

Modeling the Effects of Mesenchymal Stem Cells on Cardiomyocyte Electrophysiology

Bijay Kharel, Kevin D. Costa

System Biology Center New York, Department of Pharmacology and System Therapeutics, Mount Sinai School of Medicine, New York, NY

Mesenchymal stem cells (MSC) are considered promising as cell therapies for cardiac repair and regeneration to treat heart diseases such as myocardial infarction. Supporting this idea, our laboratory has demonstrated that 3-D engineered cardiac tissues (ECT), created from neonatal rat cardiomyocytes (NRCM) in collagen, exhibit enhanced contractile force and improved electrophysiology (i.e., reduced activation threshold voltage for pacing) when co-cultured with adult rat MSC. On the other hand, Chang et al. (*Circulation*, 2006) found that NRCM-MSC co-culture, using standard 2-D in vitro conditions, showed increased proarrhythmic potential due to reduced conduction velocity compared to NRCM-only cultures, raising concerns about the benefits of MSC therapies. To help resolve such apparent inconsistencies, we sought to develop a mathematical model of the electrical interaction of MSC with cardiomyocytes. MSC are similar to cardiac fibroblasts in that they both express the gap junction protein connexin-43, and form electrical connections with NRCM. Therefore, our approach was to adapt the model of MacCannell et al. (*Biophys J*, 2007), which was designed to study the electrical interaction between cardiac myocytes and fibroblasts. That model study showed that fibroblasts, with time- and voltage-gated K^+ currents and a resting membrane potential of -40 mV, could cause adverse changes to the action potential of a coupled cardiomyocyte, including reduction of plateau height, and shortening of the action potential duration. However, depolarization of cardiomyocyte resting membrane potential was minimal, even with a 10-fold increase in the relative size of fibroblasts coupled to each myocyte. To examine this cell size effect, we therefore used digital microscopy and image processing to measure the size of several relevant non-cardiomyocyte cell types, namely adult rat MSC, neonatal rat cardiac fibroblasts (NRCM), and adult rat cardiac fibroblasts (ARCF). Our data revealed that MSC diameter ($20.6 \pm 5.6 \mu\text{m}$, $n = 155$) was significantly larger ($p < 0.01$) than ARCF ($17.3 \pm 3.4 \mu\text{m}$, $n = 197$) and NRCF ($14.1 \pm 1.8 \mu\text{m}$, $n = 66$). However, the difference was less than the increase modeled by MacCannell. Therefore, coupling of MSC with cardiomyocytes may slightly raise the resting membrane potential without causing inactivation of Na^+ channels, resulting in a smaller applied stimulus required to reach the threshold potential and induce contraction, consistent with our data in engineered cardiac tissues. Such model studies help to enhance our understanding of how mesenchymal stem cells interact with host myocardium, hopefully leading to new and improved cell therapies for heart diseases such as myocardial infarction.