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Review article

Cardiac fibrosis and arrhythmogenesis: The road to repair is paved with perils

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ABSTRACT

In the healthy heart, cardiac myocytes form an electrical syncytium embedded in a supportive fibroblast-rich extracellular matrix designed to optimize the electromechanical coupling for maximal contractile efficiency of the heart. In the injured heart, however, fibroblasts are activated and differentiate into myofibroblasts that proliferate and generate fibrosis as a component of the wound-healing response. This review discusses how fibroblasts and fibrosis, while essential for maintaining the structural integrity of the heart wall after injury, have undesirable electrophysiological effects by disrupting the normal electrical connectivity of cardiac tissue to increase the vulnerability to arrhythmias. We emphasize the dual contribution of fibrosis in altering source–sink relationships to create a vulnerable substrate while simultaneously facilitating the emergence of triggers such as afterdepolarization-induced premature ventricular complexes—both factors combining synergistically to promote initiation of reentry. We also discuss the potential role of fibroblasts and myofibroblasts in directly altering myocyte electrophysiology in a pro-arrhythmic fashion. Insight into these processes may open up novel therapeutic strategies for preventing and treating arrhythmias in the setting of heart disease as well as avoiding potential arrhythmogenic consequences of cell-based cardiac regeneration therapy. This article is part of a Special Issue entitled "Myocyte-Fibroblast Signaling in Myocardium."

Contents

1. Introduction

Cardiovascular disease is the leading cause of mortality in industrialized countries, and arrhythmias causing sudden cardiac death constitute

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Abbreviations: CV, conduction velocity; Cx, connexin; DAD, delayed afterdepolarization; EAD, early afterdepolarization; ERP, effective refractory period; PVC, premature ventricular complex; VT, ventricular tachycardia.

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a major component. Fortunately, advances in health care have given the injured heart a greater chance to survive injury and heal its wounds. However, a cornerstone of the wound-healing process is scar formation, mediated by activated fibroblasts (myofibroblasts) secreting collagen and producing myocardial fibrosis. Although fibrosis plays a critical role in enhancing mechanical stability to prevent cardiac wall rupture during injury, it also has the undesirable consequence of disrupting the electrical coupling between adjacent strands of myocytes.

In this review, our goal is to highlight how the wound-healing process enhances the risk of potentially lethal cardiac arrhythmias. Our overriding theme is that lethal arrhythmias typically arise from the convergence of two factors: a trigger, such as a premature ventricular complex (PVC), encountering a vulnerable tissue substrate. This trigger–substrate combination promotes the initiation of anatomic or functional reentry that can degenerate to ventricular fibrillation. It has been well-appreciated that fibrosis plays a key role in creating a vulnerable tissue substrate by interposing collagen bundles between strands of myocytes. What is less widely appreciated, but just as important, is the role that fibrosis, and potentially fibroblasts themselves, play in promoting triggers, the other half of this lethal combination. These trigger-promoting effects are mediated through passive effects of fibrosis on the local source–sink relationships that allow triggers to emerge and propagate into normal tissue as PVCs. In addition, emerging but still controversial evidence indicates that activated fibroblasts can exert direct pro-arrhythmic effects on myocytes as a result of myofibroblast–myocyte gap junction coupling [1–3] and/or paracrine factors secreted by myofibroblasts [4–6]. Insight into these mechanisms may lead to new therapeutic approaches to prevent cardiac arrhythmias. Moreover, with the growing focus on cardiac regenerative medicine–in which the therapeutic goal is to induce transplanted stem/progenitor cells or injected biomaterial scaffolds to structurally and functionally integrate with surviving resident myocytes–it is imperative to better understand how endogenous wound-healing mechanisms influence the engraftment process so that the arrhythmogenic effects of myofibroblast proliferation and fibrosis can be minimized.

2. From fibroblasts to myofibroblasts: remodeling the heart in distress

In the normal healthy heart, fibroblasts play a major role in the routine maintenance of myocardial structure. They are the predominant cell type in the heart, exceeding myocytes in number, although not in volume [7]. Primarily responsible for providing myocytes with a 3D mechanical scaffold to integrate the contractile activity of myocytes into the coordinated pumping action of the cardiac chambers, fibroblasts are sentinel cells that tightly coordinate the synthesis and degradation of collagen and other components of the extracellular matrix [8]. Normally quiescent, cardiac fibroblasts are activated by myocardial injury, triggering their differentiation into myofibroblasts to facilitate the wound-healing process, including scar formation and contraction. However, fibroblast heterogeneity and pleiomorphic responses to environmental stress, coupled with the lack of specific lineage markers, present a challenge in analyzing the scope of fibroblast and myofibroblast actions in intact cardiac muscle. Particularly controversial is the extent to which cell culture conditions accurately recapitulate *in vivo* effects. Indeed, whether fibroblasts and myofibroblasts should be discriminated as separate entities rather than a continuum has been questioned [9,10]. Nevertheless, it is generally agreed that at either end of the spectrum, fibroblasts and myofibroblasts comprise distinct cell phenotypes and serve different functions at different stages of the heart evolution from birth through disease, injury, and aging. Therefore, the term 'fibroblasts' has been used loosely and conveniently at times to refer to both the 'fibroblasts' in the normal heart and the 'myofibroblasts' in the injured heart.

In the diseased, injured, or senescent heart with limited myocyte regenerative capability, myofibroblasts may arise either *de novo* or from resident quiescent fibroblasts. The former *de novo* sources may include resident progenitor stem cells, bone-marrow-derived cells, or transformed epithelial and endothelial cells *via* epithelial and endothelial–mesenchymal transitions. The latter arises from the proliferation of activated resident fibroblasts following a phenotype switch, similar but not identical to the phenotype switch of fibroblasts to myofibroblasts observed in cell culture, such that *myo*fibroblasts gain hybrid characteristics of both *smooth muscle cells* and fibroblasts [11,12]. Compared to quiescent fibroblasts, myofibroblasts are much larger [13], proliferate more actively, and deposit collagen at higher rates. They secrete cytokines to recruit other fibroblasts and inflammatory cells, upregulate connexins, readily form both homocellular and heterocellular gap junctions, and express stretch receptors as well as several smooth muscle contractile proteins (such as smooth muscle α-actin and tropomyosin among others). As a result, myofibroblasts can migrate, contract, and respond to a variety of stimuli including mechanical stretch, hypoxia and electrophysiological signals in addition to chemical signals [7]. The increased mobility and collagen-synthesizing function of myofibroblasts is critical for wound closure and maintenance of structural integrity of healing scars in the injured heart [12]. However, the resulting structural remodeling, particularly fibrosis, has important adverse electrophysiological consequences, as described below.

3. Fibrosis creates a vulnerable substrate for reentry

3.1. Patterns of fibrosis and risk of arrhythmias

Fibrosis is categorized into distinct patterns (or textures): compact, patchy, interstitial, and diffuse (Fig. 1) [14]. These different patterns do not have equivalent arrhythmogenic profiles because they differentially affect the two key features that play a critical role in making cardiac tissue vulnerable to functional and anatomic reentry: slow conduction and susceptibility to unidirectional conduction block.

Compact fibrosis, defined as large dense areas of collagen that are devoid of cardiac myocytes, *e.g.* following a myocardial infarction, has the least arrhythmogenic potential because large macroscopic scars, by themselves, neither promote slow conduction nor enhance susceptibility to unidirectional conduction block. Nevertheless, once other conditions initiate reentry, large scars can provide an inexcitable obstacle that anchors a reentry circuit. What makes ischemic heart disease arrhythmogenic is not the compact fibrosis of macroscopic scars *per se*, but the fact that scars are surrounded by a border zone, in which the other patterns of intermediate fibrosis are present to mixed degrees.

Areas of patchy fibrosis and severe interstitial fibrosis, where myocyte bundles are separated over extended distances by collagenous septa, have the greatest arrhythmogenic potential for initiating reentry, whether associated with the border zone of a compact infarct scar or in the setting of nonischemic heart disease. In these regions, strands of surviving myocytes become tenuously interconnected, thereby predisposing the tissue to slow, 'discontinuous', and 'zig-zag' conduction [15,16] (Fig. 2) as well as to unidirectional conduction block due to source–sink mismatches between the strands and adjacent normally coupled tissue (see below). Interconnected strands can also form channels that provide the substrate for anatomic reentry circuits, which manifest clinically as monomorphic ventricular tachycardia (VT) because the slowly conducting impulse in the channel exits to the normal myocardium from a consistent site (or sites) during tachycardia.

Diffuse fibrosis, in which short collagen septa are interspersed among myocardial fibers, also has increased arrhythmogenic potential by selectively reducing side-to-side gap junction connections between myocytes. This reduced homocellular gap junction connectivity slows wave propagation transversely and increases anisotropy, thus predisposing the fibrosed myocardium to wave break and anisotropic