Modulation of impulse propagation by fibroblasts

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MYOCYTES AND NONMYOCYTES COEXIST in cardiac tissue and contribute to normal myocardial cellular function and structure. Fibroblasts are nonmyocytes, whose main role is to synthesize and maintain the myocardial extracellular matrix. Fibroblasts are numerous in cardiac tissue: it has been estimated that every myocyte is in contact with one or more fibroblasts (14). Recently, there has been renewed interest on whether their presence in cardiac tissue affects propagation of the cardiac impulse. Fibroblast-related diseases like cardiac fibrosis lead to the formation of excessive connective tissue and occur during aging and disease (for example, after myocardial infarction) (18–20). Although fibrotic tissue (i.e., fibroblasts and connective tissue) is nonexcitable and electrically passive, it is well established that its presence in myocardium affects propagation of the cardiac impulse and is a cause of arrhythmogenesis (18–20). The interaction of propagating waves with nonmyocyte barriers has been extensively studied, and it has been shown to lead to slow conduction and propagation block, initiation of reentrant waves, and stabilization of drifting reentrant waves (3, 4, 16). There is no experimental evidence indicating that fibroblasts are electrically coupled to myocytes in the setting of cardiac fibrosis or that their effects on propagation and arrhythmogenesis require such an electrical coupling.

There is however experimental evidence of electrical coupling between nonmyocytes and myocytes in cell cultures. It has been shown that fibroblasts can provide a pathway for myocytes to interact electrotonically over distances up to 300 μm (10). Therefore, it is possible that fibroblasts can provide bridges that connect regions of myocytes that otherwise would be electrically isolated by connective tissue. When fibroblasts are electrically coupled to myocytes, they can act as current sinks and consequently decrease conduction velocity and maximum depolarization rate of the action potential (13, 15). Such a decrease in conduction velocity could determine successful propagation or block in areas of myocardium with Na⁺ channel function remedied by disease (1, 5). Fibroblasts have a resting membrane potential that is less negative than that of myocytes (8). Consequently, the resting membrane potential and action potential characteristics of myocytes can be altered by their electrotonic interaction with fibroblasts. Heterogeneities in density and distribution of fibroblasts can result in spatial heterogeneities in action potential duration and refractory period that could create an arrhythmogenic substrate. Transfection of fibroblasts to express various ionic channels further expands the possibilities of modulation of myocyte electrophysiology by fibroblasts (9).

In the recent article by Jacquemet and Henriquez (12), a computer model was used to investigate how electrical coupling of fibroblasts and myocytes affects impulse propagation and the action potential characteristics of atrial myocytes. Different scenarios are investigated in the computer simulations by varying parameters, such as fibroblast-myocyte conductance coupling, fibroblast resting membrane potential, fibroblast density, and distribution. The results illustrate the complexity of the interactions between the different parameters of the model. For example, conduction velocity is increased when fibroblasts and myocytes are weakly coupled, but it is decreased when coupling is strong. The action potential duration is prolonged, but the amount of prolongation depends on fibroblast resting potential and fibroblast density. Although earlier computational studies addressed some of those issues (see references in Ref. 12), Jacquemet and Henriquez extended previous findings to a wider range of fibroblast-myocyte coupling conductances. This is relevant because the actual coupling conductance between fibroblasts and myocytes is uncertain. An obvious corollary of this study is that, to quantify the physiological effect of fibroblasts on impulse propagation, additional experimental data on fibroblast-myocyte conductance coupling, fibroblast resting membrane potential, fibroblast density, and distribution are still necessary.

Jacquemet and Henriquez (12) studied the effect of fibroblasts on impulse propagation in a computer model of atrial tissue. However, impulse propagation and conduction velocity are determined by parameters such as Na⁺ channel function, intracellular and extracellular resistivity, and gap junction conductance, which are tissue specific. Therefore, it is unclear how their results would apply to other tissues in normal hearts or to tissues having Na⁺ channel function and gap junction conductance remodeled by aging or disease (1, 2, 5, 6). Although it is possible that the qualitative conclusions of the study could apply to other cardiac tissues, the quantitative details of the modulation of impulse propagation by fibroblasts will likely be tissue dependent. Similarly, prolongation of the myocyte action potential duration by electrotonic interaction with fibroblasts will depend on the morphology of the repolarization phase of the action potential, which is also tissue dependent.

Despite the demonstration of electrical coupling between myocytes and nonmyocytes in the sinoatrial node of rats (13) and rabbits (7), there is no evidence of such coupling in other regions of the heart, in either normal or diseased hearts. However, recent experiments suggest that fibroblasts transfected to express K⁺ channels affect myocyte refractory period by electrotonic interaction (21). Regardless of their electrical coupling to myocytes, fibroblasts can still modulate propagation of the cardiac impulse in the intact heart. For example, after myocardial infarction, multiple signal transduction pathways are activated and fibroblasts become activated myofibro-
blasts, which are involved in the normal immune response to inflammation and tissue repair (17). The secretion by myofibroblasts of cytokines, chemokines, and growth factors could change the cell environment and modify the action potential characteristics of myocytes. Myofibroblast proliferation could also modulate impulse propagation and initiate and/or stabilize reentrant circuits by changing the cardiac microstructure (11).

GRANTS
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REFERENCES