The genetics of vertebrate skeletal muscle assembly

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Knowledge about skeletal muscle myofibril assembly is crucial for a better understanding of the molecular basis of the pathological onset of myopathies, which are often caused by disruption of components of the sarcomere. Although the organization of the myofibril and its basic subunit the sarcomere is well characterized, the initial process of sarcomere assembly remains poorly understood. Two prominent models of sarcomere assembly have been proposed: One model suggests that randomly scattered I-Z-I bodies of Z-disk associated proteins and thin filaments recruit titin, which subsequently associates with independently assembled thick filaments to form sarcomeres. Another model suggests that thin filaments, actinin and nonmuscle myosin II form regularly patterned minisarcomeres called premyofibril. Nonmuscle myosin II is subsequently replaced by muscle myosin II and titin is added. Also the distance between Z-bodies is widened, as they align in register and mature into Z-disks. While these two models partially overlap, they are mainly distinguished by the spacing of the Z-bodies, which are suggested to be organized in either randomly scattered I-Z-I bodies or regularly arranged in minisarcomeres. In order to study the process of sarcomere assembly and gain novel insights into human myopathies, we have performed a genetic screen in zebrafish to systematically identify novel molecules that play a role in sarcomere assembly. By utilizing birefringence as a direct indicator for muscle integrity, novel mutants were isolated that disrupted the process of sarcomere assembly. The results of these studies provide support for novel models of sarcomere assembly.