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Abstract

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Grant Number:	5R01AR046911-02
PI Name:	SPENCER, MELISSA J.
PI Email:	mspencer@mednet.ucla.edu
PI Title:	ASSISTANT PROFESSOR
Project Title:	THERAPEUTIC APPROACHES FOR MUSCULAR DYSTROPHY

Abstract: DESCRIPTION (appended verbatim from investigator's abstract): Duchenne muscular dystrophy (DMD) is the most common, inherited, lethal disease of childhood. Despite its high frequency of occurrence and the extensive knowledge of the molecular genetics of DMD, the lifespan or quality of life of DMD children has not improved over that which existed before the mutant gene was discovered approximately 13 years ago. Recently, our laboratories have shown that the histologically discernible pathology of the muscles of mdx mice, the most widely used animal model of the disease, could be reduced by more than half through interventions that inhibit cytotoxic T lymphocytes (CTLs). This is the greatest systemic improvement in the pathology of dystrophic muscle attained by any intervention, and it indicates that important new avenues for approaching DMD therapeutics may exist. The general goal of the investigation proposed here is to obtain more specific information concerning the role of T Iymphocytes in the death of dystrophic muscle, so that more specific therapeutic interventions with applicability to humans can be developed in future work. This will be done by: 1) determining whether distinct populations of T lymphocytes function through independent mechanisms in the autoreactive killing of mdx muscle, 2) testing whether binding of costimulatory molecules that are involved in Tcell activation is important for activation of autoreactive Tcells in mdx mice, and whether simultaneous blockade of these molecules is maximally effective for treatment, 3) testing whether the blockade of costimulating molecu1es of Tcells in mdx mice is most effective at reducing muscle pathology when applied early in the disease process, and 4) testing whether treatment of utrophin deficient mdx mice through Tcell depletions or with blockers of Tcell costimulation is effective in reducing muscle pathology and extending lifespan. Collectively, these findings can provide the basis for design of immune interventions to reduce the pathology of dystrophin deficient muscle.

Thesaurus Terms:
T lymphocyte, cellular pathology, immunotherapy, muscular dystrophy, musculoskeletal disorder therapy, nonhuman therapy evaluation
CD28 molecule, CD40 molecule, T lymphocyte depletion therapy, cell cell interaction, disease /disorder model, immunomodulator, leukocyte activation /transformation, striated

muscle
histology, laboratory mouse

Institution:	UNIVERSITY OF CALIFORNIA LOS ANGELES 405 HILGARD AVE LOS ANGELES, CA 90024
Fiscal Year:	2001
Department:	DUCHENNE MUSC DYST RES CTR
Project Start:	05-MAY-2000
Project End:	30-APR-2005
ICD:	NATIONAL INSTITUTE OF ARTHRITIS AND MUSCULOSKELETAL AND SKIN DISEASES
IRG:	CDF

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Grant Number:	1R01AR048177-01
PI Name:	SPENCER, MELISSA J.
PI Email:	mspencer@mednet.ucla.edu
PI Title:	ASSISTANT PROFESSOR
Project Title:	LGMD 2A protein calpain 3 and its binding to titin

Abstract: DESCRIPTION (provided by applicant): The goals of the investigation proposed here are to examine the molecular interactions between calpain 3 and titin, and to test whether perturbations in those interactions create defects in normal myogenesis. The finding that null mutations in calpain 3 result in debilitating limb girdle muscular dystrophy type 2A, indicates that calpain 3 is important for normal muscle homeostasis. However, the physiological relationship between calpain 3 deficiency and muscular dystrophy is unknown, largely because of lack of information concerning the normal function and interactions of calpain 3. It is proposed here that calpain 3 exists with titin in a macromolecular, functional complex in muscle, and that perturbations of the complex can result in myopathies. Several observations support the contention that defects in titin or its binding partners can cause myopathy. If calpain 3 were also proven to be a titin-binding protein in muscle, that would further advance both our understanding of the basic biology of calpain 3, but also our knowledge of the relationship between defects in the titin macromolecular complex and muscle disease. However, current knowledge of the relationship between titin and calpain 3 is scant, because of the difficulty of isolating the unstable calpain 3 protein. Although it has been demonstrated that calpain binds titin in yeast two-hybrid assays, whether this interaction actually occurs in muscle and whether it is physiologically important remain unknown. The investigation proposed here is designed to examine the relationship between calpain 3 and titin in muscle, and to test the hypothesis that thin interactions with calpain 3 are important for normal myogenesis and muscle structure. The specific aims are: (Aim 1) To test the hypothesis that changes in calpain 3 expression or structure produce alterations in the myogenic phenotype of transgenic mice. (Aim 2) To test the hypothesis that calpain 3 interacts with titin in muscle, and to determine the functionally important domains for that binding. (Aim 3) To test whether C3 interactions with titin are required for normal myogenesis.

Thesaurus Terms:
calpain, molecular pathology, muscle protein, muscular dystrophy, myogenesis, protein protein interaction, protein structure function
gene expression, protein binding

laboratory mouse, transgenic animal

Institution:	UNIVERSITY OF CALIFORNIA LOS ANGELES 405 HILGARD AVE LOS ANGELES, CA 90024
Fiscal Year:	2001
Department:	DUCHENNE MUSC DYST RES CTR
Project Start:	24-SEP-2001
Project End:	31-AUG-2005
ICD:	NATIONAL INSTITUTE OF ARTHRITIS AND MUSCULOSKELETAL AND SKIN DISEASES
IRG:	ZRG1