The role of valve interstitial cells in valve disease

Aortic valve disease occurs in many patients, and it is a significant cause of cardiac morbidity in developed countries; however, there is no effective therapy for the progression of aortic valve disease (1). Valvular interstitial cells (VICs) are fibroblast-like cells that comprise the heart valves, and they are a useful model for research on valve physiology and disease. VICs are widely used in in vitro studies, such as valve calcification (2), tissue remodeling (3), pharmacological intervention (4), biosynthesis (5), and contractile properties (6). Therefore, the culture of VICs could provide important information on valve function, and the simple and reliable procedure for the culture of these cells may be helpful for research on the cellular basis of valvular heart diseases.

Enzymatic digestion or mechanical disruption is commonly used methods to separate VICs from the tissue specimens before seeding onto the dishes (7). The present study by Chen et al. (8) published in this issue of The Anatolian Journal of Cardiology entitled "Isolation and culture of rat aortic valve interstitial cells" is of interest because it describes an improved mechanical disruption method for the isolation and maintenance of VICs from rats. In their study, they found that cutting tissues into small fragments before seeding was feasible and that the fragments should be seeded in growth media (DMEM, 20% fetal bovine serum), which could shorten the first passage time and the culture period of the cells. It is important to note that the phenotypic characterization of the cultured VICs was analyzed by the authors. As the authors described, the phenotype of VICs may change during passage, and it is therefore necessary to characterize the cell type using specific markers after serial passage. VICs are commonly understood to be myofibroblasts in nature, with some aspects similar to fibroblasts and smooth muscle cells. VICs have been shown to express phenotypic markers such as α-smooth muscle actin, fibroblast surface antigen, and vimentin (9). In comparison to other cells isolated from vascular sources during extended culture, VICs possess many unique features, including the ability to synthesize some biologically active proteins and the contractile properties to perform vital functions. However, other cells cannot adequately mimic this wide range of functions (6, 9, 10). VICs release more prostacyclin in response to arachidonate than fibroblasts and smooth muscle cells (11). In addition, mitogen assays show that the mitotic index response to platelet-derived growth factor and fetal bovine serum are similar between these cells, but VICs respond to conditioned medium with a higher mitotic index than other cells (11). When VICs become activated myofibroblasts in some states, they significantly up-regulate contractile filaments and exhibit increased traction forces and migratory behavior, which lead to dramatic changes in matrix composition and structural organization (3, 12). Therefore, unique phenotypic markers for VICs, such as immunologic reagents directed at cell-surface or secreted proteins, will be needed to identify the specific cell type.

VICs are believed to be the predominant cell type in valve disorders. They are involved in some pathologic processes related to leaflet thickening, collagen fiber disorganization, and valve calcification (12-14). The present studies show that VICs play an important role in valve disease by secreting many macromolecules, such as collagen or glycosaminoglycans, and by changing their phenotype in response to specific cytokines (14). In the progression of calcification, activated VICs differentiate to either a myofibroblast-like phenotype, which are identified by markers of contractility such as α- smooth muscle actin, or an osteoblast-like phenotype, which is accompanied by the raise of bone morphogenetic proteins and TGF-β1 (13, 15). In a recent study, it was found that either osteogenic or myofibrogenic differentiation of VICs can result in calcification in vitro and that the two processes are distinct and respectively mimic aspects of either bone formation or apoptosis-associated calcification in vivo (2).

The isolation and culture of VICs in vitro is a useful way to study the physiology and pathophysiology of aortic valves. It will be useful to understand the mechanisms of aortic valve disease as well as to develop novel therapies.

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