Dr. Jason Choi

"The overall goal of this application is to define the molecular pathogenesis of cardiomyopathy associated with Emery-Dreifuss Muscular Dystrophy (EDMD). Autosomal dominant EDMD arises from mutations in a gene encoding A-type lamins, which are intermediate filaments involved in the maintenance of nuclear structure. Further, A-type lamins (along with suns and nesprins) are a component of the LINC complex, which establish a physical connection between the nucleus and the actin cytoskeleton. In EDMD mouse models of EDMD, mitogen activated protein (MAP) kinases ERK and JNK are activated in the heart tissue prior to the development of cardiomyopathy. As MAP kinase activation is well established to be linked to cardiomyopathy, determining how A-type lamin mutations cause activation of MAP kinases will provide key information on the molecular pathogenesis of cardiomyopathy. We hypothesize that EDMD causing mutations lamin A facilitate MAP kinase activation via two distinct mechanisms: 1) mutant lamin A may disrupt the LINC complex, compromising the integrity of the nucleo- cytoskeleton and generating a stress response that activates the MAP kinase pathway and 2) functional disruption of MAP kinase anchors by direct and indirect mechanisms. Lamin A mutations may directly inhibit the function of lamin A as a putative MAP kinase sequestering anchor to facilitate nuclear translocation. Further, mutations in lamin A may disrupt the LINC complex and hence, the function of cytoplasmic anchors that require intact cytoskeleton. To test our hypothesis, we propose two specific aims. Aim 1 will determine whether disrupting the LINC complex in primary cardiomyocytes will activate MAP kinases. We will disrupt the LINC complex by expressing mutant forms of lamin A, suns, and nesprins that prevent interactions necessary to establish the LINC complex and assess for MAP kinase activation by standard biochemical and fluorescence microscopy techniques. Aim 2 will characterize lamin A and MAP kinase interactions in intact cells by various methods and the effect of lamin A mutations on this interaction. We will assess the functional consequence of lamin A mutation on MAP kinase anchors by measuring the mobility of MAP kinases by FRAP and FLIP analysis. Heart muscle damage is the most serious and life-threatening symptom of EDMD. Understanding how defective proteins of the cell nucleus lead to EDMD-associated heart muscle damage will provide the knowledge necessary to devise an effective treatment strategy. This knowledge may also be applicable to similar heart muscle damage resulting from disorders other than EDMD."