Arrhythmogenic Cardiomyopathy is an Inflammatory Disease

Stephen P. Chelko, Angeliki Asimaki, Peter Anderson, Nuria Amat-Codina, Daniel P. Judge, Jeffrey E. Saffitz

Patients with arrhythmogenic cardiomyopathy (ACM) often have inflammatory infiltrates in their hearts. They also have elevated circulating levels of inflammatory cytokines, and cardiac myocytes themselves produce potent cytokines in ACM. Thus, inflammation in ACM involves both infiltration of inflammatory cells and activation of an innate immune response in cardiac myocytes, either of which might drive the disease. GSK3β, which plays a key pathogenic role in ACM, is known to activate NFκB signaling. Thus, to define the role of inflammation in ACM, we studied effects of the NFκB inhibitor Bay11-7082 in ACM models. Bay11-7082 prevented abnormal redistribution of intercalated disk proteins and greatly reduced myocyte apoptosis and release of inflammatory cytokines in cultured rat ventricular myocytes expressing mutant plakoglobin. Rapamycin, which blocks NFκB signaling downstream of Akt, produced similar effects. Treatment of homozygous *Dsg2* mutant mice (*Dsg2*mut/mut) with Bay11-7082 prevented development of key features of ACM seen in patients. Bay11-7082 reduced myocardial necrosis and fibrosis, preserved LV ejection fraction, and corrected ECG abnormalities. It also prevented myocardial apoptosis and abnormal redistribution of cell-cell junction proteins known to occur in ACM patients. Increased expression of inflammatory cytokines such IL-1β, IFN-γ, IL-12 and IL-33 in hearts of *Dsg*2mut/mut mice was normalized by Bay11-7082. Finally, expression of inflammatory cytokines was markedly increased in ACM myocytes subjected to pulsatile stretch in vitro to simulate exercise. These observations indicate that NFκB signaling in cardiac myocytes and/or infiltrating immune cells drives clinically relevant features in ACM. Exercise, known to increase adverse events in ACM, appears to intensify inflammation. Targeting inflammatory pathways may be an effective mechanism-based therapy in ACM.