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Emery-Dreifuss muscular dystrophy (EDMD) is characterized by weakness and wasting of certain muscle groups, early contractures and a life-threatening cardiomyopathy. EDMD can result from mutations in two genes encoding proteins of the nuclear envelope. Autosomal dominant EDMD and infrequent autosomal recessive cases result from mutations in *LMNA*. *LMNA* encodes A-type nuclear lamins, intermediate filament proteins associated with the inner nuclear membrane. X-linked EDMD is caused by mutations in *EMD*, which encodes an integral protein of the inner nuclear membrane called emerin that interacts with A-type lamins. While the genetic mutations and phenotypic abnormalities in subjects with EDMD have been well described, much less is known about pathogenesis or how alterations in two different nuclear envelope proteins cause the same disease. During the current period of this project, we made new discoveries that provide a coherent and testable pathogenic model to explain the development of muscle damage in EDMD. We have shown activation of the ERK and JNK branches of the MAP kinase cascade, prior to the development of muscle damage, in hearts of mouse models of autosomal and X-linked EDMD. We have further shown that pharmacological inhibition of ERK signaling prevents cardiomyopathy in one of these mouse models. Based on these results, we hypothesize that mutations in *EMD* and *LMNA* cause nuclear envelope abnormalities that lead to activation of MAP kinases. In cardiomyocytes, these MAP kinases activate a set of "downstream" genes that leads to cardiomyopathy. In this project, we will test this hypothesis. In Aim 1, we will investigate the link between A- type lamins and emerin, examining the turn over of emerin in cells lacking A-type lamins or expressing lamins with amino acid substitutions found in subjects with EDMD. We will also examine emerin subcellular localization in affected muscle in a mouse model of autosomal EDMD. Aim 2 is designed to examine MAP kinase signaling pathways in cells with A-type lamin and emerin alterations. The main goals of this aim are to determine how alterations in nuclear envelope proteins activate MAP kinases and to test if reversing alterations in emerin or A-type lamins ameliorates signaling abnormalities. In Aim 3, we will carry out genetic and preclinical pharmacological studies to determine if blocking MAP kinase signaling prevents cardiomyopathy in a mouse model of EDMD. The results obtained in this project will identify targets for therapeutic interventions in EDMD and related disorders caused by *LMNA* and *EMD* mutations.