Department of Internal Medicine II

Work Group: Molecular Pathogenesis of Myofibrillar Myopathies

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Myofibrillar myopathies (MFM) are progressive diseases of human heart and skeletal muscle with a severe impact on the quality of life and life expectancy of affected patients. They are histopathologically characterized by desmin-positive protein aggregates and myofibrillar degeneration. Although during the last decade some MFM disease genes, encoding sarcomeric and extra-sarcomeric proteins such as desmin, filamin C, plectin, VCP, ZASP, myotilin and αB-crystallin, could be identified, most genetic causes are still unknown due to the lack of families suitable for classical linkage analyses. Furthermore, the precise mechanisms and signaling events that translate MFM-causing mutations into the myopathic phenotype are not well understood even though they are of immense clinical importance for the development of specific therapies.

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Adult zebrafish (left), zebrafish embryo (right). For the profound dissection of novel genetic causes and pathways involved in the pathogenesis of myopathies, genetic animal models, such as the zebrafish *(Danio rerio)*, have proven extremely helpful. One of the most important advantages of the zebrafish model is the fast development and transparency of the zebrafish embryo that allows easy and direct in vivo analysis of heart and skeletal muscle development, structure and function using light microscopy. Most important is the fact that zebrafish embryos with cardiac misfunction are still able to develop to early larval stages since the lack of blood circulation can be compensated by absorbing oxygen through the skin.

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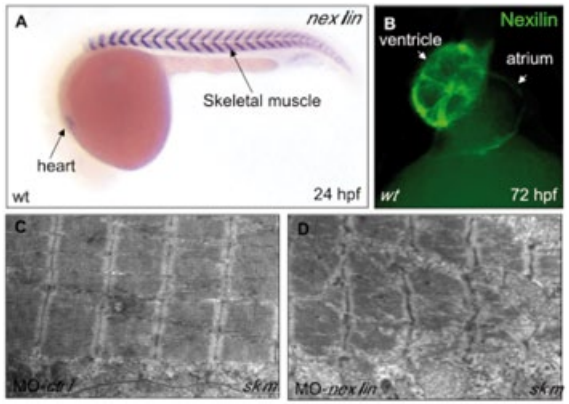
During the last decade, we successfully used forward and reverse genetic strategies in the zebrafish model to dissect novel molecular causes and mechanisms of heart and skeletal muscle myopathies. In an attempt to develop novel targeted treatment strategies for human MFMs, our research aims to elucidate further the genetic basis and the precise molecular mechanisms that translate known MFM mutations into the myopathic phenotype by using forward and reverse genetic approaches in zebrafish.



Nexilin is expressed in the heart (A, B) and skeletal muscle (A) during zebrafish development. Loss of Nexilin function leads to severe cardiac and skeletal muscle myopathy. Transmission electron microscopy analysis of skeletal muscle (skm) ultrastructure from stimulated Nexilin-deficient *(MO-nexilin)* (D) and Control *(MO-ctrl)* (C) zebrafish embryos. Sarcomeric Z-disks appear irregular and detached in Nexilin-deficient embryos.

Selected Publications:

- *Meder B, Just S, Vogel B, Rudloff J, Gartner L, Dahme T, Huttner I, Zankl A, Katus HA, Rottbauer W (2010) Junb-cbfbeta signaling is essential to maintain sarcomeric z-disc structure and when defective leads to heart failure, J Cell Sci 123, 2613-2620.*
- *Hassel D, Dahme T, Erdmann J, Meder B, Huge A, Stoll M, Just S, Hess A, Ehlermann P, Weichenhan D, Grimmler M, Liptau H, Hetzer R, Regitz-Zagrosek V, Fischer C, Nurnberg P, Schunkert H, Katus HA, Rottbauer W (2009) Nexilin mutations destabilize cardiac z-disks and lead to dilated cardiomyopathy, Nat Med 15, 1281-1288.*
- *Hassel D, Scholz EP, Trano N, Friedrich O, Just S, Meder B, Weiss DL, Zitron E, Marquart S, Vogel B, Karle CA, Seemann G, Fishman MC, Katus HA, Rottbauer W (2008) Deficient zebrafish ether-a-go-go-related gene channel gating causes short-qt syndrome in zebrafish reggae mutants, Circulation 117, 866-875.*