Cardiovascular Pathology 25 (2016) 341–352

Contents lists available at ScienceDirect

Cardiovascular Pathology

Review Article

Heart valve health, disease, replacement, and repair: a 25-year cardiovascular pathology perspective

Frederick J. Schoen [a,b,*], Avrum I. Gotlieb [c,d,e,1]

[a] Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, 75 Francis Street, Boston, MA 02115
[b] Pathology and Health Sciences and Technology (HST), Harvard Medical School, 75 Francis Street, Boston, MA 02115
[c] Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Ontario M5S 1A8, Canada
[d] Faculty of Medicine, University of Toronto, Toronto, Ontario M5S 1A8, Canada
[e] Laboratory Medicine Program, University Health Network, Medical Sciences Building, 1 King's College Circle, Rm. 6275A, Toronto, Ontario M5S 1A8, Canada

ARTICLE INFO

Article history:
Received 31 March 2016
Received in revised form 4 May 2016
Accepted 5 May 2016

Keywords:
Valve interstitial cell
Valve endocardial cell
Fibrosis
Calcification
Extracellular matrix
Bioprosthesis
Mechanical valve
Tissue engineering

ABSTRACT

The past several decades have witnessed major advances in the understanding of the structure, function, and biology of native valves and the pathobiology and clinical management of valvular heart disease. These improvements have enabled earlier and more precise diagnosis, assessment of the proper timing of surgical and interventional procedures, improved prosthetic and biologic valve replacements and repairs, recognition of postoperative complications and their management, and the introduction of minimally invasive approaches that have enabled definitive and durable treatment for patients who were previously considered inoperable. This review summarizes the current state of our understanding of the mechanisms of heart valve health and disease arrived at through innovative research on the cell and molecular biology of valves, clinical and pathological features of the most frequent intrinsic structural diseases that affect the valves, and the status and pathological considerations in the technological advances in valvular surgery and interventions. The contributions of many cardiovascular pathologists and other scientists, engineers, and clinicians are emphasized, and potentially fruitful areas for research are highlighted.

Valvular heart disease constitutes a significant global disease burden [1]. Mechanisms of disease are poorly understood and effective diagnostic tools usually require the presence of advanced disease with clinical manifestations. Moreover, therapies generally rely on surgery, including valve replacement or valve repair, both of which continue to have limitations. Nevertheless, the latter half of the 20th century and particularly the past 25 years have witnessed major advances in the understanding of the structure, function, and biology of native valves and the pathobiology and clinical management of valvular heart disease [2]. These improvements have enabled earlier and more precise diagnosis, assessment of the proper timing of surgical and interventional procedures, improved prosthetic and biologic valve replacements and repairs, recognition of postoperative complications and their management, and the introduction of minimally invasive approaches that have enabled definitive and durable treatment for patients who were previously considered inoperable. Recognition by the Albert Lasker Clinical Research Award in 2007 of Drs. Albert Starr and Alain Carpentier, surgeons who revolutionized treatment of valvular heart disease through the development and demonstration of the feasibility of implantation of mechanical and tissue valve substitutes, respectively, highlighted the impact of this progress on patients [3].

This review summarizes the current state of our understanding of the mechanisms of heart valve health and disease arrived at through innovative research on the cell and molecular biology of valves, clinical and pathological features of the most frequent intrinsic structural diseases that affect the valves, and the status of technological advances in valvular surgery and interventions. We attempt to balance scope and focus on topics of current broad research interest and translational innovation to pathologists. We also hope to emphasize the contributions of many cardiovascular pathologists and other scientists, engineers, and clinicians over the past 25 years and suggest areas for research that we believe will lead to significant progress. We recognize the role of the Society for Cardiovascular Pathology and its journal, *Cardiovascular Pathology*, in providing an informed forum for the publication and dissemination of many significant new developments and reviews in this field.

There was no funding received for preparation of this manuscript.

* Corresponding author at: Department of Pathology, Brigham and Women's Hospital; Pathology and Health Sciences and Technology (HST), Harvard Medical School, 75 Francis Street, Boston, MA 02115. Tel.: +1-617-732-5709; fax: +1-617-232-9820.
E-mail addresses: fschoen@partners.org (F.J. Schoen), avrum.gotlieb@utoronto.ca (A.I. Gotlieb).
[1] Tel.: +1,416,978 2557; fax: +1,416,978 7361.

http://dx.doi.org/10.1016/j.carpath.2016.05.002
1054-8807/

1. Structure, biology, and pathobiology of native and diseased heart valves

1.1. Heart valve structure and functional biomechanics

Multidisciplinary studies have enhanced our understanding of the functional anatomy, pathobiology, and biomechanical properties of heart valves [4–9]. Only several decades ago, the heart valves were viewed as structurally undistinguished tissues which react passively to mechanical forces during the cardiac cycle. We now recognize that valve tissue is highly dynamic in time and space, and composed of architecturally and functionally organized, mutually interacting, and biomechanically responsive extracellular matrix (ECM) and valve cells, which actively regulate valve structure and behavior in both health and disease states.

Two types of cells predominate in the cardiac valves: a confluent surface monolayer of valve endocardial cells (VECs), and mesenchymal cells deep to the endocardium called *valve interstitial cells* (VICs). VICs are embedded in ECM which they secrete and which in turn plays a role in regulating cellular function. The valvular cells and ECM of the aortic valve are distributed in three histologically and mechanically distinct layers: the fibrosa at the outflow (aortic) side, the ventricularis on the inflow (ventricular) side, and the spongiosa in the middle [4,5,8,10]. The fibrosa is rich in densely packed collagen fibers, largely oriented in the circumferential direction of the cusp; the spongiosa is composed mainly of glycosaminoglycans (GAGs) and proteoglycans; and the ventricularis contains prominent elastin, mainly oriented in the radial direction. The dense collagen of the fibrosa provides strength when the valve is shut; the spongiosa with its loose matrix of glycoproteins provides a cushion and a lubricating layer for rapid ECM reorganization when the valve opens and shuts; and the ventricularis provides elasticity through cyclical stretching and contraction of elastin. The valvular microstructure is highly dynamic throughout the cardiac cycle. Since individual collagen fibers are incompressible, cuspal shape changes throughout the cardiac cycle are accommodated by extension and restoration of collagen fibril crimping (i.e., pleating) and changes in orientation. In diastole, the crimp of the fibrosa collagen fibers is flattened, and the fibers align, thereby locking the structure with the cusps apposed over a modest area of contact to avoid regurgitation; simultaneously, elastin in the ventricularis is stretched. In systole, when the cusps open, the elastin fibers contract (i.e., return to their resting state), and the collagen fibers in the fibrosa both restore their crimp and reduce their alignment (i.e., become more isotropic in the plane of the cusp). Aortic valve cusps have approximately 30% greater area in diastole than systole [11]. During fetal development and maturation, human valves have no clearly defined layers through approximately the second trimester; the trilaminar architectural pattern emerges in a rudimentary fashion approximately during the third trimester and only fully develops after birth [12].

1.2. The cellular basis of valve development, postnatal evolution, and disease

Studies of human tissue and in vitro and in vivo models have led to transformative concepts of the cell and molecular biology of developing, normal and diseased adult heart valves [6,7,9–11,13–16]. These principles are thought to apply generally to the cells and ECM of all four valves.

The heart valves arise from mesenchymal outgrowths present in the heart tube following heart looping. At this time the endocardium is separated from the heart muscle by an ECM called *cardiac jelly*. The endocardial cells lining the surface of the tube at the outflow tract and atrioventricular canal become activated and express special properties that regulate their invasion into the cardiac jelly through a process called *endothelial (*or *endocardial) to mesenchymal transformation* (EMT) as the VECs transform into VICs [4] EMT is characterized by complex interactions between VECs and VICs involving key growth factor and transcription factor molecules, including bone morphogenetic protein 2 (BMP2), transforming growth factor-beta (TGFβ), fibroblast growth factor-beta, Notch transcription factors, and Wnt/β-catenin [17–22].

The mesenchymal cells of the endocardial cushions are highly proliferative and express Msx and Twist1 transcription factors which are found in various mesenchymal progenitor populations of several organ systems [23]. Twist1, along with Tbx20, promotes cell proliferation, migration, and primitive ECM gene expression in the endocardial cushions [24]. The transition from endocardial cushion to remodeling valve requires the transcription factor NFATc1, which promotes the expression of the ECM-remodeling gene *cathepsin K* in VECs [25,26]. BMP2 signaling activates the Sox9 transcription factor and *aggrecan* gene expression in valve progenitors, and FGF4 signaling activates *scleraxis* and *tenascin* in the remodeling valves [27,28]. Wnt signaling, active in the developing valves, promotes expression of genes characteristic of the collagen-rich fibrosa layer in cultured VICs [21]. Loss or reduction of Sox9 leads to defective valve development in the mouse [29] and a heart valve calcification phenotype in vivo [30].

We now recognize that mutations of critical genes involved in regulating cardiac development are associated with congenital valve abnormalities in experimental animals and humans [31]. Individuals with bicuspid aortic valve (BAV) [32] or mitral valve prolapse (MVP) [33], however, generally do not manifest clinical disease until later in life. BAV has been shown to be associated with gene mutations in Notch 1 [34,35], GATA5 [36], ACTA2 [37], and MVP, the TGFβ pathway [31,32,38].

Valve structure continues to evolve throughout life and likely involves both down- and up-regulation of various genes and their products in the valve cells. Biomechanical and hemodynamic forces impact and regulate the cell and matrix composition of the valve tissue; innovative studies have measured these forces [8,39]. ECM proteins, especially hyaluronan [40], periostin [41], and fibronectin [42], are also involved in the evolution of valve structure.

Moreover, additional recent findings, some of which are discussed in detail below, impact healthy states and disease conditions: (a) VICs and VECs have some similar and some unique properties relative to mesenchymal/endothelial cells in other locations; (b) Cell function is regulated by the combined actions of specific molecules that either promote or inhibit a given cellular process or function; thus, a complex balance among these molecules dictates cell function at any given moment; (c) Signaling pathways found in valves may interact through shared downstream molecules; (d) Microenvironments are important in autocrine and paracrine regulation of valve cell function, explaining the heterogeneity of function and structure within the different valve layers; (d) Cell–ECM interactions regulate valve cell function in both normal physiology and adaptation to disease; (e) Genes and pathways active in the fetus and reactivated in the normal adult valve may contribute to adult valvular disease; and (f) the response to injury paradigm has been a useful model to study the pathobiology of valve diseases [4–7,43,44]. Indeed, further understanding of how hemodynamic and biomechanical forces are transduced into biomechanical signals that affect valvular cell function is likely to lead to major breakthroughs.

1.2.1. Valve endocardial cells

A single layer of thromboresistant, confluent cells that adhere to and cover the entire surface of the valves, VECs are normally quiescent; however, when stimulated by injury, VECs migrate and proliferate to reconstitute the surface. VECs harvested and grown in culture to provide populations of cells to carry out cell and molecular biology studies have shown that VECs are heterogeneous and exhibit important differences when compared to vascular endothelial cells. Thus, when compared to vascular endothelial cells, VECs show different phenotypic responses to shear [45] and hemodynamic flow [46]. Moreover, VECs express many genes differentially on the aortic side versus the ventricular side of normal adult porcine aortic valves [47], perhaps providing a