# Myofibers deficient in connexins 43 and 45 expression protect mice from skeletal muscle and systemic dysfunction promoted by a dysferlin mutation

Fernández G.

Arias-Bravo G.

Bevilacqua J.A.

Castillo-Ruiz M.

Caviedes P.

Sáez J.C.

Cea L.A.

Dysferlinopathy is a genetic human disease caused by mutations in the gene that encodes the dysferlin protein (DYSF). Dysferlin is believed to play a relevant role in cell membrane repair. However, in dysferlin-deficient (blAJ) mice (a model of dysferlinopathies) the recovery of the membrane resealing function by means of the expression of a mini-dysferlin does not arrest progressive muscular damage, suggesting the participation of other unknown pathogenic mechanisms. Here, we show that proteins called connexins 39, 43 and 45 (Cx39, Cx43 and Cx45, respectively) are expressed by blAJ myofibers and form functional hemichannels (Cx HCs) in the sarcolemma. At rest, Cx HCs increased the sarcolemma permeability to small molecules and the intracellular Ca2+ signal. In addition, skeletal muscles of blAJ mice showed lipid accumulation and lack of dysferlin immunoreactivity. As sign of extensive damage and atrophy, muscles of blAJ mice presented elevated numbers of myofibers with internal nuclei, increased number of myofibers with reduced cross-sectional area and elevated creatine kinase activity in serum. In agreement with the extense muscle damage, mice also showed significantly low motor performance. We generated blAJ mice with myofibers deficient in Cx43 and Cx45 expression and found that all above muscle and systemic alterations were absent, indicating that these two Cxs play a critical role in a novel pathogenic mechanism of dysfernolophaties, which is discussed herein. Therefore, Cx HCs could constitute an attractive target for pharmacologic treatment of dyferlinopathies. © 2020 Elsevier B.V.

Calcium ion

Fat infiltration

Membrane permeability

Muscular dystrophy

Muscular performance

connexin 39

connexin 43

connexin 45

creatine kinase

dysferlin

gap junction protein

myogenin

unclassified drug

adult

animal cell

animal experiment

animal model

animal tissue

Article

calcium cell level

calcium signaling

cell membrane permeability

comparative study

connective tissue

controlled study

creatine kinase blood level

dysferlinopathy

enzyme activity

gastrocnemius muscle

gene mutation

human

immunoreactivity

lipid storage

male

molecular pathology

motor performance

mouse

muscle atrophy

muscle cell

muscle function

muscle injury

muscle tissue

nonhuman

priority journal

protein expression

rotarod test

sarcolemma

skeletal muscle