Inflammation, fibrosis and skeletal muscle regeneration in LGMDR9 are orchestrated by macrophages

Heike Kölbel, Corinna Preuße, Lukas Brand, Arpad von Moers, Adela Della Marina, Markus Schuelke, Andreas Roos, Hans-Hilmar Goebel, Ulrike Schara-Schmidt, Werner Stenzel

Affiliations

PMID: 33973272 DOI: 10.1111/nan.12730

Abstract

Aims: Variable degrees of inflammation, necrosis, regeneration and fibrofatty replacement are part of the pathological spectrum of the dystrophic process in alpha dystroglycanopathy LGMDR9 (FKRP-related, OMIM #607155), one of the most prevailing types of LGMDs worldwide. Inflammatory processes and their complex interplay with vascular, myogenic and mesenchymal cells may have a major impact on disease development. The purpose of our study is to describe the specific immune morphological features in muscle tissue of patients with LGMDR9 in order to enable a better understanding of the phenotype of muscle damage leading to disease progression.

Methods: We have analysed skeletal muscle biopsies of 17 patients genetically confirmed as having LGMDR9 by histopathological and molecular techniques.

Results: We identified CD206+ MHC class II+ and STAT6+ immune-repressed macrophages dominating the endomysial infiltrate in areas of myofibre regeneration and fibrosis. Additionally, PDGFRβ+ pericytes were located around MHC class II+ activated capillaries residing in close proximity to areas of fibrosis and regenerating fibres. Expression of VEGF was found on many regenerating neonatal myosin+ fibres myofibres and CD206+ macrophages also co-expressed VEGF.

Conclusion: Our results show characteristic immune inflammatory features in LGMDR9 and more specifically shed light on the predominant role of macrophages and their function in vascular organization, fibrosis and myogenesis. Understanding disease-specific immune phenomena potentially inform about possibilities for anti-fibrotic and anti-inflammatory therapeutic strategies, which may complement Ribitol replacement and gene therapies for LGMDR9 that may be available in the future.

Keywords: CD206; LGMDR9; VEGF; alpha dystroglycan; fibrosis; inflammation; macrophages; regeneration.

This article is protected by copyright. All rights reserved.