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Emery-Dreifuss muscular dystrophy (EDMD) is inherited as X-linked, autosomal dominant or rarely autosomal recessive forms. Autosomal EDMD is caused by mutations in LMNA that encodes A-type lamins. An intermediate filament protein associated with the inner nuclear membrane. Most cases of X-linked EDMD are caused by mutations in EMD that encode emerin, an integral protein of the inner nuclear membrane that binds to lamins. Lamina-associated polypeptide 1 (LAP1) is an integral inner nuclear membrane protein that also interacts directly with lamins. Very little is known about the function of LAP1. In preliminary experiments, I have found that LAP1 binds to emerin and that deletion of LAP1 causes emerin and lamin A to mislocalize into discrete structures at the nuclear envelope. Based on theses results, I hypothesize that LAP1 is involved in the pathogenesis of EDMD by regulating emerin and possibly lamin functions. To test this hypothesis, I will pursue a combination of in vivo and in vitro studies to characterize and elucidate the physiological function of the LAP1-emerin interaction in muscle as well as its possibly role in the pathology of EDMD. Specific Aim 1 is to delineate the binding domains through which LAP1 and emerin interact and define the consequences of LAP1 deletion on emerin mobility in live cells. Specific Aim 2 is to identify signaling pathways including MAP kinase, retinoblastoma protein and beta-catenin, that may be modulated by the LAP1-emerin interaction implicated in EDMD. Specific Aim 3 will address the role of LAP1 in striated muscle and test for a genetic interaction between LAP1 and emerin using in vivo mouse models. The overall goal of this proposal is to assess of the functional relevance of LAP1-emerin interaction in EDMD pathogenesis, including at the whole animal level. Dissecting the functional relationship between LAP1 and emerin will provide novel insight into molecular mechanism underlying EDMD and can identify novel targets for therapeutic agents.
