

## 6. Muscle growth and atrophy in inflammation and fibrosis

### 1 HMGB1 MEDIATES MUSCLE FATIGUE VIA TLR4 - A POSSIBLE MECHANISM FOR MUSCLE FATIGUE IN PATIENTS WITH INFLAMMATORY MYOPATHIES

Mei Zong,<sup>1</sup> Joseph D Bruton,<sup>2</sup> Cecilia Grundtman,<sup>1,3</sup> Huan Yang,<sup>4</sup> Jian Hua Li,<sup>4</sup> Karin Palmblad,<sup>5</sup> Helena Erlandsson Harris,<sup>1</sup> Ulf Andersson,<sup>5</sup> Håkan Westerblad,<sup>2</sup> Ingrid E Lundberg<sup>1</sup> <sup>1</sup>Rheumatology Unit, Department of Medicine, Karolinska University Hospital, Solna, Karolinska Institutet, Stockholm, Sweden; <sup>2</sup>Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden; <sup>3</sup>Department of Experimental Pathophysiology and Immunology, Innsbruck Medical University, Innsbruck, Austria; <sup>4</sup>Feinstein Institute for Medical Research, Manhasset, New York, USA; <sup>5</sup>Department of Women's and Children's Health, Karolinska University Hospital, Solna, Karolinska Institutet, Stockholm, Sweden

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**Background and objectives** Idiopathic inflammatory myopathies (IIMs) are chronic inflammatory diseases characterised by muscle weakness and the mechanisms are still unclear. High mobility group box protein 1 (HMGB1) is often found together with aberrant expression of major histocompatibility complex (MHC) class I in muscle fibres of patients with IIMs but not in healthy individuals. Exogenous HMGB1 can accelerate development of muscle fatigue and increase MHC-class I expression in adult mice skeletal muscle fibres. In other tissues it has been shown that HMGB1 could mediate functions via different receptors including the receptor for advanced glycation end products (RAGE) and Toll-like receptor 4 (TLR4). In this study, the authors set out to investigate whether HMGB1 contribute to increased muscle fatigue and MHC-class I expression in muscle fibres via RAGE or TLR4 in adult skeletal muscle fibres.

**Materials and methods** Intact single fibres were dissociated from flexor digitorum brevis (FDB) of wild type (WT), RAGE knockout (RAGE<sup>-/-</sup>) and TLR4 knockout (TLR4<sup>-/-</sup>) mice and cultured in the absence or presence of 10 µg/ml recombinant HMGB1. Decrease in sarcoplasmic reticulum (SR) Ca<sup>2+</sup> release, which reflects the development of muscle fatigue, was determined by measuring myoplasmic free tetanic Ca<sup>2+</sup> ((Ca<sup>2+</sup>)<sub>i</sub>) during a series of 300 tetanic contractions. MHC-class I and TLR4 expression in FDB fibres was investigated by immunofluorescence and confocal microscopy. Immunohistochemistry was used to investigate TLR4, MHC-class I and myosin heavy chain expression in muscle fibres of patients with IIMs.

**Results** Intact single muscle fibres from WT and RAGE<sup>-/-</sup> but not from TLR4<sup>-/-</sup> mice showed a greater decline in tetanic (Ca<sup>2+</sup>)<sub>i</sub> at the end of a series of 300 tetanic contractions when cultured with rHMGB1 compared to without rHMGB1; MHC-class I was detected on the membrane of single fibers from WT but not TLR4<sup>-/-</sup> mice when exposed to rHMGB1; TLR4 expression was detected on the sarcolemma of muscle fibres from WT mice. TLR4 and MHC-class I co-expression was observed

in muscle fibres from patients with IIMs and this staining was essentially confined to skeletal type II fast twitch muscle fibers.

**Conclusions** TLR4 mediates muscle fatigue and MHC-class I expression in differentiated skeletal muscle fibres after exposure to the alarmin HMGB1. TLR4, MHC-class I and HMGB1 co-localisation is frequently observed in muscle fibres of patients with IIMs, thus HMGB1-TLR4 pathway may play a role in causing muscle weakness in patients with IIMs and is thus a possible novel target for therapy in IIM patients.