytokines, and acellular environment caused by other diseases such as metabolic syndrome and chronic inflammatory disease [49–51]. Cartilage is known to have potential to differentiate in to calcifying phenotypes, and shares some common features with cardiac valves. Chondromodulin-1, an anti-angiogenic factor, maintains cartilage and cardiac valves in an avascular state. The loss of Chm-I leads to neovascularization, as well as an unusual calcification in the matrix of cardiac valves [52,53]. These findings suggest that the endochondral ossification pathway might be involved in the process of aortic valve calcification. A previous study has demonstrated that transcriptional regulation of endochondral ossification by hypoxia-inducible factor (HIF)-2 alpha is necessary for skeletal growth and osteoarthritis development. This study also has demonstrated nuclear factor (NF)-κB is a potent inducer of HIF-2α expression [54]. In human stenotic aortic valves, we also have demonstrated that signals in the HIF-2 axis from the NF-κB signaling pathway, including vascular endothelial growth factor (VEGF) and collagen X which are necessary for a calcifying pathway, were expressed in calcified aortic valves (Fig. 2). This signaling pathway might play an important role in the pathophysiology of AS.

Lipids

Histological studies have demonstrated lipid accumulation in calcifying aortic valve, suggesting that lipid accumulation could

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