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Proteomic profiling of tissue degeneration and regeneration in muscular dystrophy

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Statement of the Problem: The X-linked neuromuscular disorder Duchenne muscular dystrophy is caused by primary abnormalities in the dystrophin *Dmd* gene and is associated with progressive skeletal muscle wasting, sterile inflammation and reactive myofibrosis. The purpose of this study was to analyze tissue degeneration and regeneration in different muscle subtypes that exhibit varying degrees of pathophysiological susceptibility to fiber necrosis.

Methodology & Experimental Approach: A comparative mass spectrometry-based proteomic analysis was carried out to determine distinct alterations in various skeletal muscles from the dystrophic *mdx* and *mdx-4cv* animal models. This included the characterization of muscle proteins in mildly versus severely affected skeletal muscles, as well as the label-free mass spectrometric evaluation of proteome-wide changes following fiber regeneration. The independent verification of proteomic findings was carried out by comparative immunoblotting surveys with isoform-specific antibodies to key muscle protein markers and immune-fluorescence microscopy.

Findings: In this study, the complexity of changes in the skeletal muscle proteome during tissue degeneration and regeneration could be established. Muscle-associated proteins belonging to the contractile apparatus, excitation-contraction coupling mechanism, metabolic pathways and the cellular stress response were shown to undergo changes in their abundance and/or isoform expression pattern. Contractile proteins, molecular chaperones, mitochondrial enzymes, cytoskeletal proteins and components of the extracellular matrix exhibited differential changes in moderately versus severely dystrophic fiber populations. During regeneration cycles, the reversal of a variety of protein changes was established by comparative proteomics.

Conclusion & Significance: The newly identified proteomic markers of tissue degeneration and regeneration might represent suitable biomarker candidates to advance our general understanding of the molecular pathogenesis of muscular dystrophy, as well as being useful for improving the diagnosis, prognosis and therapy monitoring of dystrophinopathies.

Biography

Kay Ohlendieck has an Undergraduate degree in Biology from the University of Konstanz, Germany (1985), a Ph.D in Biochemistry from University College Cork, Ireland (1989) and a DSc in Muscle Biology from University College Dublin, Ireland (2011). He has worked as a Post-doctoral Associate at the University of Iowa, Iowa City and at the State University of New York, Stony Brook, as well as a Lecturer in the Department of Pharmacology, University College Dublin (1995-2001). Since 2002, he is Chair of Biology at the National University of Ireland, Maynooth, and his research focuses on skeletal muscle proteomics.

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