Trends in Cardiovascular Medicine 29 (2019) 69–70

Contents lists available at ScienceDirect

Trends in Cardiovascular Medicine

journal homepage: www.elsevier.com/locate/tcm

Editorial commentary: Another notch for bicuspid aortic valve aortopathy?☆,☆☆

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ARTICLE INFO

Keywords:
NOTCH1
Bicuspid aortic valves
Smooth muscle cell
Apoptosis

Bicuspid aortic valve (BAV) is the most common (valvular) congenital heart defect in the general population. Apart from the enhanced male prevalence, BAV is highly associated with ethnicity (white) [1]. It is anatomically defined as an aortic valve that has two leaflets instead of the normal three. The most common BAV variant is due to fusion of the left and right coronary cusps (70–80%), followed by right and noncoronary cusps (20–30%), and lastly the left and noncoronary cusp fusion pattern (1%) [2]. It is thought that BAV results from abnormal fusion during embryonic development [3–4]. In adulthood, BAV individuals are mostly affected by valvular problems, although with high variability. It is associated with serious long term health risks, such as valvular dysfunction, increased risk of infective endocarditis, and predisposition to aortic dilatation, dissection, and distant aneurysm formation [1–5]. Indeed, the risk of aortic dissection in individuals with BAV is 9x higher than that of the general population [6].

While the majority of individuals with BAV represent sporadic cases, a significant proportion have a familial history of left-sided congenital heart malformations [5]. Moreover, BAV has a relatively high heritability estimate [7]. Nonetheless, while there is evidence for an autosomal dominant inheritance pattern with incomplete penetrance and variable expressivity, it is such a heterogeneous disease [8], that it is likely that various genetic models are at play. Currently, in humans there are approximately 11 genes that are known to contribute to isolated and syndromic BAV; namely *TGFBR2, TGFB2, FBN1, ACTA2, KCNJ2, NKX2-5, NOTCH1* and *GATA5* [1–9]. More recently, it was found that mutations in *GATA4* and *SMAD6* also lead to BAV [10,11]. These genes can broadly be classified into transcription factors known to be involved in cardiovascular development (*NOTCH1, GATA4*, GATA5, *NKX2-5*) or those involved in TGFbeta signaling (FBN1, TGFBR2, TGFB2, SMAD6), which is essential to cardiovascular development. Interestingly, the TGF-beta pathway genes, and the *GATA4, GATA5* and *NOTCH1* genes are involved in endothelial to mesenchymal transition, referred to as EndoMT, a process that is critical for the formation of cardiac valves [12].

One of the earliest, and perhaps most important gene, linked to BAV development is *NOTCH1* [13], an important regulator of signaling and transcription. In humans, *NOTCH1* mutations/variations are known to cause BAV and other cardiovascular defects such as aneurysms [13,14]. Furthermore, pluripotent stem cells with a *NOTCH1* mutation show impaired differentiation into smooth muscle cells and endothelial cells [15], the main aortic cell types. This finding underlines that improper maturation of heart valves and aorta, may cause many of the cardiovascular abnormalities in BAV and related aortopathy. Remarkably, endothelial-specific haploinsufficiency of *NOTCH1* already causes abnormal outflow tract and valve development [16]. Similarly, in humans, NOTCH1-dependent EndoMT potential is attenuated in endothelial cells isolated from patients with aortic aneurysm and BAV [17]. The importance of endothelial cells in BAV-related aortopathy was recently thoroughly reviewed [9].

Regarding smooth muscle cells (SMCs), it has been described that BAV aortic aneurysm tissue shows signs of improper SMC maturation [18]. Interestingly, there is an intrinsic role for NOTCH1 in SMC phenotype and behavior [19]. While NOTCH1 signaling induces EndoMT in endothelial cells, it also regulates the contractile phenotype in SMCs [20]. Indeed, Notch1 haploinsufficiency specifically in SMCs results in an increased contractile phenotype,

☆ Conflict of interest: We have no conflict of interest to declare.

☆☆ **Acknowledgement:** A.V. Postma is supported by CVON2014-18 "CONCOR-genes".

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https://doi.org/10.1016/j.tcm.2018.06.014

with reduced repair capacity in an aneurysm model in mice [21]. Moreover, *NOTCH1* mutations lead to valvular calcification [22] and enhanced arterial microcalcification has been observed in dilated ascending aortas of BAV patients [23], which is thought to cause additional SMC damage. Taken together, there is evidence of decreased repair and enhanced cell death due to altered NOTCH signaling in SMCs. This relatively novel role of NOTCH signaling is highlighted in an interesting review by Harrison et al. [24] in this issue of Trends in Cardiovascular Medicine. They argue that NOTCH1 signaling is necessary as part of a protective process that promotes vascular SMC viability and aortic repair. Notwithstanding the myriad of functions that have been demonstrated for NOTCH1 signaling in BAV pathology, it seems worthwhile to investigate this specific aspect of NOTCH signaling in SMC function further, for instance in the ascending aorta of BAV patients, or by functionally studying this hypothesis in model systems. This new role for NOTCH1 in SMC death could open novel roads to treatment of the degenerative process in BAV-related aortopathy.

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