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Review article

The extracellular matrix: At the center of it all

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ABSTRACT

The extracellular matrix is not only a scaffold that provides support for cells, but it is also involved in cell–cell interactions, proliferation and migration. The intricate relationships among the cellular and acellular components of the heart drive proper heart development, homeostasis and recovery following pathological injury. Cardiac myocytes, fibroblasts and endothelial cells differentially express and respond to particular extracellular matrix factors that contribute to cell communication and overall cardiac function. In addition, turnover and synthesis of ECM components play an important role in cardiac function. Therefore, a better understanding of these factors and their regulation would lend insight into cardiac development and pathology, and would open doors to novel targeted pharmacologic therapies. This review highlights the importance of contributions of particular cardiac cell populations and extracellular matrix factors that are critical to the development and regulation of heart function.

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1. Introduction

Responding to stimuli is a hallmark of the definition of life, and we are constantly adapting to our surrounding environments. Individual cells also read and respond to various signals that surround them. Communication between cells is essential, and is profoundly influenced by the extracellular matrix (ECM). In addition to providing structural support, the ECM contributes to individual cellular and collaborative organ-level functions. In cardiac physiology, the ECM facilitates mechanical, electrical and chemical signals during homeostasis and the developmental process, as well as in response to physiological stress or injury. These signals modulate cellular activities and interactions such as cell proliferation, migration, adhesion and changes in gene expression during homeostasis and development. Furthermore, during post-myocardial infarction (MI) or

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hypertensive remodeling, components of the ECM can play agonistic and antagonistic roles that may contribute to progression towards a healthy recovery or heart failure. This paradoxical relationship and the array of distinct cellular and acellular signals that are involved in cell–ECM communication have made research in this area attractive at both the molecular and cellular levels. This review discusses several developmental processes that illustrate how cell–ECM communication is vital for proper cell–cell communication and cell behavior in the development of the heart, and how some of the same principles apply to cardiac disease and pathological remodeling. Because of the large degree of crosstalk between spatiotemporal and context-dependent signals of the ECM, it is imperative that we approach research involving cell–ECM communication collaboratively, and interpret results from as many angles as possible. We will discuss areas of focus that should help elucidate the cellular mechanisms involved in cell–cell and cell–ECM interactions in the heart, and likely other organ systems as well.

Studies involving the complexity of the ECM in the heart are directly applicable to a host of other physiological conditions. The cellular relationships and ECM factors discussed here are applicable to a wide range of physiological conditions that must be considered when studying any one system. Factors involved in the wound healing process, such as scar formation, collagen turnover, matrikines and cellular migration, are also found in cardiac development and response to injury [1–3]. In cancer progression and metastasis, epithelial–mesenchymal transition (EMT)-like transformations and interactions among tumor and stromal cells are similar to the cellular and acellular milieu seen in the heart [2,4]. Likewise, the basis of an appropriate immune response involves a conglomerate of autocrine, paracrine and hormonal signals, which are differentially released by particular cells, and include spatiotemporal receptor–ligand interactions and expression, just as in cardiac development and adult function. Furthermore, research pertaining to obesity and diabetes, vascular biology and the nervous system offers other areas of crossover, as patients with disorders in these areas present with conditions sufficient to alter homeostatic and pathologic cardiac function.

2. The malleable ECM

It is important to regard the truly dynamic nature of the ECM and the variety of functions it is required to serve. Numerous studies reveal differences in the presence of specific ECM components during distinct physiological states (Fig. 1). The diversity of the ECM composition is illustrated by the unique environments that are required for cell survival and proper function in the developing heart, a normal adult heart and a heart under pathological stimulation. Each cellular environment is subject to a host of autocrine and paracrine signals through cytokines, growth factors and hormones. Moreover, the different microenvironments within the developing or adult heart present with unique biochemical niches, largely driven by cell–cell and cell–ECM interactions.

Early cardiac development is largely dependent upon genetic integrity (i.e., mutations and DNA damage) and more immediate environmental signals (i.e., maternal hormones, mechanical and chemical signaling). Conversely, the adult heart is subject to a multitude of circulating factors and reciprocating signals from other organ systems within the body, especially in response to pathological conditions (i.e., from the kidneys, the central nervous system and the immune compartment). The presence of these "external" signals could alter the sensitivity of the myocardium and cardiac vasculature to more proximal signals from the surrounding cellular environment, during both homeostatic and pathological conditions. Although discussion of circulating factors and other organ systems is not within the scope of this review, they are an important element of the cellular microenvironment of the heart.

3. The ECM in the developing and adult heart

During cardiac development, there is an array of environmental signals that ensures that cell migration and transformation occur in a specific spatiotemporal order. These signals include chemical and mechanical signals originating from both the cells and the ECM. During neonatal development, the ECM constitutes a thin layer within the epicardium, where epicardial mesenchymal cells and ECM thickening (collagen deposition) arise concomitantly [5]. These observations coincide with the differential functions of the fetal and postnatal heart, where ventricular wall thickness and tensile strength (stiffness) increase to accommodate changes in functional requirements following birth and the opening of the ductus arteriosis [6]. In addition, the developing heart tube is arranged as an endothelial cell (EC) layer surrounded by myocardial cells, with an acellular matrix composed of proteoglycans, collagens and glycoproteins found in between the inner EC layers [7]. This matrix serves to maintain tube structure and proper regulation of flow during embryologic heart development.

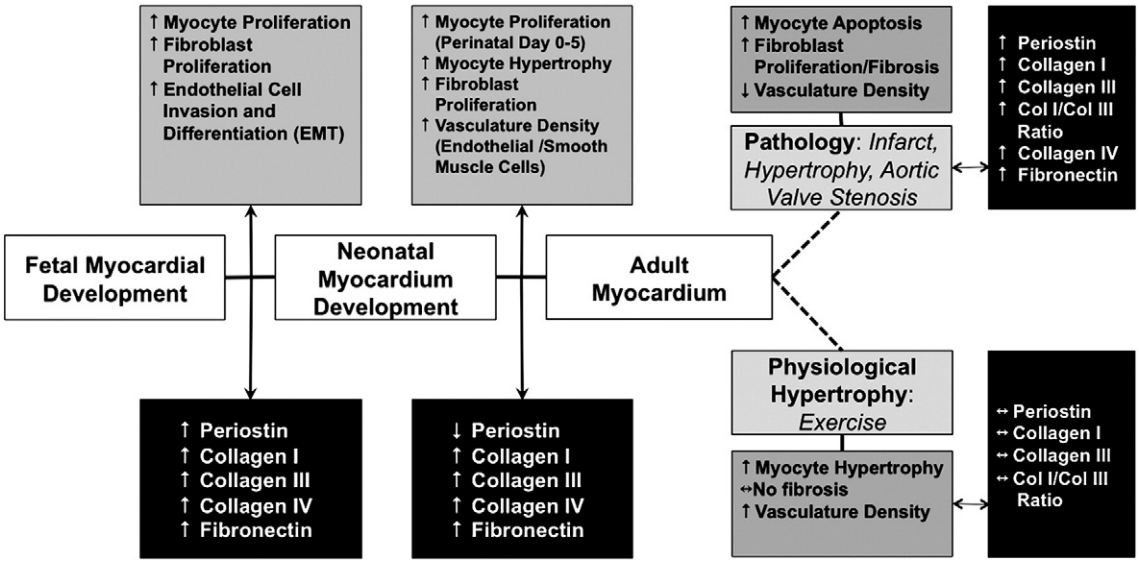

Fig. 1. Schematic of cellular changes (grey boxes) and ECM factor expression (black boxes) during various physiological cardiac states (white boxes).