Nucleus. 2018 Jun 12. doi: 10.1080/19491034.2018.1471947. [Epub ahead of print]

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

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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

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