Dr. Howard Worman

Emery-Dreifuss muscular dystrophy (EDMD) is a syndrome that can result from mutations in several different genes, most of which encode proteins of the nuclear envelope. Skeletal muscle wasting and weakness, joint contractions and life-threatening cardiomyopathy are the classical clinical features. Autosomal EDMD results from mutations in *LMNA*, which encodes A-type lamins, intermediate filament proteins lining the inner nuclear membrane. Most cases of X-linked EDMD result from mutations in *EMD*, which encodes an integral protein of the inner nuclear membrane called emerin. Emerging human genetic data demonstrate that mutations in the gene encoding LAP1, another integral protein of the inner nuclear membrane that interacts with A-type lamins and emerin, also cause muscular dystrophy. Based on our previous research, we have devised a hypothesis regarding the pathogenesis of EDMD proposing that: 1) A-type lamins, emerin and LAP1 form a complex in the nuclear envelope that plays a critical role in striated muscle maintenance, 2) this complex regulates the MAP kinase ERK1/2 and its disruption activates this kinase and 3) the dual-specific phosphatase DUSP4 links activation of ERK1/2 to enhanced AKT-mTOR signaling, which impairs autophagy and induces metabolic defects that lead to heart and skeletal muscle pathology. Using novel murine and cellular models, we will test this hypothesis. In Aim 1, we will use mice with genetic depletions of A-type lamins, emerin and LAP1 to test to establish that these proteins function together in striated muscle cell maintenance *in vivo*. In Aim 2, we will use biochemical and biophysical methods to characterize the lamin-emerin-LAP1 complex and examine its interactions with ERK1/2 and DUSP4. We will also determine if disruption of the lamin-emerin-LAP1 complex activates ERK1/2. In Aim 3, we will test the third part of our hypothesis by crossing mice with alterations in the lamin-emerin-LAP1 complex to mice lacking DUSP4 and determining if this reduces AKT-mTOR activity, reverses defects in autophagy, normalizes cellular energy metabolism and ameliorates pathology. From a public health standpoint, this project will provide an understanding of how mutations in different genes encoding nuclear envelope proteins cause EDMD and related myopathies and identify novel targets for therapies that could change current treatment paradigms.