Up-regulation of Toll-like receptors 7 and 9 and its potential implications in the pathogenic mechanisms of LMNA-related myopathies.

Cappelletti C¹, Salerno F¹, Canioni E¹, Mora M¹, Mantegazza R¹, Bernasconi P¹, Maggi L¹.

Author information
1  a Neurology IV - Neuroimmunology and Neuromuscular Diseases Unit, Fondazione IRCCS Istituto Neurologico "Carlo Besta", Milan, Italy.

Abstract
Laminopathies are a heterogeneous group of diseases with overlapping phenotypes that are caused by mutations in the nuclear envelope proteins lamin A and C. The most common group of laminopathies affects skeletal and cardiac muscle tissue, and is defined as LMNA-related myopathies (LMNA-RM). In LMNA-RM patients, muscle histological findings are very variable, ranging from mild and unspecific changes to dystrophic features, sometimes with inflammatory evidence. As recently demonstrated in Duchenne muscular dystrophy, we wondered whether in LMNA-RM muscle tissue the genetic defect might determine the activation of an innate immune response, mainly mediated by Toll-like receptors (TLRs), leading to a chronic inflammation and contributing to myofiber necrosis and fibrosis. By qPCR, we found a significant up-regulation of TLR7 and TLR9 transcripts in LMNA-RM muscles compared to other myopathic and non-myopathic control muscles. By confocal microscopy we observed a marked TLR7/9 staining on LMNA-RM blood vessels and muscle fibers and, when present, on infiltrating cells. Characterization of TLR7/9 positive inflammatory cells showed a prevalence of CD68 positive macrophages, which were scattered in the tissue or localized close to degenerated muscle fibers and connective tissue deposits, with a minor presence of CD11c myeloid cells, and T lymphocytes. Our results recognize innate immunity as a player in LMNA-RM pathogenesis. Modulation of TLR7/9 signaling pathways and the decrease of macrophage-mediated inflammation in LMNA-RM might to be considered as potential therapeutic strategies in LMNA-RM management.

KEYWORDS: Toll-like receptors; laminopathies; macrophages; muscle damage; skeletal muscle

PMID: 29895224  DOI: 10.1080/19491034.2018.1471947