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PROTEOMIC PROFILING OF THE BIOFLUID MARKER SIGNATURE OF DYSTROPHINOPATHIES

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The extremely large and multi-promoter DMD gene encodes several dystrophin protein isoforms ranging from 45 to 427 kDa. The full-length muscle isoform of dystrophin (Dp427-M) functions as a membrane cytoskeletal protein that is closely associated with dystroglycans, sarcoglycans, sarcospan, dystrobrevins and syntrophins at the sarcolemma membrane. The dystrophin complex forms a key hub for the provision of lateral force transmission, integration of the cytoskeletal network, stabilization of the myofiber surface by linking the basal lamina to the actin membrane cytoskeleton and supporting cellular signaling (1). Mutations in the DMD gene are associated with the severely progressive muscle wasting disorder of early childhood, Duchenne muscular dystrophy, and later-onset and more benign Becker muscular dystrophy. The chronic degeneration of contractile fibres, inflammation, fat substitution, reactive myofibrosis and satellite cell dysfunction are hallmarks of the cellular pathogenesis of dystrophinopathy (2). For diagnostic and prognostic purposes, invasive muscle biopsy procedures for histological, histochemical and immunochemical studies (3), as well as traditional blood tests with general muscle damage markers, such as creatine kinase, myoglobin and lactate dehydrogenase, are often employed in clinical practice. To improve the biomarker signature of X-linked muscular dystrophy, mass spectrometry-based proteomics (4) has been applied for studying both tissue-associated markers (3) and biofluid-related proteins (5). This presentation focuses on the identification and characterization of biofluid marker candidates found in serum, saliva and urine. This includes muscle-derived cytosolic proteins, such as fatty acid binding protein FABP3 and carbonic anhydrase isoform CA3. In addition, proteins derived from the sarcomere, including myomesin, myosin light chain, myosin binding protein and titin fragments are discussed. Besides myonecrosis, biofluid markers of reactive myofibrosis have been identified, including fibronectin and collagens. Importantly, the usage of liquid biopsies has considerable advantages over invasive procedures, including cost effectiveness, assay robustness and repeated sampling options. The optimum application of biofluid markers promises to improve the screening of muscular dystrophy, and its diagnosis, prognosis and therapeutic monitoring.

Keywords: *biomarker: dystrophin, mass spectrometry, muscular dystrophy, proteomics.*

PATHOGENESIS AND MANAGEMENTS OF GENETIC MUSCLE DISEASES

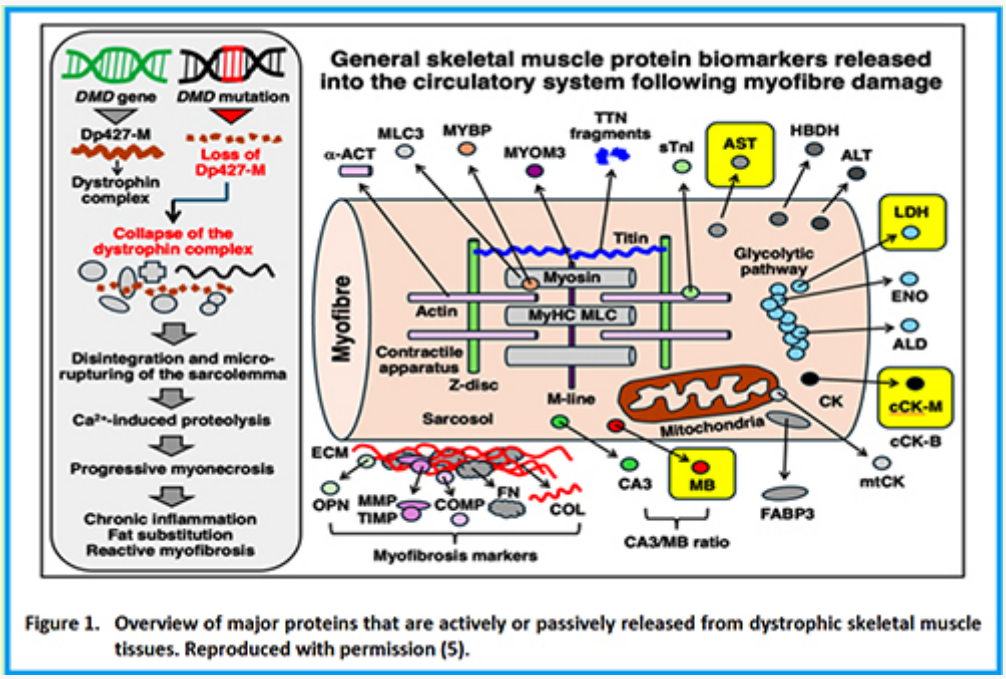

Figure 1. Overview of major proteins that are actively or passively released from dystrophic skeletal muscle tissues. Reproduced with permission (5).