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MYOCARDIAL INTERSTITIUM: FROM HISTOPHYSIOLOGY TO CARDIOSCLEROSIS AND ECTOPIC CALCIFICATION

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ABSTRACT

Introduction. A fundamental paradigm shift has occurred in modern cardiology: the myocardial interstitium (stroma) is no longer considered a passive scaffold, but a highly dynamic, metabolically active neuro-immune-vascular niche that maintains structural homeostasis, regulates electrophysiology and contractility, and determines the trajectory of pathological cardiac remodeling.

Aim. To systematize current data on the structural and cellular organization of the myocardial stroma and to characterize the mechanisms of crosstalk between stromal elements and cardiomyocytes underlying fibrosis and ectopic calcification.

Materials and Methods. A systematic review of PubMed/MEDLINE, Scopus, and Web of Science was performed; 48 of over 200 identified sources (2005–2026), predominantly from Q1-Q2 journals, were selected for analysis.

Results. The myocardial architecture possesses a laminar spatial organization formed by collagen fibers of the endomysium and perimysium. The cellular composition of the interstitium is highly heterogeneous. Telocytes form a three-dimensional scaffold via telopodes, physically integrating tissue structures while stimulating cardiomyocyte maturation and maintaining regenerative potential through microRNA secretion. Pericytes control capillary blood flow — their pathological spasm underlies the "no-reflow" phenomenon during ischemia — and orchestrate regeneration through a secretome that stimulates neoangiogenesis and limits fibrosis. Cardiac fibroblasts govern matrix biosynthesis; their stepwise activation into myofibroblasts and matrifibrocytes drives replacement or reactive fibrosis, and fibroblast-derived TGF-β directly suppresses cardiomyocyte contractility. Beyond fibrosis, disrupted collagen turnover and ectopic stromal calcification (e.g., due to Fetuin-A deficiency) produce myocardial stiffness and diastolic dysfunction (HFpEF) refractory to pharmacological treatment.

Conclusions. The physiological and pathological state of the heart depends entirely on bidirectional crosstalk between cardiomyocytes and the stroma; future cardiological and regenerative therapies must target the integrated multi-tissue microenvironment rather than the isolated cardiomyocyte.

Keywords: myocardial stroma, telocytes, fibroblasts, extracellular matrix, cardiosclerosis, ectopic calcification.

INTRODUCTION

In classical cardiology and physiology, the myocardium was traditionally viewed primarily through the prism of the contractile function of cardiomyocytes, which form myocardial fibers whose coordinated contraction ensures the pumping function of the heart. Within this historical paradigm, the interstitium (stroma) was described as a passive connective tissue framework whose role was traditionally considered to be limited to providing mechanical support for myocardial fibers and distributing mechanical stress during systole and diastole. However, the substantial body of fundamental evidence accumulated over recent decades has prompted a major revision of this oversimplified concept. In contemporary translational medicine, the myocardial stroma is regarded as a highly dynamic, metabolically active neuroimmune-vascular niche [1-6]. This complex microenvironment plays a crucial role not only in maintaining myocardial structural homeostasis but also in regulating electrophysiological processes, modulating the contractile capacity (inotropy and lusitropy) of the heart, and shaping the trajectory of pathological remodeling in cardiovascular diseases.

The foundation of the myocardial stroma is the extracellular matrix (ECM), which is interwoven with a dense network of microcirculatory blood vessels. This matrix serves not merely as a biomechanical buffer but also as a reservoir for a large pool of growth

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factors, cytokines, chemokines, and proteolytic enzymes, ensuring intricate spatiotemporal control of intercellular communication [3-6]. The cellular composition of the stroma is remarkably heterogeneous. It encompasses endothelial cells forming the inner lining of capillaries, perivascular cells (primarily pericytes and adventitial cells), tissue-specific subpopulations of fibroblasts, a distinct class of interstitial cells known as telocytes, adipocytes, and immune cells [1-6].

The physiological function of the myocardium, as well as its adaptive or maladaptive remodeling in ischemic heart disease, arterial hypertension, metabolic syndrome, and heart failure, is strongly influenced by synchronized bidirectional interactions (crosstalk) between cardiomyocytes and stromal elements [7-10]. Elucidating the molecular mechanisms underlying this crosstalk opens new avenues for cardiovascular pharmacology and tissue engineering, shifting the therapeutic focus from the isolated cardiomyocyte toward the integrated multi-tissue complex (Fig. 1).

AIM

The aim of this review is to systematize and critically analyze current data on the structural and cellular organization of the myocardial interstitium (stroma), characterize the mechanisms of bidirectional crosstalk between its principal cellular populations – telocytes, pericytes, and fibroblasts – and cardiomyocytes, and elucidate the role of this crosstalk in the pathogenesis of myocardial fibrosis, stiffness, and ectopic stromal calcification underlying diastolic dysfunction (HFpEF).

MATERIALS AND METHODS

This work is a systematic scientific review conducted in accordance with the principles of evidence-based medicine. The search for scientific literature was performed across leading international databases: PubMed/MEDLINE, Scopus, and Web of Science. The following keywords and their combinations were utilized: "cardiac stroma", "myocardial extracellular matrix", "cardiac fibroblast", "pericyte secretome", "telocytes heart", "endothelial-cardiomyocyte crosstalk", "myocardial fibrosis", "HFpEF diastolic dysfunction", "mechanoelectric coupling". The analysis included original articles, systematic reviews, and meta-analyses published predominantly between 2005 and 2026. Priority was given to publications in first and second quartile (Q1–Q2) journals according to the SCImago Journal Rank. In total, over 200 sources were analyzed, from which 48 of the most relevant and methodologically robust studies were selected for citation. Inclusion criteria comprised: relevance to the research topic (structure and functions of the myocardial stroma, intercellular interactions in cardiac tissue), a sufficient level of evidence, and the availability of the full text.

RESULTS

The myocardial architecture exhibits a pronounced laminar (sheet-like) spatial organization. Cardiomyocytes are grouped into functional muscle fibers that can branch and form anastomoses. They

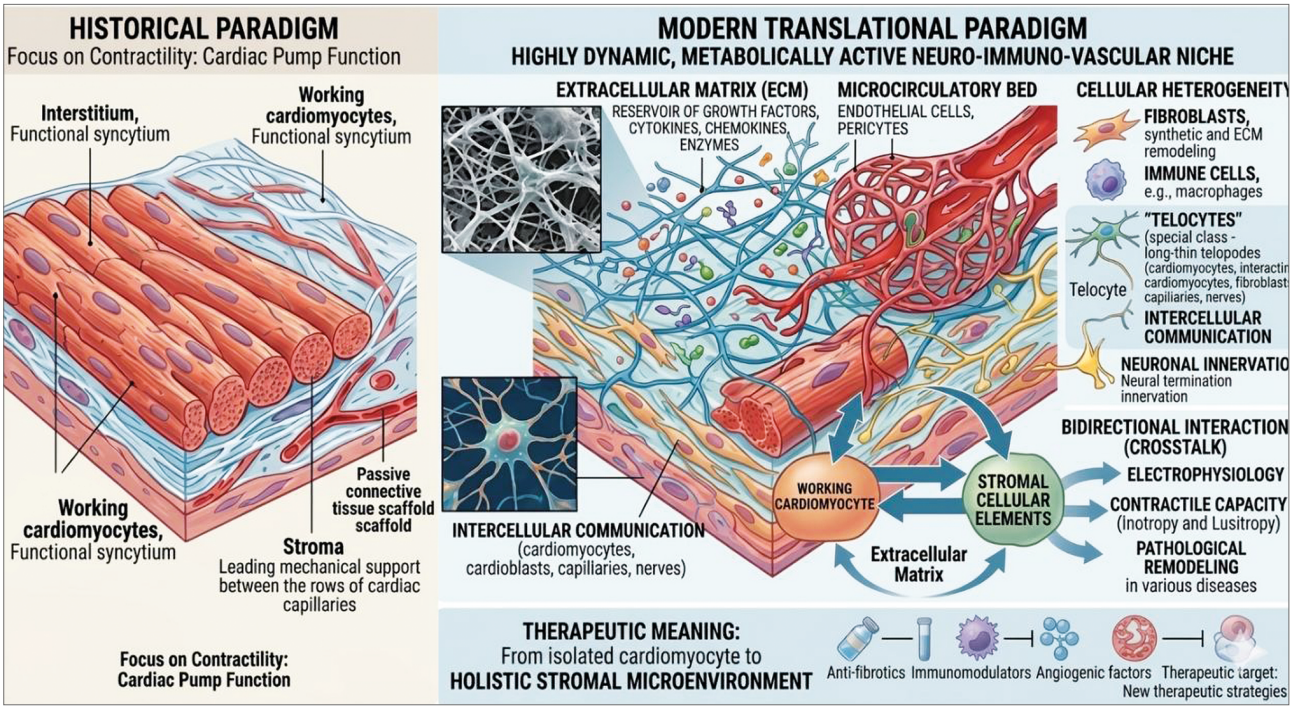

Fig. 1. Contemporary understanding of myocardial structure: from the contractile unit to a complex multi-tissue complex (Author's elaboration using AI Sider & Gemini_

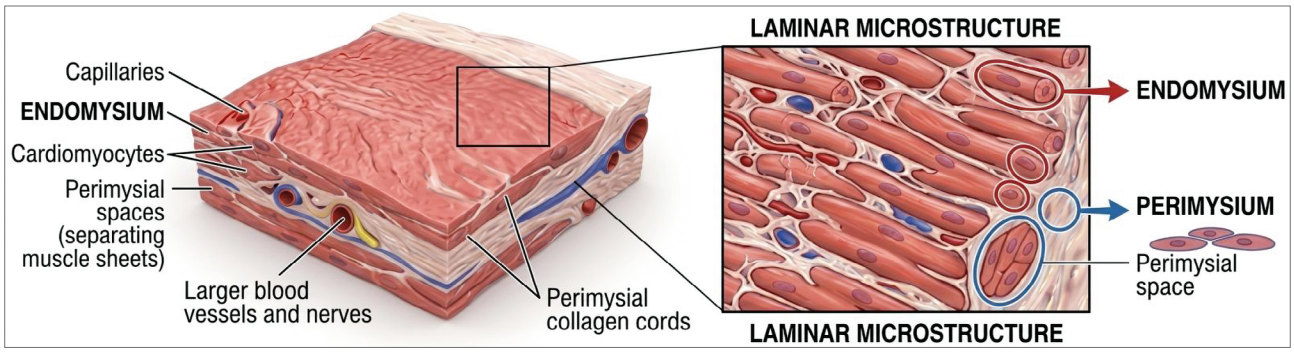

Fig. 2. Spatial organization of the myocardial architecture (Author's elaboration using AI Sider & Gemini)

share a common spatial orientation and are tightly interconnected by endomysial elements, forming laminae or sheets. Consequently, the ventricular myocardium is not an absolutely homogeneous continuum of fibers. Instead, it features a complex three-dimensional architecture in which functional muscle fibers are bound together by endomysial elements into distinct laminae. The thickness of a single lamina typically spans 4-6 cardiomyocytes (approximately 80-120 μm). The laminae are separated by connective tissue perimysial cleavage planes, which provide optimal mechanics for the twisting and untwisting of the left ventricle during the cardiac cycle [11-13]. The network of collagen fibers is the predominant component of the stroma and is classically subdivided into the epimysium (covering the entire muscle), endomysium (surrounding functional muscle fibers), and perimysium [11, 14].

Endomysial collagen fibers play a pivotal role in shaping the laminar architecture of the interstitium. Three-dimensional confocal microscopy reveals their highly ordered arrangement, forming three distinct morphological elements: 1) a meshwork on the surfaces of laminae (the so-called myolaminae); 2) thick, convoluted fibers that cross the cleavage planes and mechanically connect adjacent layers; and 3) longitudinal fibers [11, 19]. Notably, although myolaminae form the basis of structural organization throughout most of the thickness of the left ventricular wall, they are absent in the subepicardial zone, where perimysial collagen is represented exclusively by longitudinal fibers [11]. In regions containing a single population of laminae, aggregates of cardiomyocytes are oriented along the local radial direction of the left ventricular wall, branch, and merge into a complex network around the junction points of different laminae, as well as curve to accommodate the passage of blood vessels [12, 15, 19, 20].

The microcirculatory bed is inextricably integrated into this fibrillar matrix. Through the application of cutting-edge three-dimensional reconstruction techniques, specifically serial block-face scanning electron microscopy (SBF-SEM) and high-resolution X-ray phase-contrast microtomography, it has become possible to visualize the spatial relationships of cells within the perivascular niche with unprecedented precision [6]. Blood vessels (capillaries and postcapillary venules) are densely ensheathed by pericytes, whose cell bodies are predominantly oriented longitudinally along the capillary axis. Pericytes extend multiple thin processes toward the endothelium. Although these processes physically cover only a minor fraction of the total outer surface of endothelial cells, they are strategically positioned at critical sites, particularly capillary branching points. At these bifurcation zones, some pericytes are positioned to maintain simultaneous contact with both capillaries emerging from the branching point, indicating their important role in the local regulation of blood flow [23]. The most critical ultrastructural feature defining pericyte identity is that their cell bodies and all cytoplasmic processes, without exception, are entirely embedded within a shared basement membrane [23-25].

Beyond the capillary basement membrane, directly within the stroma, reside other vessel-associated cells, notably telocytes. They form a complex interstitial network [1-6]. It has been established that telocyte processes penetrate the endothelial basement membrane, forming specialized electron-dense contact zones directly with endothelial cells. The presence of these specialized contact zones provides evidence of direct functional crosstalk between telocytes and the endothelium [6]. At the same time, despite their close spatial proximity within the perivascular niche, no zones of direct structural contact have been identified between pericytes and telocytes, suggesting that their interaction may be predominantly paracrine in nature (Fig. 3) [6].

Understanding this intricate spatial configuration is directly relevant to the processes of embryogenesis and regeneration. During heart development, the epicardium plays a critical role in forming the myocardial stromal compartment. Epithelial-to-

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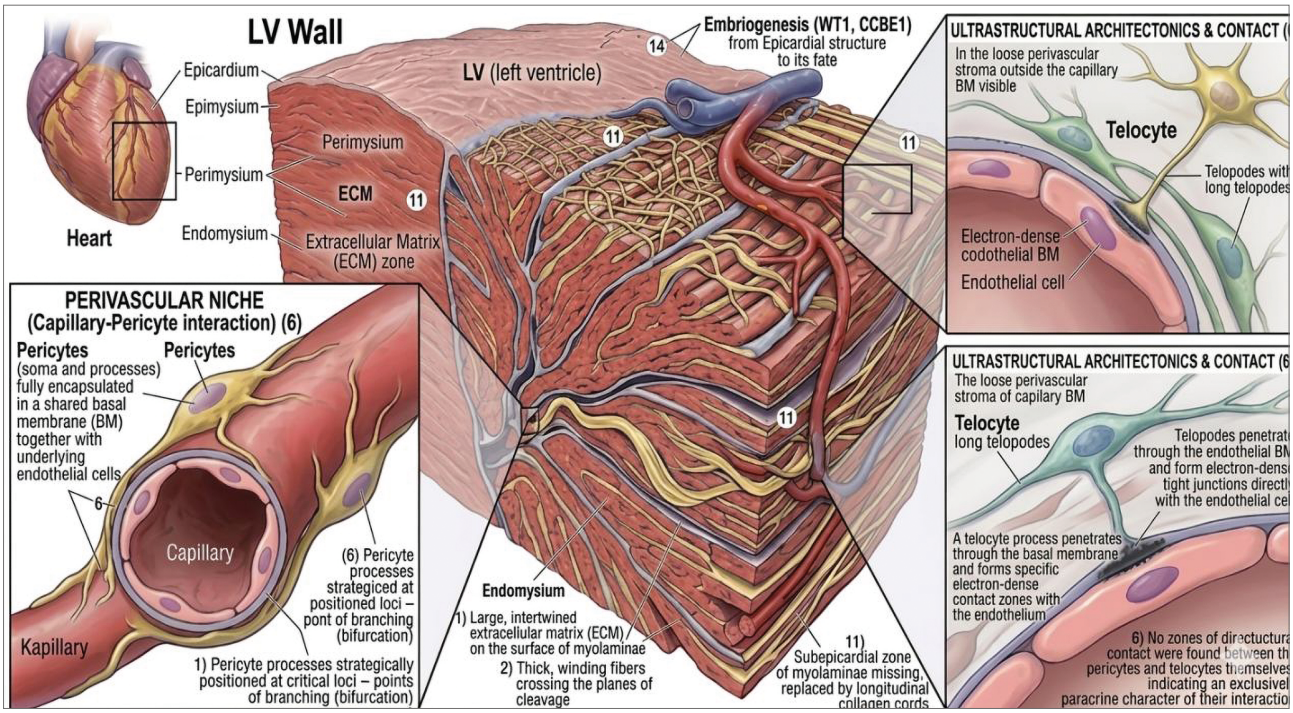

Fig. 3. Three-dimensional spatial organization and ultrastructural architecture of the myocardial perivascular stroma (Author's elaboration using AI Sider & Gemini)

mesenchymal transition (EMT) in the epicardium, regulated by transcription factors such as WT1 and extracellular proteins such as CCBE1 (collagen and calcium-binding EGF-like domains 1), supplies a pool of progenitor cells to the developing myocardium [14, 15, 23–25]. These progenitors subsequently differentiate into fibroblasts, pericytes, and smooth muscle cells of the coronary vessels [14, 16, 17]. In adulthood, these stromal niches retain traces of their ontogenetic origin, which may influence their reactivity under pathological conditions.

Telocytes are a distinct, recently identified type of interstitial cells that fundamentally differ from classical fibroblasts and pericytes. Surface markers that allow reliable verification of telocytes in tissue include the CD34 and CD44 antigens [1-11]. Morphologically, they are characterized by a small cell body and extremely long, thin, convoluted processes-telopodes, which permeate the entire thickness of the myocardium, forming a complex 3D network [6].

Telocytes serve as an essential link in the spatial organization of the three-dimensional myocardial architecture and the maintenance of stem cell niche functional status (Fig. 4). As demonstrated by SBF-SEM data, telopodes construct a sort of biological "framework" or scaffolding for other cell types, ensuring the physical integration of cardiomyocytes, capillaries, and nerve endings into a single functional organ [12, 28, 29, 30].

A key aspect of telocyte biology is their indispensable role in early heart development (embryogenesis) and cardiomyocyte maturation. It is known that human induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs) cultured in vitro initially possess an infantile "embryonic" phenotype. They exhibit a poorly developed T-tubule system, an immature sarcomere structure, and deficient calcium processing (they are forced to rely solely on internal Ca^{2+} pools via ryanodine RyR receptors, unlike mature myocytes where calcium entry is tightly coupled to L-type plasma membrane Ca^{2+} channels) [27, 31]. The incorporation of telocytes into co-cultures or 3D bioengineered constructs promotes the rapid maturation of iPSC-cardiomyocytes, the formation of definitive cytoarchitecture, and a qualitative improvement in their electromechanical properties [6].

In severe pathological states, such as myocardial infarction or chronic heart failure (as well as in congenital defects like tetralogy of Fallot), a progressive depletion of the telocyte population is observed, which directly correlates with the loss of myocardial regenerative potential and the progression of adverse remodeling [6]. Telocyte transplantation into the damaged myocardium mitigates the negative consequences of the disease. It has been experimentally proven that the cardioprotective function of telocytes is largely mediated by exosome secretion. Telocyte microvesicles contain a rich transcriptomic cargo, notably the specific microRNA miRNA-21-5p. Its transfer to adjacent endothelial cells triggers the transcriptional silencing of the pro-

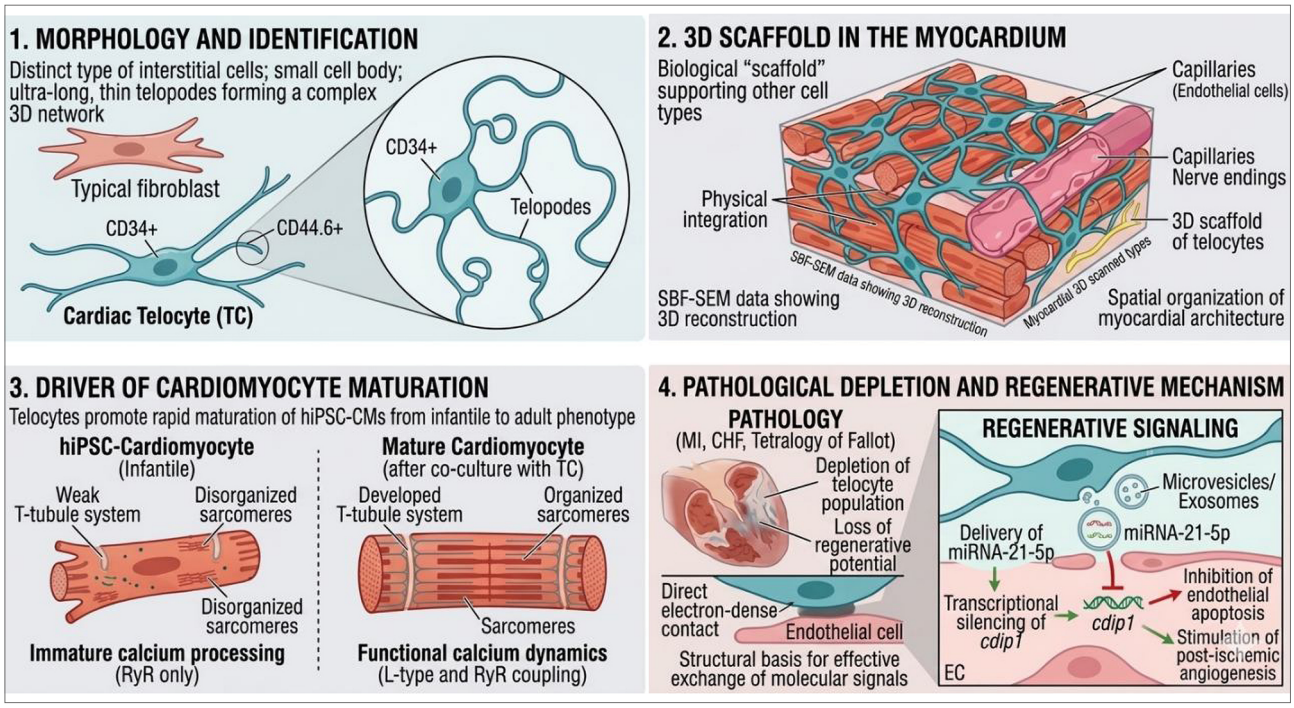

Fig. 4. Cardiac telocytes: microarchitectural scaffold and drivers of myocardial maturation (Author's elaboration using AI Sider & Gemini)

apoptotic gene cdip1. Consequently, endothelial apoptosis is blocked, post-ischemic angiogenesis is robustly stimulated, and the degradation of the microcirculatory bed is prevented. The establishment of direct electron-dense contacts between telocytes and the endothelium, revealed by 3D reconstruction, provides the structural foundation for the efficient and rapid exchange of molecular signals [6].

The most abundant cellular population of the cardiac interstitium, primarily responsible for the biosynthesis, assembly, and remodeling of ECM components, including fibrillar collagens types I, III, and V, fibronectin, and various proteoglycans, is composed of cardiac fibroblasts [32-35]. Under physiological conditions, cardiomyocytes and fibroblasts are densely and evenly interspersed; typically, each contractile cardiomyocyte is surrounded by one or more fibroblasts, facilitating continuous structural and metabolic interactions [9]. The homeostatic regulation of fibroblast function is partially mediated by autocrine and paracrine signaling through the bone morphogenetic protein 4 (BMP4) axis and its receptors (BMPR1A and BMPR2) [32-35].

Under conditions of biomechanical stress (volume or pressure overload), ischemia, or prolonged neurohumoral hyperstimulation (e.g., elevated tissue levels of angiotensin II, aldosterone, or catecholamines), quiescent resident fibroblasts, identified by markers such as Ly6A/Sca1, undergo a complex, multistep cascade of phenotypic activation [33, 36]. This process is accompanied by marked upregulation of pro-inflammatory cytokines and profibrotic markers, such as periostin. A subsequent key stage is their differentiation into myofibroblasts. This phenotype is characterized by increased contractile capacity through de novo expression of alpha-smooth muscle actin (α-SMA) and a substantial increase in ECM biosynthesis [3]. Myofibroblast induction is regulated by intracellular signaling pathways, including kinases such as ROCK2, which controls cytoskeletal dynamics and the expression of CTGF and FGF2, as well as extracellular mechanisms, particularly crosstalk with immune cells (e.g., mediated by the T-cell factor KLF10) [33]. Upon degranulation in the stroma, mast cells release histamine, which stimulates fibroblast proliferation and collagen synthesis via H2 receptors, potentially through enhanced CTGF production [34].

Depending on the triggering mechanism, two fundamentally distinct types of fibrosis develop in the myocardium [33]:

- **Replacement fibrosis** develops secondarily in response to massive cardiomyocyte death (coagulation necrosis in myocardial infarction). Myofibroblasts actively migrate into the aseptic injury zone, eventually forming a dense, rigid collagenous scar. This is an adaptive, life-saving mechanism designed to prevent the catastrophic rupture of the thinned ventricular wall.
- **Reactive fibrosis** occurs without prior loss of viable cardiomyocytes, predominantly in response to a systemic increase in hemodynamic load (arterial

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hypertension, aortic stenosis). This involves a diffuse, excessive, and inadequate accumulation of connective tissue in the interstitial and perivascular spaces, causing generalized organ stiffness [33].

Single-cell RNA sequencing transcriptomic studies have enabled the identification of a novel subpopulation of myocardial interstitial cells—matrifibrocytes [33, 37]. Matrifibrocytes are highly specialized stromal cells that emerge during the late stages of adaptation to chronic injury. When the acute phase of infarct healing concludes and the need for active myofibroblast proliferation subsides, matrifibrocytes contribute to the long-term stabilization of the mature collagen matrix. They maintain the mechanical integrity of the scar and chronic reactive fibrosis by expressing a distinctive set of matrix-related genes [33].

The crosstalk between activated fibroblasts/myofibroblasts and cardiomyocytes is highly complex and bidirectional [36–38]. On the one hand, cardiomyocytes secrete factors that regulate fibroblast proliferation. On the other hand, paracrine mediators secreted by fibroblasts, such as transforming growth factor-β (TGF-β), connective tissue growth factor (CTGF), and fibroblast growth factor 2 (FGF2), directly influence the phenotype and function of adjacent cardiomyocytes [3]. Co-culture experiments have demonstrated the pathological potential of this crosstalk: myofibroblasts isolated from the hearts of animals with pressure overload significantly reduce the viability of adult cardiomyocytes during co-culture and substantially decrease the amplitude of intracellular Ca^{2+} transients, leading to impaired systolic contractile function [36]. Pharmacological blockade of type I TGF-β receptors using SB431542 abolishes these pathological effects, supporting a central role for the profibrotic TGF-β secretome in myocardial dysfunction and remodeling (Fig. 5) [36].

Pericytes constitute a unique, highly specialized population of perivascular cells, historically first described by C. Eberth and comprehensively characterized by C. Rouget, whose classic works demonstrated the intimate morphological apposition of these cells to the endothelium [20]. For a long time, the conceptual function of pericytes was restricted solely to the regulation of capillary blood flow at the microcirculatory level. This was due to the discovery of contractile filaments-actin and myosin-in their cytoplasm [20-25].

Under physiological conditions, the contractile activity of pericytes controls local tissue perfusion, flexibly responding to the metabolic demands of the myocardium [20]. However, in settings of severe myocardial ischemia (e.g., during coronary artery occlusion), pericytes play a fatal role. Microenvironmental alterations lead to pathological pericyte hypercontractility, causing irreversible narrowing of the capillary lumen. This mechanism underpins the formidable clinical "no-reflow" phenomenon, wherein tissue perfusion in the

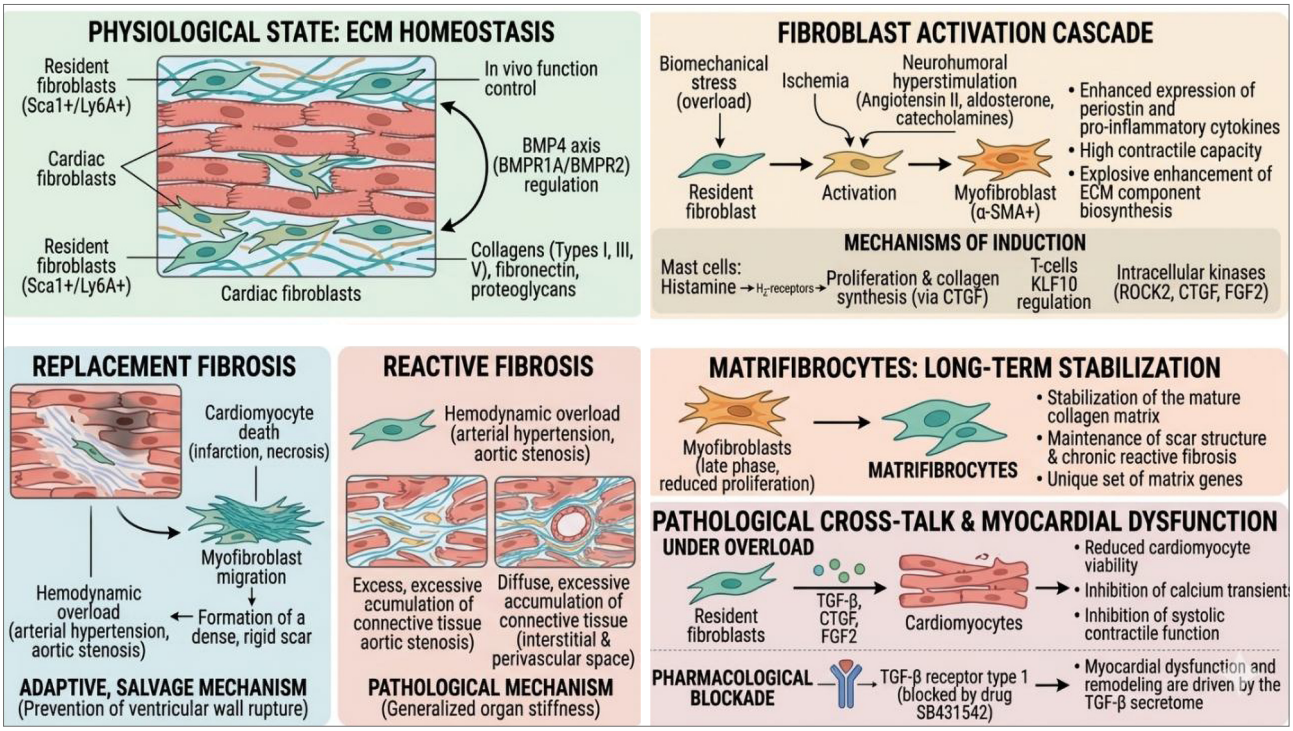

Fig. 5. Fibroblasts, myofibroblasts, and matrifibrocytes in extracellular matrix remodeling (Author's elaboration using AI Sider & Gemini)

myocardium fails to recover even after successful surgical recanalization of a large epicardial artery due to spasm at the capillary level [20]. Experimental pharmacological relaxation of pericytes (e.g., via adenosine administration) promotes a reduction in their contractility, relieves capillary compression, and significantly improves cardiac tissue blood flow [20]. Conversely, genetic disruption of the PDGF-B/PDGFR-β signaling pathway, which is responsible for pericyte adhesion to the endothelium, results in the loss of their contractile function and a paradoxical increase in blood flow [20].

Nevertheless, hemodynamic function is merely the tip of the iceberg. Contemporary transcriptomic research has unveiled the colossal, truly orchestrating role of the pericyte secretome in regulating cardiomyocyte vitality and maintaining the structural integrity of the entire myocardial stroma [22, 40, 41]. In response to microenvironmental stimuli (hypoxia, high glucose levels, inflammation), pericytes release numerous bioactive molecules into the extracellular space and via microvesicles, acting as potent paracrine regulators [22].

The pericyte secretome harbors potent trophic factors. Specifically, they produce vascular endothelial growth factor (VEGF) and specific microRNAs (miR-132) that engage cardiomyocyte receptors, inducing anti-apoptotic cascades and ensuring a survival response under conditions of severe hypoxia [20]. Furthermore, pericytes secrete stromal cell-derived factor-1 (SDF-1), which acts as a robust chemoattractant. SDF-1 activates the homing (targeted migration) of resident cardiac stem cells and circulating progenitor cells to the zone of injury, which is critically important for initiating neoangiogenesis and cardiac muscle regeneration [20].

During myocardial infarction, a massive inflammatory response is activated in the tissue, threatening secondary injury. Pericytes are capable of actively dampening this inflammation via the secretion of inhibitory factors such as leukemia inhibitory factor (LIF) and enzymes like COX-2 (cyclooxygenase-2) and HMOX-1 (heme oxygenase-1) [22]. They also mitigate inflammation indirectly by suppressing the hyperactivity of endothelial cells. Pericytes serve as inhibitors of excessive fibrogenesis. By secreting matrix metalloproteinases (MMPs), they restrict pathological collagen accumulation and suppress the proliferation of activated fibrotic cells. The attenuation of interstitial fibrosis activity holds direct protective significance-it rescues surviving cardiomyocytes from mechanical compression and electrical isolation [22].

There is also experimental evidence indicating that certain subpopulations of cardiac pericytes (along with adventitial cells) exhibit phenotypic characteristics of mesenchymal stem or progenitor cells [2].

Since some pericytes share a common embryonic origin with cardiomyocytes (deriving from epicardial cells), they retain a latent myogenic potential [22]. It has been shown in vivo and in vitro that under the influence of specific cues (e.g., TGF-β molecules and miR-132), pericytes are capable of direct differentiation into structures resembling immature cardiomyocytes, thereby directly contributing to cardiovascular regeneration and the replacement of necrotic scar tissue [20].

The capacity of stromal cells to support vessel formation (angiogenesis) varies depending on their ability to synthesize specific extracellular matrix components. Clonal lines of human bone marrow stromal cells (hMSCs) that support the formation of endothelial networks have been identified. These pro-angiogenic hMSCs express high levels of versican—a chondroitin sulfate proteoglycan that modulates wound healing and angiogenesis. Upon transplantation of such cells into rat hearts, chimeric blood vessels are formed that anastomose with the recipient's circulation, thereby proving the critical role of the quality of the ECM synthesized by cells for myocardial vascularization [24].

Additionally, perivascular adipose tissue (PVAT), anatomically intimately associated with the adventitia of coronary vessels, contributes to paracrine regulation by releasing adiponectin, omentin-1, and lipids associated with extracellular vesicles (the secretion of which is regulated by the RAB27a protein). This confers further cardioprotection and influences vascular smooth muscle cell tone and myocardial contractility (Fig. 6) [25].

One of the most severe clinical consequences of myocardial stromal alterations, which remains challenging to treat, is the development of heart failure with preserved ejection fraction (HFpEF), the fundamental pathophysiological basis of which involves severe diastolic dysfunction [35]. The ability of the myocardium to relax adequately and rapidly (active lusitropy) and to passively distend during diastole to accommodate incoming blood is strongly influenced by the compliance and biomechanical properties of the extracellular matrix.

In a healthy heart, a dynamic equilibrium exists between the synthesis of new collagen fibrils and their enzymatic degradation. This process is mediated by the matrix metalloproteinase (MMP) family, whose activity is tightly regulated by endogenous tissue inhibitors of metalloproteinases (TIMPs) [41-45]. During aging and in conditions

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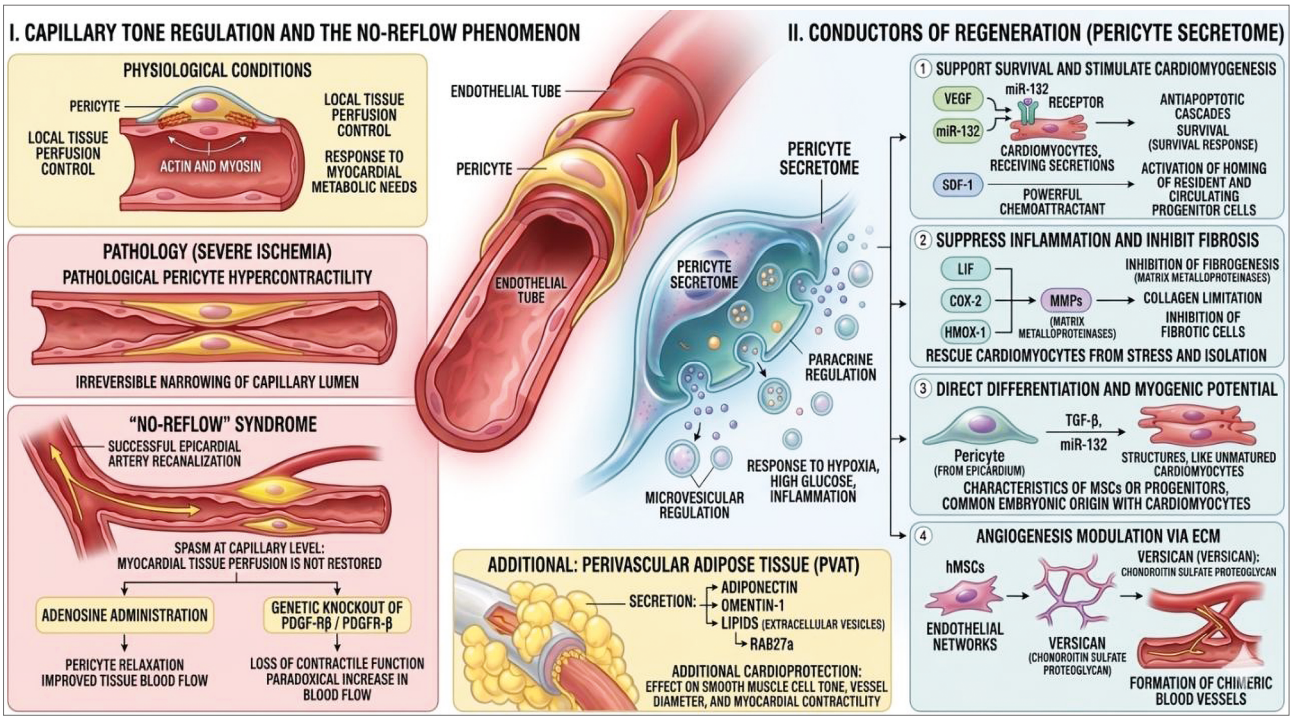

Fig. 6. Pericytes and perivascular cells: from regulators of capillary tone to orchestrators of regeneration (Author's elaboration using AI Sider & Gemini)

such as arterial hypertension and diabetes mellitus, this balance may become disrupted. For instance, pathological increases in MMP-1 activity may lead to fragmentation of the normal matrix and disorganized collagen deposition, whereas reduced activity of other proteases, which may occur in the context of increased secretion of the profibrotic factor TGF-β by myofibroblasts, can contribute to the accumulation of thick, rigid collagen fibrils [45, 46].

However, total myocardial stiffness is determined not only by the absolute collagen content per unit volume of tissue but also by the degree of molecular cross-linking. Specific proteoglycans in the interstitium, such as syndecan-4, as well as matricellular proteins, notably periostin, which regulates collagen fibrillogenesis, contribute to the organization and stabilization of the collagen network. Increased enzymatic cross-linking promotes the formation of covalent bonds between adjacent collagen molecules, transforming a relatively compliant matrix into a more rigid structure [15]. Pronounced perivascular sclerosis, characterized by the accumulation of dense collagen around intramural arterioles and venules, may restrict the ability of coronary microvessels to dilate in response to increased oxygen demand. This can reduce coronary flow reserve and contribute to chronic subendocardial ischemia [35]. Ischemia results in reduced intracellular ATP availability, which is required for the function of the SERCA2a calcium pump responsible for transporting calcium from the cytosol into the sarcoplasmic reticulum. Consequently, impaired calcium reuptake may delay myofilament relaxation and further contribute to ventricular diastolic stiffness [27].

A distinct pathophysiological mechanism contributing to increased myocardial stiffness is associated with disturbed mineral metabolism within the stroma and the development of ectopic calcification. Fetuin-A (α2-Heremans-Schmid glycoprotein) is a highly abundant serum protein synthesized by the liver that acts as an important systemic inhibitor of calcium-phosphate precipitation [47, 48]. Chronic kidney disease and uremia in humans are frequently associated with reduced Fetuin-A levels, which have been linked to increased cardiovascular mortality. Experimental studies in transgenic knockout mice deficient in Fetuin-A (fetuin-KO) demonstrated spontaneous and extensive dystrophic soft-tissue calcification, with the myocardial stroma being particularly affected and exhibiting a 60-fold increase in tissue calcium content, whereas large conduit arteries remained relatively unaffected [48].

Dystrophic calcification of the myocardial interstitium is not necessarily a biologically inert process. The deposition of calcium crystals within the stroma may act as a pathogenic stimulus, promoting induction of the profibrotic factor TGF-β and subsequent upregulation of fibronectin and collagen mRNA expression [48]. This may result

in increased myocardial stiffness independent of arterial vascular stiffness. Hemodynamically, this is associated with impaired diastolic function: fetuin-KO specimens exhibited a statistically significant reduction in basal cardiac output, a 23% decrease in the left ventricular relaxation index, and markedly reduced responsiveness to inotropic stimulation with dobutamine [48]. Furthermore, in experimental models of ischemia, calcified hearts demonstrated increased susceptibility to ischemic injury, with a pronounced reduction in developed ventricular pressure during reperfusion [48]. Collectively, these findings suggest that myocardial stromal calcification may represent an underrecognized contributor to heart failure progression and impaired contractile reserve.

CONCLUSIONS

The myocardial stroma is not a passive mechanical framework, but rather a highly dynamic, vital tissue system composed of unique cellular populations and the extracellular matrix. It is precisely the continuous and intricate crosstalk between stromal components and cardiomyocytes that determines both normal cardiac function and the mechanisms underlying severe cardiovascular pathologies (fibrosis, no-reflow phenomenon during ischemia, critical myocardial stiffness, and heart failure). Therefore, the future of efficacious cardiological therapy and regenerative medicine necessitates a paradigm shift: redirecting the therapeutic focus from the isolated cardiac muscle cell toward the management of the integrated multi-tissue myocardial complex.

Article Declarations

Perspectives for further research. Further research should focus on translating the cellular and molecular mechanisms outlined in this review into experimentally and clinically validated strategies. Priority directions include: (1) targeted modulation of the pericyte and fibroblast secretome to promote neoangiogenesis while limiting the transition to replacement fibrosis; (2) exploration of telocyte-mediated regenerative signaling, including microRNA-based approaches, as a means of preserving cardiomyocyte maturation and repair capacity; (3) large-scale studies of Fetuin-A and other regulators of ectopic stromal calcification as potential biomarkers and therapeutic targets for preventing myocardial stiffness and HFpEF; and (4) mechanistic and clinical trials evaluating whether interventions directed at the stroma, rather than the cardiomyocyte alone, can alter the trajectory of pathological cardiac remodeling. Advances in single-cell and spatial transcriptomics, combined with three-dimensional imaging techniques, are expected to further refine the identification of stromal cell subpopulations and their disease-specific functional states, guiding the development of stroma-targeted therapies.

Study limitations. The authors of the manuscript explicitly acknowledge that the limitations of this review are determined both by the previously outlined scope of the topic, timeframes, and research types, and by the availability of sources. The search strategy encompassed PubMed (https://pubmed.ncbi.nlm.nih.gov/).

Primary data and materials. The authors of the manuscript explicitly acknowledge that primary medical documentation (including medical histories, outpatient records, examination protocols, and laboratory and instrumental test results of specific patients) and statistical databases were not utilized in this study.

Research ethics. The researchers adhered to all protocols and procedures prescribed by the Biomedical Research Ethics Committee, as well as the requirements of Ukrainian healthcare legislation and the provisions of the Declaration of Helsinki (2000).

Declaration of AI use. During the preparation of this work, the authors utilized ChatGPT-4 to generate phrasing options. Following the use of this tool, the authors reviewed and edited the material as necessary and take full responsibility for the content of the publication. The authors utilized the AI Sider & Gemini software to generate the illustrations.

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ІНТЕРСТИЦІЙ МІОКАРДА: ВІД ГІСТОФІЗІОЛОГІЇ ДО КАРДІОСКЛЕРОЗУ ТА ЕКТОПІЧНОЇ КАЛЬЦИФІКАЦІЇ

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РЕЗЮМЕ

Вступ. У сучасній кардіології відбулася фундаментальна зміна парадигми: міокардіальний інтерстицій (строма) більше не розглядається як пасивний каркас, а є високодинамічною, метаболічно активною нейроімунно-судинною нішею, яка підтримує структурний гомеостаз, регулює електрофізіологію та скоротливість і визначає траєкторію патологічного ремоделювання серця.

Мета. Систематизувати сучасні дані щодо структурної та клітинної організації міокардіальної строми та охарактеризувати механізми взаємодії (crosstalk) між стромальними елементами та кардіоміоцитами, що лежать в основі фіброзу та ектопічної кальцифікації.

Матеріали та методи. Проведено систематичний огляд баз даних PubMed/MEDLINE, Scopus і Web of Science; з понад 200 виявлених джерел (2005–2026 рр.), переважно з журналів квартилів Q1–Q2, для аналізу було відібрано 48.

Результати. Архітектоніка міокарда має ламінарну просторову організацію, сформовану колагеновими волокнами ендомізію та перимізію. Клітинний склад інтерстицію є високогетерогенним. Телоцити формують тривимірний каркас за допомогою телоподій, фізично інтегруючи тканинні структури, стимулюючи при цьому дозрівання кардіоміоцитів і підтримуючи регенераторний потенціал за рахунок секреції мікроРНК. Перицити контролюють капілярний кровотік — їхній патологічний спазм лежить в основі феномену «no-reflow» при ішемії — і координують регенерацію через секретом, що стимулює неоангіогенез та обмежує фіброз. Серцеві фібробласти керують біосинтезом матриксу; їхня поетапна активація у міофібробласти та матрифіброцити зумовлює замісний або реактивний фіброз, а TGF-β, що продукується фібробластами, безпосередньо пригнічує скоротливість кардіоміоцитів. Окрім фіброзу, порушення обміну колагену та ектопічна стромальна кальцифікація (наприклад, унаслідок дефіциту Fetuin-A) призводять до жорсткості міокарда та діастолічної дисфункції (СНзФВ), рефрактерної до фармакологічного лікування.

Висновки. Фізіологічний і патологічний стан серця повністю залежить від двонаправленої взаємодії між кардіоміоцитами та стромою; майбутні кардіологічні та регенеративні терапії мають бути спрямовані на інтегроване багатотканинне мікрооточення, а не на ізольований кардіоміоцит.

Ключові слова: строма міокарда, телоцити, фібробласти, позаклітинний матрикс, кардіосклероз, ектопічна кальцифікація.

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