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Review

Integrins and integrin-related proteins in cardiac fibrosis

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ABSTRACT

Cardiac fibrosis is one of the major components of the healing mechanism following any injury of the heart and as such may contribute to both systolic and diastolic dysfunction in a range of pathophysiologic conditions. Canonically, it can occur as part of the remodeling process that occurs following myocardial infarction or that follows as a response to pressure overload. Integrins are cell surface receptors which act in both cellular adhesion and signaling. Most importantly, in the context of the continuously contracting myocardium, they are recognized as mechanotransducers. They have been implicated in the development of fibrosis in several organs, including the heart. This review will focus on the involvement of integrins and integrin-related proteins, in cardiac fibrosis, outlining the roles of these proteins in the fibrotic responses in specific cardiac pathologies, discuss some of the common end effectors (angiotensin II, transforming growth factor beta 1 and mechanical stress) through which integrins function and finally discuss how manipulation of this set of proteins may lead to new treatments which could prove useful to alter the deleterious effects of cardiac fibrosis.

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Abbreviations: α-SMA, α-smooth muscle actin; Ang II, angiotensin II; CFs, cardiac fibroblasts; CM, cardiac myocyte; ED-A FN, ED-A fibronectin; EC, endothelial cells; EndMT, endothelial–mesenchymal transition; EMT, epithelial–mesenchymal transition; ECM, extracellular matrix; FAK, focal adhesion kinase; FN, fibronectin; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HSC, hepatic stellate cells; ILK, integrin-linked kinase; LLC, large latent complex; LAP, latency associated peptide; LTBP, latent TGFβ binding proteins; LV, left ventricle; LFA-1, lymphocyte function-associated antigen; Mac-1, macrophage-1 antigen; MMP, metalloproteinase; MI, myocardial infarction; OPN, osteopontin; Pax, paxillin; PECAM-1, platelet endothelial cell adhesion molecule; PDGF, platelet-derived growth factor; PO, pressure overload; Pyk2, proline-rich tyrosine kinase-2; SIV, Simian immunodeficiency virus; SLC, small latent complex; STZ, streptozotocin; VSMC, vascular smooth muscle cells; Tln, talin; TSP-1, thrombospondin-1; TGFβ1, transforming growth factor beta 1; Vcl, vinculin.

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1. Introduction

Heart failure is a major cause of morbidity and mortality in the western world with limited numbers of therapeutics that impact the primary disease process [1]. Both heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF) display a range of physiological and morphological changes, including fibrosis of the myocardium. Fibrosis is the excessive deposition of extracellular matrix (ECM) proteins into tissues, leading to scar formation, disruption of normal tissue architecture and potentially to organ failure [2]. In particular, cardiac fibrosis is one of the major components of the healing mechanism following any injury of the heart and as such may contribute to both systolic and diastolic dysfunction in a range of pathophysiologic conditions [3]. Canonically, it can occur as part of the remodeling process that occurs following myocardial infarction (MI) or that follows as a response to pressure overload (PO). It can even be currently tracked non-invasively in man, through use of gadolinium-based magnetic resonance imaging [4].

Multiple organs in the body can be affected by fibrosis, and a large effort has been focused on studying the fibrotic response that occurs in diseases of lung, kidney, liver and skin. Although the triggering events which lead to the fibrotic disorders in these non-cardiac organs could be quite different, the fundamental processes that drive fibrosis are likely to be common in most tissues throughout the body, including the heart. Importantly, disorders that lead to fibrosis can share the complex interplay between inflammatory, epithelial, myofibroblast and ECM responses [5–7]. Myofibroblasts are a main cell type that fuel fibrosis and have combined characteristics of fibroblasts and smooth muscle cells. As such they have a contractile phenotype and contribute significantly to the formation of scarring by secreting ECM components [8]. The origin of myofibroblasts in different organs has been intensely studied, with potential sources suggested to include resident fibroblasts, circulating progenitors (fibrocytes) and also potentially cells that arise by the process of epithelial–mesenchymal transition (EMT) [9,10].

Integrins are cell surface receptors which act in both cellular adhesion and signaling. Most importantly, in the context of the continuously contracting myocardium, they are recognized as mechanotransducers [11–13]. They have been implicated in the development of fibrosis in several organs, including the heart [14]. In addition to their direct effects on cellular proliferation, migration and survival, mediated by their binding to ECM proteins, integrins can potentiate signals from soluble growth factors such as transforming growth factor β1 (TGFβ1), and act as a receptors for matricellular proteins [15]. All of these properties allow integrins and proteins which interact with them, to play essential roles in the fibrotic process.

This review will focus on the involvement of integrins and integrin-related proteins, in cardiac fibrosis. While fibrosis can occur as a component of a wide variety of myocardial diseases, this review will focus on examples that occur following MI and as a result of hemodynamic overload, aging and diabetes. Here we will provide information on how integrins are affected and involved in cardiac fibrosis. In the first part we will introduce basic information about integrins and integrin-related proteins. Then, we will outline the roles of these proteins in the fibrotic responses of specific cardiac pathologies, discuss some of the common end effectors through which integrins function and finally discuss how manipulation of this set of proteins may lead to new treatments which could prove useful to alter the deleterious effects of cardiac fibrosis.

2. Integrins and integrin-related proteins

There have been several recent excellent reviews written about the structure, function, expression and extensive animal modeling studies of integrins and integrin-related proteins. These include ones relevant to the heart, by our own group and others [11,12]. Given this, here we will only provide a brief background on these proteins prior to our discussion of their role in the fibrotic process.

2.1. Integrins

Integrins are transmembrane receptors which act as bridges for cell–ECM connections and in some instances, cell–cell interactions. Thus one of their prime functions is to couple the ECM outside cells, to the cytoskeleton inside the cell. Integrin receptors are obligate heterodimers, composed of two different chains, termed the α and β subunits. In mammals there are 18 α and 8 β subunits, which combine to make up 24 different integrin combinations [16]. The integrin subunits can vary from 90 to 160 kDa and generally consist of a large extracellular domain, a single transmembrane spanning domain, and a short cytoplasmic tail [17]. The cytoplasmic domain of many of the β subunits is highly homologous, while the α subunit sequences are significantly more diverse. It is through the cytoplasmic tail, dominantly of β subunits, that the integrins bind both cytoskeletal linkers and also signal (Fig. 1).

Cell attachment to the ECM is a basic requirement to build a multicellular organism. Integrins are part of the cell adhesion complexes, which along with many cytoplasmic structural and signaling proteins, such as talin (Tln), vinculin (Vcl), paxillin (Pax), focal adhesion kinase (FAK), β-actin and integrin-linked kinase (ILK), serve to link two networks across the plasma membrane: the ECM and the intracellular actin filamentous system [18]. Thus integrins and their associated proteins, are not simply hooks in a cellular meshwork, but provide the cell with critical inputs about the nature of its surroundings. Although integrins do not possess their own enzymatic activity, they are potent bidirectional signaling receptors, playing an important role in cell signaling [19,20]. When triggered by ligands, integrins can influence a host of downstream biochemical pathways in the cell interior, a process commonly termed *outside-in signaling*. This type of signaling may allow sensing of both chemical composition and mechanical status of the ECM outside the cell. Then, depending on the integrin's regulatory impact, the cell can experience growth, proliferation, division, differentiation or other means of remodeling. In addition, the control of integrin function occurs via regulatory signals that originate within the cell cytoplasm and are then transmitted to the external ligand-binding domain of the receptor. This concept is known as *inside-out signaling*. It can increase both binding of integrin to ligand (ECM) and lead to clustering of multiple integrins in close spacing within the cell membrane.

The variety of integrin receptors expressed on a particular cell type can be unique. Further, expression of integrins may not only be restricted to a particular cell type, but can vary depending on developmental stage or pathological state. In addition, functional complexity of integrins also occurs since a single integrin receptor can bind to one or several ligands, and in addition, a single ligand can be bound by several integrin heterodimers. For example, in the cardiac myocyte (CM), the integrin heterodimers most highly expressed are α1β1, α5β1, and α7β1, which are predominantly collagen, fibronectin, and laminin-binding receptors, respectively. In addition, α6, α9, and α10 are also detected in myocytes. β1 is the dominant CM β integrin subunit, but β3 and β5 subunit function have also been studied [21–23]. In contrast,