Interstitial Cells of the Heart Valves Possess Characteristics Similar to Smooth Muscle Cells

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Although the cellular organization of the heart valves appears as a rather simplified version of the vascular intima, the actual nature and functional role of the valvular cells are still poorly understood.

In a morphometric study of mouse cardiac valves, we showed that the major cell population is formed by fibroblast-like interstitial cells that, in the atrioventricular valves, represent about 30% of volumetric density. In addition, these cells have several distinct nonfibroblastic features. In the atrioventricular leaflets, the interstitial cells are more concentrated in the ventricular region (lamina fibrosa), where they are the sole cell type, whereas in the atrial region (lamina spongiosa) they are interspersed among other cell types. Since it was implied that the interstitial cells probably synthesize all valvular matrix components, their pure fibroblastic nature was generally not questioned in studies of valve ultrastructure in man, rabbit, dog, and hamster. However, in man and guinea pig, interstitial connective tissue cells not resembling typical fibroblasts were reported in the distal part of atrioventricular valves.

In the present study we report ultrastructural, biochemical, and physiological evidence suggesting that the cardiac valvular interstitial cells (VICs) have morphological and functional characteristics similar to smooth muscle cells.

Materials and Methods

We used 100 normal adult male and female C57 Bl/6 and RAP mice (~25 g), 15 R rats (~90 g), 30 golden hamsters (~100 g), 25 chinchilla and New Zealand rabbits (~2,500 g) kept in standard housing conditions, on pelleted food, with water ad libitum. Five human heart valves were obtained from patients with rheumatic heart disease who underwent bioprosthetic heart valve replacement and were kindly provided by Dr. R. Deac (Clinic for Cardiovascular Surgery, Tirgu Mures, Romania). These specimens were processed for electron microscopy, as described below, by D. Simionescu (Biochemical Department of the Medical Academy of Sciences, Tirgu Mures, Romania).

Experimental Procedure and Tissue Processing for Electron Microscopy

Mice, rats, and hamsters were anesthetized by an intraperitoneal injection of 5% chloral hydrate (1 ml/100 g b. wt.), and rabbits by an intramuscular injection of diazepam 5 mg/kg b. wt. and an intraperitoneal injection of phenobarbital 150 mg/kg b. wt. The thorax was opened, the heart excised and, while still beating, washed in several changes (2 minutes each) of oxygenated Dulbecco’s phosphate-buffered saline (PBS) supplemented with 14 mM glucose, at 37°C. Atria and the two distal thirds of ventricles were cut away and the rest of the heart immersed in 2% glutaraldehyde in 0.1 M HCl—Na cacodylate buffer, pH 7.4, for 90 minutes at 22°C. While in fixative, the interventricular septum was cut and the valve leaflets detached by cutting successively the ventricular walls at valve...
commissures, the chordae tendineae and the myocardium close to the annuli. Valvular leaflets were further fixed in 1% osmium tetroxide in 0.1 M HCl–Na cacodylate buffer pH 7.4, for 90 minutes at 4°C, stained in block with 0.5% uranyl acetate in acetate veronal buffer pH 5 for 30 minutes, dehydrated in ethanol, and embedded in Epon 812 in flat molds. Sections were cut on Sorvall MT-2B, American Optical Ultracut, and Reichert OmU 3 microtomes, mounted on single hole grids, stained with uranyl acetate and lead citrate and examined with Philips 201C and Philips 400 HM electron microscopes. In some experiments, 1% lanthanum nitrate was added to the solutions, and for other specimens, a 2-minute incubation in 10^{-5} M L-norepinephrine preceded the fixation.

The procedure used was that previously reported, except that up to 6 mouse valve leaflets were placed on carriers in a drop of 4% agar-agar in 25% glycerol in HCl–Na cacodylate buffer pH 7.4 to facilitate transversal fracture through the tissue.

Cell Culture
As a source of interstitial cells, we used valvular explants in culture. Mouse, rat, and rabbit hearts were removed in sterile conditions, and only the distal parts of valve leaflets were microdissected and placed on glass Petri dishes in Dulbecco-Eagle medium supplemented with 10–15% fetal calf serum (Sigma Chemical Co.). The cultures were maintained in a humidified 5% carbon dioxide incubator at 37°C. Within 3–4 days, interstitial cells started to emerge from the explants, and their outgrowth dominated the primary culture. In the case of mouse explants, after 2–3 weeks, the interstitial cells were harvested by mild tripsinization and subcultured for three passages. From rabbit explants a VIC line was established (manuscript in preparation). Fibroblasts were obtained from mouse abdominal skin explants and were kept in culture in the same conditions.

Electron Microscopy of VIC in Culture
A rapid procedure for transmission electron microscopy of vascular cells in culture was used (Jinga V.V., personal communication). Briefly, after a rapid wash in 0.1 M HCl–Na cacodylate buffer supplemented with sucrose (298 mOsM), the cultures were fixed in 2.5 M glutaraldehyde in the same buffer for 5 minutes, postfixed in 1% osmium tetroxide for 10 minutes at 4°C on ice and treated with 1% tannic acid for 7 minutes. The cultures were then rapidly dehydrated in graded concentrations of ethanol (70%, 2 times for 15 seconds; 95%, 2 times for 15 seconds; 100%, 3 times for 5 seconds), and infiltrated with Epon:ethanol 1:1 for 30 minutes. After discarding the resin mixture and allowing a 10-minute incubation at 37°C for ethanol evaporation from the small quantity of resin mixture remaining in the culture dish, the cultures were embedded in Epon 812 and polymerized 1 hour at 37°C and 48 hours at 60°C.

Preparation of S1 Fragment of Heavy Meromyosin (S1-HMM)
S1-HMM was prepared from glycerinated rabbit leg muscles by papain digestion according to Cooke. For F-actin sedimentation, the S1-HMM preparation was centrifuged 1 hour at 140,000 g, then precipitated by 0.94 M ammonium sulfate. The purity was assessed by electrophoretic criteria using denaturing and nondenaturing polyacrylamide gel electrophoresis (PAGE). To test the binding capacity of S1-HMM to actin, 140 μg/ml S1-HMM and 40 μg/ml F-actin were allowed to react for 1 minute at 22°C; then the mixture was placed on grids and negatively stained with 1% uranyl acetate to check for the appearance of characteristic actin decoration. Protein concentrations were determined according to Bradford.

Decoration of VIC Microfilaments with S1-HMM in Situ
Four mouse and two rabbit atrioventricular valves were processed following Bond and Somlyo’s procedure using a low ionic strength solution.

Testing cell-to-cell communication. For these tests mouse VICs in vitro were used either in primary culture (8 experiments) or in the third passage (2 experiments). Through an intracellularly placed micropipette, the cells were microinjected iontophoretically with 300 mM carboxyfluorescein. The injection current was 5 nA, and the injection time varied from 30 seconds to 3 minutes. Tracer spreading to neighboring cells was observed by incident light fluorescence microscopy in a NU-2 universal photomicroscope (Zeiss, Jena, D.R. Germany). Photographs were taken 7–14 minutes after the injection, as fluorescence/phase contrast pairs.

Immunohistochemical Localization of Cyclic-GMP-Dependent Protein Kinase (cGK)
Antisera. The antiserum raised against affinity-purified bovine lung cGK and the preimmune serum were a generous gift from Dr. Ulrich Walter (Department of Physiological Chemistry and Medicine, University of Wurtzburg, F.R. Germany). The antiserum has been extensively characterized as a monospecific reagent, as a specific inhibitor of GMP-dependent protein kinase from several sources including smooth muscle, and as a cytochemical marker for cerebellar Purkinje cells and smooth muscle cells. The antiserum was found to cross-react with cGK from several species, including mouse and rat.

Immunofluorescence. Six primary cultures of mouse and rat valvular interstitial cells and mouse skin fibroblasts were used. Cells were briefly washed in PBS, fixed in absolute ethanol for 15 minutes at 22°C, and permeabilized by a procedure slightly modified after Lohman using 0.3% Triton X-100 in 20 mM sodium phosphate buffer pH 7.4, containing 0.45 M sodium chloride and 0.1% bovine serum albumin (BSA). Cells were incubated in Petri dishes for 2 hours with anti-cGK diluted 1:10 in Triton buffer, then, after washing, exposed for 1 hour to fluorescein-conjugated...
goat anti-rabbit IgG (Miles Scientific, U.S.A.) diluted 1:50 in the same buffer. After PBS washing, the cells were mounted in glycerol: PBS (1:1) and examined by epifluorescence and phase contrast in a NU-2 microscope. Controls were performed in parallel cultures using preimmune serum, rabbit serum, or by omitting the primary antiserum. All steps of the immunostaining were done at 22°C.

**IMMUNOPEROXIDASE ON WHOLE MOUNTS.** Mice hearts, collected as previously described, were fixed in absolute ethanol for 30 minutes at 22°C. Valve leaflets were excised and permeabilized with 0.3% Triton X-100 in 40 mM sodium phosphate buffer pH 7.4 containing 0.5 M sodium chloride and 0.1% BSA (instead of ovalbumin) for 1 hour at 22°C, according to Joyce et al. All the subsequent steps were done at room temperature, under continuous shaking with the Triton buffer as antibody diluent and washing medium. The valves were incubated for 24 hours with anti-cGK diluted 1:100 followed by 24 hours of washing, 19 hours of incubation in peroxidase-labelled goat anti-rabbit IgG (Sigma Chemical Co., St. Louis, Mo.) diluted 1:50, and further washed for 24 hours. Peroxidase reaction was performed according to Joyce et al. The reaction, monitored under a stereomicroscope, was stopped by dilution with phosphate buffer. The valves were spread on gelatin-coated glass slides (0.5% gelatin in water), air-dried, delipidated by immersion in acetone and xylene (5 minutes each), and fixed in osmium tetroxide vapors for 1 hour at 22°C. After washing in water, the tissue was slowly dehydrated in ethanol and cleared with increasing concentrations of glycerol in ethanol. The thinness of mouse valves (~20 μm) made this whole mount preparation suitable for observation. In control experiments, the incubation with the primary antiserum was omitted.

**Tests for VIC Contractility (in Culture)**

For testing VIC capability to contract, the flexible silicone rubber substrata technique of Harris et al. was used. This procedure was employed by Clark et al. to assess the direct contraction of smooth muscle cells by leukotriene C4. Briefly, 60,000 centistokes silicone fluid (Sigma Chemical Co.) was spread on 28 x 28 mm sterile coverslips, and after 10 minutes, its outermost layer was polymerized by flaming for 2 seconds. Rabbit VICs (at primary or secondary passage) were seeded on the coverslips at a density of 2.5 X 10⁴ or 1 X 10⁵ cells/cm². At time intervals of 4, 21, 24, 78, and 120 hours after plating the cells were stimulated with 10⁻⁷ M L-epinephrine (Fluka) and 10⁻⁵ M angiotensin II (CIBA) (final concentrations) in KRB buffer were used. The response was detected using a sensitive mechano-optical transducer (system devised by Dr. C. Neacsu, Institute of Cellular Biology and Pathology, Bucharest). To check the reversibility of the phenomenon observed, ~25 minutes later the epinephrine- or angiotensin-containing medium was replaced by KRB buffer.

**Results**

In all species studied, including humans, VIC are numerous, elongated cells with many long, slender processes extending throughout the valvular stroma. Through these processes, VIC are connected to each other establishing a system of three-dimensional cellular network spanning the entire valve (Figure 1). VICs

![Figure 1.](http://circres.ahajournals.org/doi/abs/10.1161/01.RES.59.3.312)
FIGURE 2. Communicating junctions between VICs in situ. a) Distal part of hamster bicuspid valve, ventricular aspect (× 13,500): The valvular interstitial cells (VICs) lack a continuous basal lamina, have numerous extensions, and come in close contact with the extracellular collagen (c) of the valvular stroma. Note the focal close apposition between VICs and endothelial cells (ECs) (arrowhead), as well as between neighboring interstitial cells (arrow). b) Communicating junction established between two VIC cytoplasmic processes (rabbit bicuspid valve). c) Communicating junctions (arrows) between a VIC body and a process of a neighboring VIC (mouse bicuspid valve; × 72,000). The developed VIC cytoskeleton made up by intermediate filaments is apparent. d) Tangential section of a lanthanum-treated bicuspid valve (mouse) showing the characteristic pattern of a communicating junction (× 250,000).
possess structural features intermediary between fibroblasts and vascular smooth muscle cells. Like fibroblasts, VICs are devoid of basal lamina (basement membrane), have long, thin cytoplasmic extensions, and appear in intimate association with the components of the interstitial matrix (collagens, microfibrillar component of elastin, and proteoglycans) (Figure 2a). Characteristically, their cytoplasms have well-developed rough endoplasmic reticulum and Golgi apparatus and are extremely rich in microfilaments and intermediate filaments. Similar to smooth muscle cells, VICs a) are coupled by communicating (gap) junctions; b) contain numerous bundles of actin filaments and dense bodies; c) express cGMP-dependent protein kinase; d) have motor nerve terminals that appear closely apposed (30-80 nm) to the VICs; and e) are capable of contraction in vitro. These characteristics are common to all valves studied (atrioventricular and sigmoid).

To test for the actual coupling between these cells, carboxyfluorescein was iontophoretically microinjected in VICs in culture. Immediately after, the dye filled the cytoplasm and the processes of the injected cell and within 7 to 14 minutes it spread into the neighboring cells (Figure 4a,b). No trace of dye was detected extracellularly. The results were identical in cells in primary or third passage cultures. These findings demonstrate that the communicating junctions established between VICs are functionally active. Communicating junctions in which a process of one cell penetrated deeply into, and became surrounded by, the partner cell (annular junctions) were often observed (Figure 3a,b). Usually, the tip of the penetrating cell process and the adjoining cytoplasm of the host cell appeared very rich in filaments. We also frequently found situations in which coupling was established between two parts of the same cell (reflexive junction), as reported for other cell types, including vascular smooth muscle cells.

Characterization of VIC Filament Bundles

Numerous filaments, ~7 nm in diameter, organized in prominent bundles interspersed with dense bodies commonly occurred in the VIC cytoplasm. The trajectories of microfilament bundles generally followed the long axis of the cell and usually ended in dense bodies located near the plasma membrane (Figure 5a). They frequently occurred in cell regions close to extracellular microfibrils or were inserted in areas resembling hemidesmosomes.

To characterize the VIC microfilaments, we tried their decoration with S$_2$-HMM based on the known specific interaction between actin and myosin. S$_2$-HMM decorated the filaments forming characteristic arrowheads (Figure 5b) pointing away from the dense bodies (Figure 5b, inset). It was possible to differentiate between a peripheral actin web and the highly oriented actin bundles traversing the cytoplasm. The organization of actin bundles was similar in all species investigated, but their dimensions varied, being the smallest in the mouse and extensively developed in the rabbit.

**Immunohistochemical Detection of Cyclic-GMP-Dependent Protein Kinase**

Two approaches were followed: immunofluorescence of VICs in culture and immunoperoxidase staining using whole mounts of mouse valves.

In culture, mouse and rat VICs incubated with anti-cGK followed by a fluorescent second antibody showed a strong fluorescence of their cytoplasms and slender processes (Figure 6a,b). Nuclei and nucleoli were also strongly stained. In control experiments using preimmune serum, the cytoplasm displayed only a weak reaction, whereas nuclei and nucleoli were stained, suggesting an unspecific decoration (Figure 6c,d). In these experiments, the relation between cells in culture could be easily distinguished, e.g., close contacts (most probably by gap junctions) either between cytoplasmic processes (Figure 6a) or between the cell processes of one cell and the body of a neighboring cell (Figure 6b). In additional experiments we used the same technique for detection of cGK on bo-

**Figure 3.** "Annular" type of communicating junction (arrows) between two VICs as it appears in cross section: a) rat bicuspid valve and longitudinal section (× 100,000); b) rabbit VICs in culture (× 70,800). The junctions are established between a cell process of an interstitial cell (VIC$_1$) invaginated deeply into the body of another VIC (VIC$_2$). Such junctions are found both in situ (a) and in cultured cells (b).
vine aortic smooth muscle cells, endothelial cells, and mouse skin fibroblasts in culture. The results showed the presence of the cGK in smooth muscle cells as already reported by Lohman et al.\textsuperscript{16} No reaction was obtained in endothelial cells or fibroblasts (Figure 6d); it may be possible that the amount of cGK in these cells is under the resolution of our technique.

Using whole mount preparations of the valve, incubated with anti-cGK and followed by immunoperoxidase reaction (see "Materials and Methods") the staining was present in the cytoplasm of numerous elongated cells spanning the stroma (Figure 7). The distribution of these reacting cells paralleled the distribution of VICs. Though a limitation in resolution is inherent to the method of whole mount preparation, the results confirmed those obtained with VICs in culture.

VIC Contractility

Two tests were performed using a) isolated VIC grown in culture and b) strips of atrioventricular valves maintained in an organ bath.

a) Cultures of VIC grown on silicone rubber and stimulated by $10^{-7}$ epinephrine contracted slowly and changed their shape. Most of the cell bodies became smaller, and their cytoplasmic extensions shorter. In the same time contraction of strongly adhering cells induced wrinkles of the elastic substratum. The cells often showed higher refrigence correlated with the change in the cell shape (Figure 9). The effects were observed as early as 3 minutes after stimulation and increased with time. Similar results were obtained irrespective of the density of cells or the time after plating. After replacing the epinephrine-containing medium with a drug-free medium, the VICs regained slowly their initial shape and size. In control experiments using only Krebs-Ringer bicarbonate buffer for comparable periods of time, no contraction was observed.

b) Distal areas of valve leaflets maintained in an organ bath contracted on stimulation with $10^{-6}$ M L-epinephrine and $10^{-5}$ M angiotensin II. The effect was observed in ~3 minutes after stimulation and increased slowly reaching a plateau at ~10 minutes;
after ~20 minutes, a slow decrease in the response was observed. By replacing the epinephrine- or angiotensin-containing medium with KRB buffer, the valves regained their initial state (Figure 10).

Discussion

Interstitial cells or fibroblast-like cells are ubiquitous components of the connective tissue, being generally considered as the main source of extracellular matrix. In addition, they may play other roles according to their location. In the lung, interstitial cells have been found to have a contractile function. In granulation tissue, fibroblasts can assume smooth muscle cell characteristics and contract the wound and are named myofibroblasts.

In the heart valves, contractile elements represented by sparse bundles of atrial myocardium were reported in the proximal third of valve leaflets, close to the annuli. Bundles of smooth muscle cells were also found in human and porcine atrioventricular valves and canine aortic valve. In addition, numerous fibroblast-like cells, variously named interstitial cells, myofibroblasts, or intermediate-type cells, were observed in the valvular tissue. When present, smooth muscle cells are found in the proximal and middle portion of the valve, whereas the distal region is populated mostly by interstitial cells.

Moreover, according to our previous study in mouse, this type of cell forms the main valvular cell population and is the sole cell type found in the matrix.
at the ventricular aspect of atrioventricular valves and vascular aspect of sigmoid valves.

The present inquiry shows that in all valves studied, interstitial cells possess features similar to smooth muscle cells: They are functionally coupled by communicating junctions; they contain numerous bundles of actin filaments; they possess cGMP-dependent protein kinase; they are innervated; and they contract after epinephrine and angiotensin II stimulation in vitro.

Coupling of VICs by communicating junctions both in situ and in vitro may provide the means for transmitting metabolic information from one cell to another, thus forming an integrated system. No junctions were found between VIC and the valvular endothelial cells, but very close apposition between the latter and the processes of VICs occurs. In some instances, this apposition is reminiscent of that observed in microvessels between smooth muscle cells and the endothelium.29

Smooth muscle actomyosin was detected by immunofluorescence in the atrioventricular and semilunar valves,30 but its precise cellular localization was not established. Our results demonstrate the presence of actin filaments in VIC. Although cGMP protein kinase is present in small amounts in many cell types, there are only few cells that contain the soluble enzyme in quantities detectable by immunocytochemistry, i.e., smooth muscle cells, pericytes, and Purkinje cerebellar cells.31 The presence of cGMP protein kinase in VICs revealed by immunocytochemistry indicate a possible filiation of VICs with smooth muscle cells and pericytes.

The existence of nerve terminals located next to VICs suggests that these cells may be able to receive stimuli that can propagate between neighboring cells by communicating (gap) junctions, so that the activity set up in one cell readily spreads to the next cell without significant delay.

The direct proof of the capability of VICs to contract was observed in culture or using strips of valves, stimulated with epinephrine or angiotensin II. In culture a change in shape denoting a slight contraction was observed 3 minutes after epinephrine stimulation. In the organ bath, the distal portions of the valves contracted upon stimulation, reaching a plateau that was maintained for 20 minutes. This long plateau phase suggests a tonic type of contraction. Since the distal parts of the valves are populated by interstitial cells only, we pre-
FIGURE 7. Immunoperoxidase localization of cGK in whole mount of a mouse valve. The specimen was treated with antibody against cGK followed by a peroxidase-conjugated second antibody (see "Materials and Methods"). Note the overlapping 2-3 layer of VICs present in the depth of focus: Cells are delineated by the peroxidatic reaction product developed in their cytoplasm. (× 780).

sume that they are the sole cells responsible for the contraction. These results corroborate well with those obtained in culture.

In some recent experiments we found out that in rabbits fed a hyperlipidemic diet, VICs may become loaded with lipids containing cholesterol esters, a feature commonly observed in smooth muscle cells of the aorta and coronary artery (manuscript in preparation).

All these data attest that VICs are more closely related to smooth muscle cells and pericytes than to fibroblasts. In addition, it was shown that normal VICs possess Fc receptors, a feature not found in connective tissue fibroblasts. 

Heart valves were considered for a long time as passive devices moving in the bloodstream only by the interplay of hemodynamic forces generated by the cardiac contractions. According to previously reported findings and the data presented here, the atrioventricular valves seem to be endowed with a complex system, capable of contraction, made up of bundles of myocardium (proximal) and smooth muscle cells (proximal and middle region), both located atrially, and interstitial cells present along the entire leaflet but especially at its ventricular aspect. Toward the distal end of the valve, interstitial cells may constitute the sole contractile element. A similar system exists in sigmoid valves, except the myocardium is absent and the interstitial cells are located toward the vascular aspect, where the hemodynamic forces are perpendicular to the leaflets. This complex contractile system present in various proportions in all heart valves and in all species studied, including humans, may function to sustain the load of hemodynamic forces exerted perpendicularly to the valvular tissue during the systole and the closure of the valves.

FIGURE 8. Mouse tricuspid valve. Motor nerve terminal (nt) present in close contact with a cytoplasmic process of an interstitial cell (VIC1) which in turn is coupled via a junction (arrow) with a neighboring interstitial cell (VIC2). EC, endothelial cell (× 41,600).
of the valvular leaflets. Such a contractile cellular system would imply a strong relation between the cells and the surrounding matrix (elastin, microfibrils, collagens, proteoglycans). The VIC–matrix relations and their impairment in pathological conditions are under current investigation.

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**References**


**Figures**

**Figure 9.** Cultured rabbit VIC (second passage) were plated on silicone rubber substratum; after 24 hours 7.5 x 10^{-7} L-epinephrine in Krebs-Ringer bicarbonate buffer was added. Pictures were taken by phase-contrast microscopy before epinephrine administration (a), and at 3 minutes (b), 17 minutes (c), and 22 minutes (d) after. The cells respond to epinephrine stimulation as a function of time by changing their shape, reducing their size (arrows) and by wrinkling the elastic substratum (×150).

**Figure 10.** Recordings of typical changes in mechanical activity of the rat tricuspid valve (anterior leaflet, distal part) stimulated by 10^{-5} M angiotensin II (Ang II) in Krebs-Ringer bicarbonate buffer (KRB). Three minutes after stimulation, contraction reaches a plateau which is maintained for ~20 minutes. After replacing the angiotensin-containing medium with the buffer, the initial baseline is regained.

KEY WORDS • valvular interstitial cells • heart valves • cell communicating junctions • actin filaments • cGMP-dependent protein kinase • nerve endings • cell contraction
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