The Role of Inflammatory Macrophages in Post-MI Electrical Remodeling
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Hypothesis:

I hypothesize that inflammatory macrophages play an important role in post-myocardial infarction (MI – heart attack) electrical remodeling and arrhythmia, thus presenting a novel anti-arrhythmic target.

Proposed Research Accomplished:

My goals were two-fold: to develop a robust, repeatable mouse model of MI and to determine if myocardial levels of macrophage activity correspond to electrical remodeling and arrhythmias following MI.

Results (what actually happened):

The major cause of death following post-myocardial infarction (MI) is sudden cardiac death due to electrical remodeling and ventricular arrhythmias. Although there are current therapies that target cardiac ion channels to prevent deadly arrhythmias post-MI, these attempts have failed or have actually been shown to be pro-arrhythmic. This project thus attempted to determine if the inflammatory macrophage represents a novel therapeutic target. Clinical studies have shown MI patients with ventricular tachycardia/fibrillation (VT/VF) have higher circulating inflammatory cytokines compared to post-MI patients without VT/VF. This experiment developed a MI wild-type mouse model through surgical permanent ligation or ischemia reperfusion of the left anterior descending coronary artery. Four days post-MI, quantum dots (Qdots) were injected into the tail vein. Five days post-MI, arrhythmia propensity and electrophysiological properties were determined via optical mapping, and phagocytic macrophage activity was quantified via imaging of fluorescent Qdot uptake. In hearts with ventricular tachycardia (VT), there was an increased uptake of quantum dots, presumably due to increased phagocytic macrophage activity. Also, hearts with VT had longer mean action potential durations (APDs), indicative of increased arrhythmogenesis. Histological characterization in hearts with MI showed reduced connexin 43 (the major gap protein found in the ventricles of the heart and is responsible for cell-cell electrical communication), reduced alpha actinin (a protein responsible for actin cytoskeleton attachment to the plasma membrane found in myocytes), and increased CD68 (a glycoprotein that is expressed on macrophages) in areas of infarction.