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The Role of the Cardiac Interstitium in Heart Function and Repair: Insights into Structure, Mechanisms, and Therapeutic Potential

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Abstract: The cardiac interstitium is a multifaceted network comprising cells, extracellular matrix (ECM), and signaling molecules that play a critical role in maintaining heart function and facilitating repair mechanisms. This review elucidates the structural composition of the cardiac interstitium, its influence on heart function, and its responses to injury. Recent advancements have highlighted the interstitium active role in modulating mechanical and biochemical signals vital for cardiac function. Key components such as fibroblasts, myofibroblasts, immune cells, and ECM proteins collaborate to sustain the heart's structural integrity and adaptive responses. In the context of cardiac injury, such as myocardial infarction, the interstitium governs processes like inflammation, tissue remodeling, and repair, with dysregulation potentially leading to adverse outcomes like heart failure. This review explores the therapeutic potential of targeting the cardiac interstitium, providing insights into innovative treatments aimed at enhancing cardiac repair and function. By integrating recent research findings, the review aims to offer a comprehensive understanding of the cardiac interstitium role in both health and disease, paving the way for novel therapeutic strategies for heart disease..

Keywords: *Cardiac Interstitium, Extracellular Matrix (ECM), Cardiac Fibroblasts, Heart Function, Myocardial Infarction, Tissue Remodeling*

Introduction

The cardiac interstitium, a complex and dynamic component of the heart, plays a pivotal role in maintaining cardiac function and facilitating repair mechanisms. This intricate network of cells, extracellular matrix (ECM), and signaling molecules provides structural support, regulates cellular communication, and orchestrates tissue homeostasis (1). Understanding the cardiac interstitium contributions to heart function and its responses to injury is essential for developing novel therapeutic strategies for heart disease, a leading cause of morbidity and mortality worldwide (2).

Recent advancements in molecular biology and imaging technologies have shed light on the intricate architecture and multifaceted roles of the cardiac interstitium. The interstitial space, traditionally viewed as

merely a scaffold for cardiomyocytes, is now recognized for its active involvement in modulating mechanical and biochemical signals critical for heart function (3). Components such as fibroblasts, myofibroblasts, immune cells, and a diverse array of ECM proteins collaborate to maintain the heart's structural integrity and adaptive responses to physiological and pathological stimuli (4).

Cardiac repair following injury, such as myocardial infarction, heavily relies on the dynamic interplay within the interstitial compartment. The initial inflammatory response, resolution of inflammation, and subsequent tissue remodeling are processes governed by the cellular and molecular constituents of the interstitium. Dysregulation of these processes can lead to adverse remodeling and heart failure, highlighting the interstitium therapeutic potential (5).

There is a scarcity of comprehensive techniques for specifically addressing the heart interstitium in order to enhance the process of healing and increase functionality after damage. This review explores the composition of the cardiac interstitium, elucidates its impact on heart function and regeneration, and explores novel treatment strategies that specifically target this crucial cardiac compartment. Therefore, the aim of this review is to provide a comprehensive understanding of the role of the cardiac interstitium in health and disease, paving the way for innovative treatments that enhance cardiac repair and function by integrating insights from recent research.

1. Cardiac Interstitium (CI)

1.1. Definition:

It is a network of extracellular matrix and cells within the heart. The cardiac interstitium is the intricate network of extracellular matrix (ECM) components and resident cells within the heart that provides structural support, facilitates communication among cells, and plays a crucial role in maintaining normal cardiac function. It includes various types of cells such as fibroblasts, endothelial cells, immune cells, and newly identified progenitor cells, as well as ECM proteins like collagen, elastin, fibronectin, and proteoglycans (6).

1.2. Components:

The cardiac interstitium comprises various components that work together to maintain the structural integrity, mechanical properties, and functional dynamics of the heart. These components include the extracellular matrix (ECM) and resident cells, each playing crucial roles in the heart's physiology and pathology (1).

1.2.1. Extracellular Matrix (ECM):

The ECM is a complex network of proteins and glycoproteins that provides structural support and regulates cellular behavior. Key components include (Figure 1):

- Collagen: Primarily types I and III, which provide tensile strength and structural integrity to the heart tissue (7).
- Elastin: Contributes to the elasticity and resilience of the cardiac tissue, allowing it to stretch and recoil during the cardiac cycle (8).
- Fibronectin: A glycoprotein involved in cell adhesion, migration, and wound healing. It helps anchor cells to the ECM (9).
- Proteoglycans: These are proteins with glycosaminoglycan chains that contribute to the ECM's viscosity and hydration, playing roles in cell signaling and mechanical resilience (10).
- Laminin: A key glycoprotein in the basal lamina, influencing cell differentiation, migration, and adhesion (11).
- Matricellular proteins: Such as thrombospondins and osteopontin, which modulate cell-ECM interactions and cellular responses to injury (12).

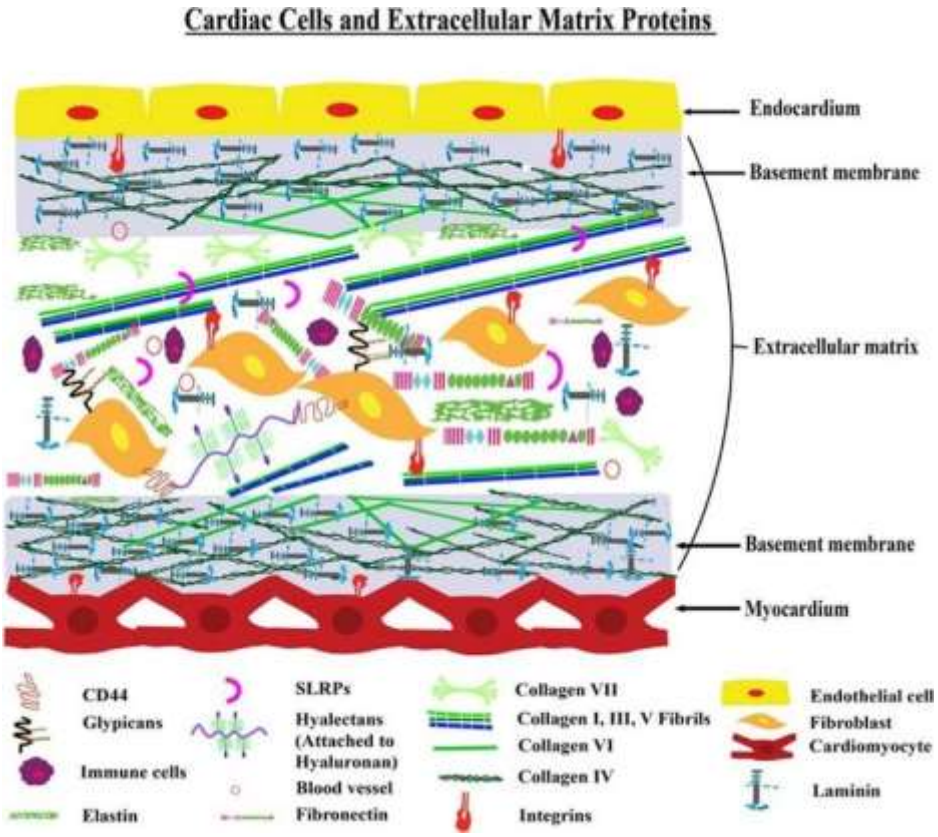

Figure 1: Architecture of Cardiac ECM, The figure shows a model transverse section of the heart's myocardium and endocardium layers. Cardiac muscle cells with a basement membrane make up the myocardium layer, while endothelial cells with a basement membrane make up the endocardium layer. There is an interstitial matrix between the myocardium and endocardium layers. This interstitial space contains fibroblast and extracellular matrix proteins, including collagen, elastin, and fibronectin. Different inflammatory cells are also present in the interstitial matrix (6).

1.2.2. Resident Cells:

Several types of cells reside within the cardiac interstitium, each contributing to its maintenance, repair, and function (Figure 2):

- Fibroblasts: The most abundant cells in the cardiac interstitium, responsible for synthesizing and remodeling the ECM. They respond to mechanical stress and injury by altering ECM composition and secreting growth factors (13).
- Endothelial Cells: Line the blood vessels within the heart, facilitating nutrient and oxygen delivery. They play roles in angiogenesis (the formation of new blood vessels) and modulating inflammation (14).
- Immune cells: Include macrophages, lymphocytes, and mast cells. These cells are involved in the inflammatory response, tissue remodeling, and repair processes following injury (10).
- Cardiac progenitor cells (CPCs): Recently identified cells that can differentiate into various cardiac cell types, including cardiomyocytes, endothelial cells, and smooth muscle cells. They contribute to cardiac repair and regeneration (15).
- Pericytes: Associated with microvessels, these cells support vascular stability and can differentiate into multiple cell types, aiding in tissue repair (11).
- Epicardial-derived cells (EPDCs): Cells originating from the epicardium that can differentiate into fibroblasts, smooth muscle cells, and endothelial cells, particularly active during cardiac injury (16).

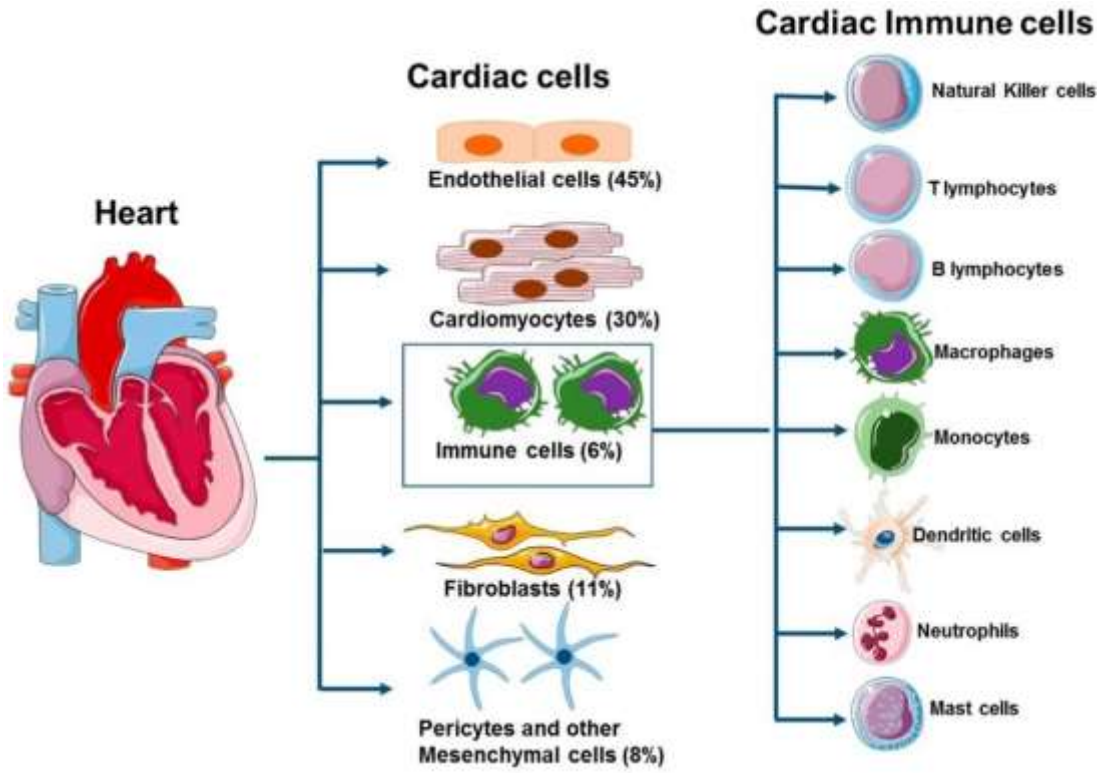

Figure 2: Cellular components of steady-state heart. Heart tissue consists of endothelial cells, myocytes, fibroblasts, pericytes, mesenchymal cells, and various types of immune cells. The macrophages are the major immune cell population in the resting heart and are found in the interstitium and around endothelial cells. Inflammatory monocytes and neutrophils are not present in myocardial tissue but can be observed upon tissue damage. Mast cells, dendritic cells, B cells, natural killer (NK) cells and regulatory T cells are found sporadically in cardiac tissue (17).

2. Role of CI in Cardiac Function

2.1. Structural Support

2.1.1. Provides mechanical stability to the heart.

First, let's look at the extracellular matrix (ECM): the cardiac interstitium (CI) has a lot of ECM proteins, including collagen, elastin, fibronectin, and proteoglycans. These components form a scaffold that maintains the heart's three-dimensional structure. Collagen, particularly types I and III, provides tensile strength, ensuring that the heart can withstand the mechanical forces generated during contraction (systole) and relaxation (diastole) (1).

Secondly, fibroblasts' role: Tallquist & Molkentin (2017) (13) defined that cardiac fibroblasts are responsible for synthesizing and maintaining the ECM. They produce collagen and other ECM components, ensuring that the ECM network is constantly renewed and repaired. This maintenance is crucial for preserving the structural integrity of the myocardium (heart muscle tissue).

2.1.2. Maintains the alignment of cardiac myocytes.

This is reached through two behaviors:

Elastic properties: Frangogiannis (2019) (10) clarified that elastin in the ECM contributes to the elasticity of the heart tissue, allowing it to stretch and recoil with each heartbeat. This elasticity is essential for the heart's ability to expand during diastole (the filling phase) and contract during systole (the pumping phase).

Stress distribution: The interstitium helps distribute mechanical stress throughout the myocardium. According to Eckhouse and Spinale (2012) (18) and Hilgendorf et al. (2024) (19), the interstitium keeps the heart's overall

function by connecting cardiomyocytes to the ECM. This makes sure that the compression forces are spread out evenly, preventing damage in certain areas.

2.2. Electrical Conduction

2.2.1. It contributes to the propagation of electrical signals and ensures the coordinated contraction of the heart in two directions.

Structural support and organization: The cardiac interstitium serves as a scaffold that helps maintain the alignment and organization of cardiomyocytes. Proper alignment ensures that electrical impulses propagate efficiently from cell to cell, facilitating coordinated contraction (3).

The ECM, composed of collagen, elastin, fibronectin, and other proteins, maintains the structural integrity of the myocardium. This structural support helps to stabilize the position of cardiomyocytes and other cells involved in electrical conduction (1).

2.2.2. Facilitates electrical signal propagation and coordinated contraction.

Cell-ECM Interactions: Integrins and other cell adhesion molecules mediate the attachment of cardiomyocytes to the ECM. These interactions determine the structural integrity of the cardiac tissue and the effective transmission of electrical signals between cells (13).

Mechanical-Electrical Feedback: The ECM provides a mechanical environment that influences the electrical properties of cardiomyocytes. Mechanical signals from the ECM can alter electrical signals, influencing ion channel function and cell membrane potentials (20).

2.2.3. Influence on gap junctions and electrical properties.

Gap junction distribution: Gap junctions are specialized cell-cell junctions made up of connexins (like connexin 43) that let cardiomyocytes talk to each other directly through electrical and chemical signals. The ECM and the structural organization of the interstitium influence the organization and distribution of gap junctions (21).

Stabilization of Gap Junctions: The ECM helps stabilize gap junctions and maintain their proper function. Disruption of the ECM can lead to alterations in gap junction distribution and function, which can impair electrical conduction (22,11).

2.3. Biochemical Environment

2.3.1. Regulates the local biochemical environment, facilitating cell signaling and homeostasis.

Proteins such as collagen, elastin, fibronectin, laminin, and proteoglycans make up the extracellular matrix (ECM) composition and signaling. In addition to providing structural support, these molecules serve as reservoirs for signaling molecules such as growth factors and cytokines, releasing them in a controlled manner to influence cellular activities (10).

The ECM provides biochemical cues through its composition and bound molecules that regulate cellular processes such as proliferation, differentiation, migration, and apoptosis. These cues are essential for maintaining the homeostasis and function of cardiac cells (23).

2.3.2. Regulation of ion homeostasis.

Ion exchange and homeostasis: The cardiac interstitium controls the levels of ions, especially calcium, sodium, and potassium, which are necessary for electric activity in the heart and muscle contraction. Proper ion homeostasis is essential for the rhythmic contraction and relaxation of the heart muscle (24).

Ability to buffer: Proteoglycans in the ECM, like heparan sulfate and chondroitin sulfate, can bind and release ions, which helps keep the balance of ions in the heart's interstitial space (25).

2.3.3. Nutrient and oxygen supply.

Vascular network support: The cardiac interstitium contains a rich network of capillaries and blood vessels, supported by ECM components and pericytes. This network ensures an adequate supply of oxygen and nutrients to cardiomyocytes and other cells (26).

Metabolite clearance: The interstitial vascular network makes sure that blood flows efficiently, which also gets rid of metabolic waste products. This is important for keeping the biochemical environment healthy (27).

2.3.4. Paracrine and autocrine signaling.

Cardiac fibroblasts and other interstitial cells secrete various cytokines, growth factors, and extracellular vesicles that influence neighboring cells' behavior. These signaling molecules play crucial roles in cell communication, tissue repair, and regeneration (10).

The interstitium helps modulate inflammatory responses by controlling the release of pro-inflammatory and anti-inflammatory cytokines. This balance is vital for responding to injury without causing excessive inflammation that can lead to tissue damage (28).

2.3.5. Matrix Metalloproteinases (MMPs) and Tissue Inhibitors of Metalloproteinases (TIMPs).

ECM remodeling: MMPs are enzymes that degrade ECM components, allowing for remodeling and repair of the ECM. TIMPs regulate MMP activity to ensure controlled ECM turnover. This balance between MMPs and TIMPs is important for keeping the heart's interstitium structure and biochemistry in good shape (29).

ECM dynamics regulation: Proper ECM remodeling regulation ensures that the ECM remains functional and supportive, preventing excessive fibrosis or degradation that could impair cardiac function (10).

2.3.6. Intercellular Communication.

Gap junctions and connexins: The cardiac interstitium helps gap junctions form and stay in place. These are important for direct communication between cells and the transmission of electrical signals. The biochemical environment that the interstitium maintains has an effect on connexins, which are protein parts of gap junctions (30).

Mechanical-electrical coupling: The biochemical environment of the interstitium affects mechanical-electrical coupling in cardiomyocytes, which makes sure that the heart contracts in sync and works well (31).

2.3.7. Immunomodulation.

Immune cell interaction: The cardiac interstitium contains resident immune cells, such as macrophages, which play a role in immune surveillance and injury response. The interstitial ECM and secreted factors help control the activity of immune cells. This creates a balanced immune response that helps the body heal without too much inflammation (7).

3. Functional Roles of the Cardiac Interstitium:

The cardiac interstitium not only provides structural support but also actively participates in various physiological and pathological processes:

- Structural support: Maintains the three-dimensional architecture of the heart, ensuring proper alignment and function of cardiomyocytes (7).
- Th e role of cardiac interstitium in mechanical properties: Contributes to the heart's ability to contract and relax efficiently, enabling effective blood pumping (32).
- Cell communication: Facilitates signaling between cells through biochemical and mechanical cues, influencing cell behavior, differentiation, and response to injury (13).
- Tissue repair and remodeling: Plays a vital role in the heart's response to injury by regulating inflammation, ECM remodeling, and regeneration processes. This includes activating fibroblasts and recruiting progenitor cells to repair damaged tissue (10,33).

4. Importance in Health and Disease:

In a healthy heart, the cardiac interstitium maintains homeostasis and ensures optimal cardiac function. However, in pathological conditions such as myocardial infarction, cardiac hypertrophy, and heart failure, the interstitial environment undergoes significant changes. These changes often involve:

- Excessive ECM deposition: Leading to fibrosis and stiffening of the heart (7.).
- Fibroblast activation: Resulting in increased ECM production and remodeling (13).
- Inflammation: Infiltration of immune cells and chronic inflammation, contributing to tissue damage and adverse remodeling (10).
- Altered cell composition: Changes in the populations of resident cells, affecting repair and regeneration processes (34).

Conclusion

The cardiac interstitium, once a mere scaffold for cardiomyocytes, is now recognized as a vital component of the heart, crucial for maintaining cardiac function and facilitating repair mechanisms. Its intricate network of cells and endothelial cells (ECM) plays a crucial role in modulating mechanical and biochemical signals essential for heart function. The interstitium involvement in inflammation, tissue remodeling, and repair, especially following cardiac injuries like myocardial infarction, underscores its therapeutic potential. Recent studies reveal that the interstitium fibroblasts, myofibroblasts, immune cells, and ECM proteins collaborate to ensure the heart's structural integrity and adaptive responses. Dysregulation in these components can lead to pathological conditions such as fibrosis, adverse remodeling, and heart failure. Understanding the precise mechanisms by which the interstitium influences cardiac repair and function is pivotal for developing targeted therapies. Emerging therapeutic approaches focus on modulating the interstitial environment to enhance repair and regeneration while preventing adverse remodeling. Advanced molecular and imaging technologies provide deeper insights into the interstitium complex roles, enabling the development of more effective interventions. Future research should explore interstitial cell interactions, ECM remodeling, signaling pathways, and regulatory mechanisms. Targeting the cardiac interstitium, immune cell role, and mechanical/biochemical signals' influence are crucial. Advanced imaging and molecular techniques can guide therapeutic strategies.

References:

(1).del Monte-Nieto, G., Fischer, J. W., Gorski, D. J., Harvey, R. P., & Kovacic, J. C. (2020). Basic biology of extracellular matrix in the cardiovascular system, part 1/4: JACC focus seminar. Journal of the American College of Cardiology, 75(17), 2169-2188.

(2).Hashimoto, H., Olson, E. N., & Bassel-Duby, R. (2018). Therapeutic approaches for cardiac regeneration and repair. Nature Reviews Cardiology, 15(10), 585-600.

(3).Montero, P., Flandes-Iparraguirre, M., Musquiz, S., Pérez Araluce, M., Plano, D., Sanmartín, C., ... & Mazo, M. M. (2020). Cells, materials, and fabrication processes for cardiac tissue engineering. Frontiers in Bioengineering and Biotechnology, 8, 955.

(4).Souders, C. A., Bowers, S. L., & Baudino, T. A. (2009). Cardiac fibroblast: the renaissance cell. Circulation research, 105(12), 1164-1176.

(5).Prabhu, S. D., & Frangogiannis, N. G. (2016). The biological basis for cardiac repair after myocardial infarction: from inflammation to fibrosis. Circulation research, 119(1), 91-112.

(6).Sarohi, V., Chakraborty, S., & Basak, T. (2022). Exploring the cardiac ECM during fibrosis: A new era with next-gen proteomics. Frontiers in Molecular Biosciences, 9, 1030226.

(7).Travers, J. G., Kamal, F. A., Robbins, J., Yutzey, K. E., & Blaxall, B. C. (2016). Cardiac Fibrosis: The Fibroblast Awakens. Circulation Research, 118(6), 1021-1040.

(8).Lin, C. J., Cocciolone, A. J., & Wagenseil, J. E. (2022). Elastin, arterial mechanics, and stenosis. American Journal of Physiology-Cell Physiology, 322(5), C875-C886.

(9).Diller, R. B., & Tabor, A. J. (2022). The role of the extracellular matrix (ECM) in wound healing: a review. Biomimetics, 7(3), 87.

(10). Frangogiannis, N. G. (2019). The extracellular matrix in myocardial injury, repair, and remodeling. Journal of Clinical Investigation, 127(5), 1600-1612.

(11). Zhou, P., & Pu, W. T. (2016). Recounting Cardiac Cellular Composition. Circulation Research, 118(3), 368-370.

(12). Nyström, A., & Bruckner-Tuderman, L. (2019, May). Matrix molecules and skin biology. In Seminars in Cell & Developmental Biology (Vol. 89, pp. 136-146). Academic Press.

(13). Tallquist, M. D., & Molkentin, J. D. (2017). Redefining the identity of cardiac fibroblasts. Nature Reviews Cardiology, 14(8), 484-491.

(14). Krüger-Genge, A., Blocki, A., Franke, R. P., & Jung, F. (2019). Vascular endothelial cell biology: an update. International journal of molecular sciences, 20(18), 4411.

(15). Barreto, S., Hamel, L., Schiatti, T., Yang, Y., & George, V. (2019). Cardiac progenitor cells from stem cells: learning from genetics and biomaterials. Cells, 8(12), 1536.

(16). Iyer, D., Gambardella, L., Bernard, W. G., Serrano, F., Mascetti, V. L., Pedersen, R. A., ... & Talasila, A. (2016). Robust derivation of epicardium and its differentiated smooth muscle cell progeny from human pluripotent stem cells. Development, 143(5), 904-904.
(17). Lafuse, W. P., Wozniak, D. J., & Rajaram, M. V. (2020). Role of cardiac macrophages on cardiac inflammation, fibrosis and tissue repair. Cells, 10(1), 51.
(18). Eckhouse, S. R., & Spinale, F. G. (2012). Changes in the myocardial interstitium and contribution to the progression of heart failure. Heart failure clinics, 8(1), 7-20.
(19). Hilgendorf, I., Frantz, S., & Frangogiannis, N. G. (2024). Repair of the infarcted heart: cellular effectors, molecular mechanisms and therapeutic opportunities. Circulation Research, 134(12), 1718-1751.
(20). Nakayama, K. H., Hou, L., & Huang, N. F. (2014). Role of extracellular matrix signaling cues in modulating cell fate commitment for cardiovascular tissue engineering. Advanced healthcare materials, 3(5), 628-641.
(21). Hervé, J. C., Derangeon, M., Bahbouhi, B., Mesnil, M., & Sarrouilhe, D. (2007). The connexin turnover, an important modulating factor of the level of cell-to-cell junctional communication: comparison with other integral membrane proteins. Journal of membrane biology, 217, 21-33.
(22). Dhein, S., & Salameh, A. (2021). Remodeling of cardiac gap junctional cell–cell coupling. Cells, 10(9), 2422.
(23). Mierke, C. T. (2024). Extracellular Matrix Cues Regulate Mechanosensing and Mechanotransduction of Cancer Cells. Cells, 13(1), 96.
(24). Shattock, M. J., Ottolia, M., Bers, D. M., Blaustein, M. P., Boguslavskyi, A., Bossuyt, J., ... & Xie, Z. J. (2015). Na+/Ca2+ exchange and Na+/K+-ATPase in the heart. The Journal of physiology, 593(6), 1361-1382.
(25). Frantz, C., Stewart, K. M., & Weaver, V. M. (2010). The extracellular matrix at a glance. Journal of cell science, 123(24), 4195-4200.
(26). Su, H., Cantrell, A. C., Zeng, H., Zhu, S. H., & Chen, J. X. (2021). Emerging role of pericytes and their secretome in the heart. Cells, 10(3), 548.
(27). Joyner, M. J., & Casey, D. P. (2015). Regulation of increased blood flow (hyperemia) to muscles during exercise: a hierarchy of competing physiological needs. Physiological reviews.
(28). Chen, L., Deng, H., Cui, H., Fang, J., Zuo, Z., Deng, J., ... & Zhao, L. (2018). Inflammatory responses and inflammation-associated diseases in organs. Oncotarget, 9(6), 7204.
(29). Cabral-Pacheco, G. A., Garza-Veloz, I., Castruita-De la Rosa, C., Ramirez-Acuña, J. M., Perez-Romero, B. A., Guerrero-Rodriguez, J. F., ... & Martinez-Fierro, M. L. (2020). The roles of matrix metalloproteinases and their inhibitors in human diseases. International journal of molecular sciences, 21(24), 9739.
(30). Rodríguez-Sinovas, A., Sánchez, J. A., Valls-Lacalle, L., Consegal, M., & Ferreira-González, I. (2021). Connexins in the heart: regulation, function and involvement in cardiac disease. International journal of molecular sciences, 22(9), 4413.
(31). Stoppel, W. L., Kaplan, D. L., & Black III, L. D. (2016). Electrical and mechanical stimulation of cardiac cells and tissue constructs. Advanced drug delivery reviews, 96, 135-155.
(32). Emig, R., Zgierski-Johnston, C. M., Timmermann, V., Taberner, A. J., Nash, M. P., Kohl, P., & Peyronnet, R. (2021). Passive myocardial mechanical properties: meaning, measurement, models. Biophysical reviews, 1-24.
(33). Frangogiannis, N. G., & Kovacic, J. C. (2020). Extracellular matrix in ischemic heart disease, part 4/4: JACC focus seminar. Journal of the American College of Cardiology, 75(17), 2219-2235.
(34). Lerman, D. A., Alotti, N., Ume, K. L., & Péault, B. (2016). Cardiac repair and regeneration: the value of cell therapies. European Cardiology Review, 11(1), 43.