Research Unit 1228: Molecular Pathogenesis of Myofibrillar Myopathies

**Aims and Structure**

The multilocation research unit (FOR) 1228 was funded by the DFG from November 2009-2015. This research unit aimed at clarifying the molecular processes that lead to progressive skeletal muscle and cardiac damage in myofibrillar myopathies. FOR 1228 combined the scientific expertise of physicians, biologists, and biochemists and was composed of 13 distinguished groups from the Universities of Erlangen, Bonn, Bochum, Köln, Heidelberg, Ulm, and Vienna. After a positive evaluation in July 2012, FOR 1228 was granted a second funding period until November 2015. The financial support of the DFG summed up to 3.6 million Euro for a six year term of funding.

**Research**

Myofibrillar myopathies (MFM) are progressive and devastating diseases of human skeletal and cardiac muscles that often lead to premature death. MFM are histopathologically characterized by desmin-positive protein aggregates and myofibrillar degeneration. While about half of all MFM are caused by mutations in genes encoding sarcomeric and extra-sarcomeric proteins (desmin, filamin C, plectin, VCP, FH11, ZASP, myotilin, and B-crystallin, BAG3, DNAJB6), the other half of these diseases is due to still unresolved gene defects. During the first funding period, FOR 1228 has made substantial contributions to our current understanding of the molecular pathogenesis of desminopathies, plectinopathies, filamin C-, FH11- and VCP-related MFM. Major joint achievements have been the establishment and validation of MFM-related animal and cell models, the adaptation and refinement of laser microdissection and proteomic analysis of pathological protein aggregates and biochemical approaches to address molecular pathways contributing to the pathogenesis of MFM. In the second funding period, FOR 1228 focused on the following major goals:

1) Characterization of individual and shared disease mechanisms in myofibrillar myopathies due to pathogenic desmin-, plectin-, filamin C-, and VCP-mutations.
2) Systematic analyses of disease-specific cell and animal models.
3) Validation of cell and animal models for pharmacological treatment strategies.
4) Proteomic characterization of the composition of pathological protein aggregates in skeletal muscle biopsies from patients with genetically proven MFM-causing gene mutations and mouse models.
5) Identification of novel candidate genes that cause human myofibrillar myopathies by laser dissection microscopy followed by proteomic analysis and genomic DNA sequencing.
6) A multi-scale approach addressing biomechanical properties of MFM in myoblasts, myofibers, and whole muscles. FOR 1228 offered the unique opportunity to unravel the molecular “MFM sequence” that leads to pathological protein aggregation and progressive muscle damage. Currently no causative or ameliorating therapy is available for MFM. The joint work of FOR 1228 therefore not only provided deeper mechanistic and preclinical insight into the pathogenesis of MFM, but also aimed at paving the way to novel targeted treatment concepts. As translational approach we therefore studied the therapeutic effect of drugs and compounds that directly target pathological protein aggregation processes. In addition, gene replacement strategies by AAV-mediated gene transfer were evaluated.

**Teaching**

The participating groups of FOR 1228 were supervising PhD and/or medical theses. The principal investigators of individual projects were also actively participating in the teaching of students in the field of medicine, molecular medicine, biology, and biochemistry.

Visualization of pathological protein aggregates in a diagnostic skeletal muscle biopsy from a patient with genetically confirmed desminopathy.

A) Double-immunofluorescence labelling of pathological protein aggregates (yellow) using antibodies against desmin and alphaB-crystallin.
B) Ultrastructural demonstration of granulofilamentous protein aggregates (*) in direct vicinity to myofibrils.