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Epigenetic Markers in Cardiac Fibrosis

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Introduction

Organ fibrosis and failure are linked to one-third of all fatalities that occur naturally over the world. Cardiovascular fibrosis is a particularly important fibrotic illness, and knowing its etiopathogenesis may help to reduce cardiac morbidity and death. Cardiac fibrosis, like other cardiovascular disorders is caused by a complex combination of genetic, epigenetic, and environmental variables like nutrition and lifestyle. As a result of this information, biomarkers and therapeutic targets for patient management have been identified. Cardiac fibrosis is a cardiac remodeling process caused by injury or stresses that result in the replacement of functional myocardium with non-functional fibrotic tissue, resulting in ventricular systolic and diastolic dysfunction, as well as atrial and ventricular arrhythmias and heart failure. Cardiac myositis makes up about 75% of the total volume of typical cardiac tissue, yet they only make up 30% of the cells. Non-myocytes make up the majority of the remaining cells in the myocardium: 60% endothelial cells, 13% fibroblasts, and 6% vascular smooth muscle cells. Other cell types, such as hematopoietic-derived cells and vascular smooth muscle cells, are seen in tiny numbers [1].

Cardiac fibroblasts are involved in many aspects of heart development and remodeling, as well as the definition of cardiac form and function. Following an injury, local cardiac fibroblasts, as well as bone marrow-derived circulating fibrocystic, get activated, migrate to the injury site, trans differentiate into myo fibroblasts, and secrete ECM components [2]. Pathological alterations such as chamber dilation, cardiomyocyte hypertrophy, and apoptosis occur as a result of this remodeling activity, ultimately leading to heart failure. Increased collagen and other matrix protein deposition, in particular, increases scar formation, which is necessary for myocardial reparative healing. Sustained cardiac damage, on the other hand, leads to persistent myofibroblast activation and proliferation, which results in an unbalanced collagen/matrix metalloproteinase production, interstitial fibrosis, myocyte ischemia, and arrhythmogenicity [3]. In addition to local cardiac fibroblasts and perhaps bone marrow-derived fibroblasts, fibroblast-like cells originate from endothelial cells *via* an Endothelial-to-Mesenchymal Transition (EndMT) driven by TGF-1. EndMT is routinely activated throughout embryonic heart development, but abnormal EndMT activation in adult animals contributes to the onset and progression of fibrosis. As a result, the formation of new fibroblasts by endothelial cells appears to be a promising therapeutic target for cardiac fibrosis. The molecular mechanisms causing TGF-induced EndMT, on the other hand, are unknown, significantly limiting the breadth of clinical intervention [4]. It has been observed that abnormal ECM deposition is linked to epigenetic alterations in ECM-producing genes such collagen, lamina, and fibronectin. The discovery of epigenetic modifications in activated fibroblasts during cardiac fibrosis not only adds to our understanding of the disease's mechanisms, but it also poses a significant challenge in identifying new cellular targets that could be altered for medicinal purposes.

Cardiac Fibrosis

In this review, we look at the role of epigenetics in the genesis and progression of cardiac fibrosis, as well as recent research into epigenetic signatures that may be relevant for cardiac fibrosis prevention, diagnosis, and follow-up. Furthermore, we discuss developing anti-fibrotic epigenetic medicines as well as the possible positive effects of dietary substances with epigenetic activity on fibrotic heart remodeling.

Although cardiac fibrosis is an adaptive and protective mechanism, it advances uncontrollably over time, causing irreversible remodeling and severe reduction in heart function [5]. The activation of cellular events and molecular pathways that involve numerous cardiac cell types such as cardiomyocytes, fibroblasts, vascular, and immune cells results in ventricular remodeling, which is a dynamic and complex process. Clinical ventricular remodeling in pathological conditions can take three forms: (I) Concentric remodeling, in which pressure overload causes cardiomyocyte thickening and ECM protein deposition; (II) Eccentric remodeling, in which volume overload causes cardiomyocyte lengthening; and (III) Post-MI remodeling, in which pressure and volume overload on the non-infarcted area cause cardiomyocyte lengthening [6].

In this study, we focus on post-MI remodeling, which happens after MI injury and results in cardiomyocyte necrosis, resulting in a wound healing process known as reparative fibrosis. In this type of fibrosis, the newly deposition ECM, notably in collagen fibers, takes the place of necrotic cells from a molecular standpoint. Several molecular and cellular inflammatory mediators have a major part in the creation of the fibrotic process, according to a large number of researchers analyzed. In detail, cardiac healing following a MI is the result of a series of processes that begin with a sterile inflammation and immune cell infiltration phase, commonly known as the inflammatory phase.

This crucial phase allows injured cells and ECM to be digested and cleared. This particular stage involves a huge number of well-known danger-associated molecular patterns. HMGB1, S100 proteins, fibronectin's extra domain A and many cytokines and chemokines, such as Interleukin (IL)-1, IL-6, and TNF-, are among them. After that, a reparative phase takes place, which determines the resolution of the inflammatory state, fibroblast proliferation and differentiation into Myo Fibro Blasts (MFB), scar formation, and neovascularization. Despite the fact that inflammation plays a critical role in the course of post-MI ventricular remodeling, there is currently no selective treatment intervention that can successfully turn it off.

Despite the fact that the initial stimulus that leads to fibrous tissue varies, there are several molecules that lead to increased production of pro-fibrotic mediators, such as the anti-inflammatory IL-10 and the Transforming Growth Factor- (TGF-), which act as a "master switch" from inflammation to the reparative process locally. TGF- is a pleiotropic cytokine that regulates a wide range of cell processes, including growth, proliferation, differentiation, and ECM deposition.

Three physically identical TGF isoforms (TGF-1, 2 and 3) have been found in mammalian species, each encoded by three different genes [7].

TGF-1 is the most common isoform, found practically everywhere, whereas the other isoforms are expressed in a narrower range of cells and organs. Many cell types generate TGF-, which is secreted as a Latent Small Complex (LSC) including the C-terminal mature TGF- and the Latency-Associated Peptide (LAP) at its N-terminus. To form the large latency complex, this complex is coupled to the Latent TGF-Binding Proteins (LTBP), an ECM fibrillin-like protein family. Extracellular tissue transglutaminase activity covalently cross-links LLC to ECM proteins after it is secreted [8]. TGF- is unable to bind with its receptor in this shape therefore its activation is predominantly controlled by its release from the LLC. It has been demonstrated over the last few years that stimuli that cause protein denaturation (e.g., acid or alkaline pH in the extracellular milieu, brief increases in temperature, and exposure to oxidants) or proteolysis by the activity of proteases, thrombospondin-1, Matrix-Metalloproteinase (MMP)-2, and MMP-9, determine TGF- release and activation. The released TGF- can bind to the TGF- type II receptor which is constitutively activated [9]. The ligand-receptor complex then recruits the Type I TGF Receptor (TRI), also known as ALK5, which is expressed by a wide range of cell types. ALK1 is a second TRI found in endothelial cells.

The trans-phosphorylation of both TRI types causes downstream intracellular signals to be propagated through the SMAD proteins. SMAD2 and SMAD3 are triggered by ALK5 phosphorylation, although ALK1 activates SMAD1, SMAD5, and SMAD8. The key role of TGF–1 in inducing cardiac hypertrophy by driving (I) Cardiomyocyte hypertrophy, (II) Fibroblast activation and proliferation, and (III) ECM protein synthesis (*i.e.*, collagen) in cardiac tissue is well-known to date. Notably, just a tiny fraction of latent TGF-1 must be activated to achieve maximum cellular response. *In vitro* and *in vivo* research with TGF-1 knockout mice helped to highlight the protein's significance in a variety of cell processes while also revealing its pleiotropic nature and the difficulty in managing it [10].

In this respect, gene therapy experiments using TRII extracellular domain transfection on a MI model reveal that early suppression of TGF-1 may increase cardiac dysfunctions, but late neutralization of TGF signaling may protect against interstitial fibrosis and hypertrophic remodeling. Furthermore, inhibition of TGF- following MI was linked to an increased risk of myocardial rupture, whereas cardiomyocyte-specific suppression of both TRI and TRII induced anti-inflammatory and cytoprotective responses. Thus, early TGF suppression after MI may not have a direct effect on cardiomyocyte survival, but it may result in a loss of anti-inflammatory function in all cardiac cell types (e.g., inflammatory cells, endothelial cells, fibroblasts). The well-known phenotypic switch of fibroblast into MFB is one of TGF-1's primary functions. MFB are distinguished morphologically by the presence of a contractile apparatus made up of bundles of -SMA microfilaments and contractile proteins. This apparatus contains a mechano-transduction system that can generate forces *via* stress fibers, which can then be conveyed and transduced into intracellular signals by the surrounding ECM. ECM production by MFB is increased during the remodeling process to further provide the tension required to activate this mechano-transduction. Type I, III, IV, V, and VI collagen are the most well-known MFB-derived ECM components. The ED-A FN, which is expressed in modest levels by cultured fibroblasts and vascular smooth muscle cells both *in vivo* and *in vitro* is the most accurate marker of MFB-derived ECM. Type VI collagen has recently gotten a lot of interest since it is up regulated during cardiac interstitial fibrosis and the fibrotic process in other tissues. It's vital to note that MFB aren't found in healthy myocardium, but they can be found in this area after a heart attack. The formation of MFB in the infarcted area could be attributed to resident fibroblasts and/or circulating bone marrow progenitors, however this is still a controversial topic.

In response to elevated amounts of bioactive TGF- and the resulting changes in ECM composition, interstitial fibroblasts that survive ischemia injury and/or cells recruited from neighboring viable areas may undergo MFB differentiation. Endothelial-to-mesenchyme transformation of endothelial cells, epicedial epithelial cells, and predicates may be additional sources of MFB in the healing infarcted area. Furthermore, chemokine production in response to significant cardiac necrosis may result in the recruitment and activation of new subsets of reparative fibroblasts, which are critical in scar formation.

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