Aortic valve disease

Exploring methods, models, and mechanisms

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Chapter 12.

Summary in English

Calcific aortic valve disease (CAVD) is the leading cause of aortic stenosis (AS) in the western world. CAVD is characterized by fibrotic and calcific thickening and stiffening of the aortic valve leaflets. It is primarily a disease of the elderly and its prevalence is projected to triple within the next forty years. At this time, there is no non-invasive therapy to treat AS, and available valve prostheses for aortic valve replacement are significantly flawed. The main purpose of this thesis was to study (1) the pathogenesis of aortic valve disease, and to (2) improve upon current models for *in vitro* research and tissue engineering alternatives.

Chapter 1 is a general introduction that describes the rationale for this thesis and underlines the complexity of CAVD pathogenesis and CAVD research. The aortic valve form and function are summarized and the intricate relationship between the valvular cells and its microenvironment are described. Aortic valve disease is multifactorial, and for a successful step to the clinic, the collaborative effort of multidisciplinary researchers is needed. This chapter ends with the thesis outline.

Chapter 2 studied the effect of altered hemodynamics on aortic valve homeostasis. We characterized aortic valves of patients supported by continuous-flow left ventricular assist devices (LVADs). LVAD implantation severely alters blood flow through the aortic valve and leads to the rapid development of valve pathologies. Continuous closure and coaptation resulted in commissural fusion, rendering the valve dysfunctional when the goal of LVAD-support is bridge-to-recovery. Altered hemodynamics and mechanical stresses additionally induced valvular interstitial cell (VIC) activation and an M2 macrophage response in the ventricularis layer, which does not resemble the typical M1 macrophage-associated sclerotic lesions underlying CAVD.

Chapter 3 aimed at analyzing the effect of altered blood flow on aortic valve microRNA (miRNA) expression. Microarray identified a number of differentially expressed miRNAs that are known for their contribution to cardiovascular biology. Validation of selected miRNAs confirmed a significant upregulation of miR-143-3p after LVAD-support. We were able to localize expression of miR-143-3p to activated myofibroblast-like VICs using dual *in situ* hybridization/IHC. This may point to a role of miR-143-3p in phenotypic activation of VICs during altered hemodynamics, similarly to its role in vascular smooth muscle cells. In addition, this miRNA has recently been linked to CAVD, justifying further investigation.

Chapter 4 describes histological changes associated with radiation-associated valve disease, a serious complication after thoracic radiotherapy in breast cancer and malignant lymphoma patients. Thoracic irradiation greatly increases the risk of developing aortic valve disease two to three decades later. Our findings suggest that high dose radiation at young age, as observed in lymphoma patients, results in premature fibrotic AS and cell loss. The response to radiation is possibly dose-dependent, as aortic valves of irradiated breast cancer patients, which receive less radiation, are more typical to age related CAVD. We underline the importance of field reduction and lowering

radiation dose to further decrease cardiac exposure and premature RAVD.

Chapter 5 presents a rare necropsy finding of a quadricuspid aortic valve. Congenital malformations of the aortic valve are commonly related to absence or presence of extra leaflets. Bicuspid valves are relatively common with an estimated prevalence of 1-2%. Much rarer are unicuspid and quadricuspid valves, which affect roughly one in 5000. Typically, quadricuspid aortic valve is detected in young-to middle aged adults as pure aortic regurgitation, as this patient had shown in retrospect.

Chapter 6 gives an overview of approaches and techniques used to culture VICs *in vitro*. To yield biologically relevant results, cell culture models should mimic the highly dynamic native aortic valve, because the microenvironment is linked to cellular phenotype and response to stimuli. We show that major steps can still be made in terms of standardization and implementation of 3D, co-culture and a dynamic environment to improve translation of *in vitro* findings.

In **Chapter 7**, we tested a novel microwell platform for 3D culture of aortic valve cells. Under conventional, two-dimensional culture conditions, VICs undergo spontaneous activation similar to pathological differentiation, which intrinsically limits the use of these models to study CAVD. We propose a novel matrix-free 3D culture model that is suitable for high-content screening. Using our platform, VICs rapidly formed aggregates and showed excellent survival for up to 21 days. VICs maintained a quiescent phenotype similar to healthy native heart valves. Furthermore, we showed that co-culture with valvular endothelial cells is possible. The ultimate goal is to create a platform able to simulate the native physiological environment of VICs that can be used for screening and identification of novel compounds directed against CAVD.

With the lack of pharmaceutical therapies for CAVD and the limitations of currently available valve prosthesis, it is sensible to investigate alternative materials for aortic valve replacement. In **chapter 8,** we implanted decellularized porcine small intestinal submucosa extracellular matrix (pSIS-ECM) in sheep to evaluate its use as right-sided heart valved conduit in a xenogeneic animal model. This particular pSIS-ECM is commercially available as CorMatrix® and stands out because it is not treated with glutaraldehyde, which should prevent premature calcification. Improper masking of antigens and decellularization of xenogeneic material however may elicit an adverse host immune response. This possibly explains the high rate of graft dysfunction, intense inflammation, and lack of remodeling observed in our implants. CorMatrix is used off-label in heart valve surgery and an increasing number of clinical studies have shown functional failure at short- and mid-term FU. We therefore believe that the use of CorMatrix® pSIS-ECM in heart valve surgery should be considered with great care.

Chapter 9 describes a case of carcinoid heart disease that affected both the native tricuspid valve and its replacing bioprosthesis. Serotonin released from the metastasized neuroendocrine tumor led to thickening and retraction of the native tricuspid valve,

and to formation of thick, plaque-like deposits of fibrous ground substance on the ventricular surface of the bioprosthesis. Although rare, this case emphasizes the importance of tumor management and closely monitoring valve function.

Chapter 10 illustrates the importance of an autopsy to determine the cause of death after transcatheter aortic valve implantation (TAVI). At the same time, we show the vulnerability to rupture of the heavily calcified left ventricular outflow tract and aortic root, or 'device landing zone', during TAVI.

The answer is out there, Neo, and it's looking for you,
and it will find you if you want it to.'

- Trinity, The Matrix, 1999