**SUBPROTEOMIC ANALYSIS OF CARDIOMYOPATHIC CHANGES IN X-LINKED MUSCULAR DYSTROPHY**

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**Objective:** The majority of patients suffering from the muscle wasting disorder Duchenne muscular dystrophy display serious cardiorespiratory complications during the second decade of life. The primary genetic defect in the *Dmd* gene triggers the almost complete absence of the membrane cytoskeletal protein dystrophin, which in turn destabilizes the surface membrane system of cardiomyocytes. Building on findings from previous proteomic studies of dystrophic heart extracts, we have extended here the comparative analysis of the dystrophin-deficient heart to the membrane-enriched fraction. The main objective was to identify new protein alterations in dystrophinopathy-related cardiomyopathy.

**Method:** A mass spectrometric analysis was carried out with the microsomal fraction from the dystrophic *mdx-4cv* mouse model of X-linked muscular dystrophy. Proteomic data sets were analysed in relation to potential cardiac protein interactions by systems bioinformatics and altered protein expression patterns were confirmed by comparative immunoblot analysis.

**Results:**The label-free mass spectrometric analysis of the membrane-enriched fraction confirmed the loss of the Dp427 isoform of dystrophin in cardiomyopathy and the concomitant reduction in dystrophin-associated membrane proteins. Importantly, the abundance of various mitochondrial enzymes and key structural proteins was shown to be reduced. In contrast, a variety of sarcomeric proteins including distinct isoforms of myosin, actin, titin and troponin were identified to be increased in the dystrophic phenotype.

**Conclusion:** The secondary reduction in the dystrophin-associated glycoprotein complex results in the loss of sarcolemmal integrity and an increased susceptibility to abnormal ion handling and stretch-induced fibre damage. Cardiac membrane dysfunction is a common feature of dystrophinopathy-associated cardiomyopathy. The mass spectrometric analysis of the microsomal fraction suggests that considerable proteome-wide changes occur in the dystrophin-deficient heart, which probably present both degenerative pathways and potential adaptive mechanisms to counteract contractile weakness in cardiomyopathy.