Zebrafish Integrin-linked Kinase is required in Skeletal Muscles for strengthening the Integrin-ECM Adhesion Complex.

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Deficiencies that influence the stability of skeletal muscle cells in humans often lead to various forms of muscular dystrophy (MD). MD is a group of autosomal recessively inherited muscular disorders characterised by hypotonia and weakness at birth or within the first few months of life. The disease is caused by deficiencies in components that facilitate and regulate the connection of the skeletal muscle plasma membrane with the basement membrane and the cytoskeleton. Identification of novel components involved in this connection increases our understanding on the cause of MD. By using the model system zebrafish we identified the focal adhesion protein integrin-linked kinase (Ilk) as a novel component involved in connecting the skeletal muscle plasma membrane with the basement membrane and the cytoskeleton. Via laminins in the extracellular matrix (ECM) and integrin α1β1 in the skeletal muscle plasma membrane, Ilk connects via β-parvin the actin cytoskeleton. Loss of Ilk in zebrafish results in skeletal muscle instability and eventually detachment of the skeletal muscle cells from the myotendinous junction. This reveals Ilk as the link between the cytoskeleton and integrins in skeletal muscle cells. In addition, the laminin/integrinα1β1/Ilk/β-parvin complex acts in parallel with the dystrophin glycoprotein complex (DGC) in maintaining mechanical stability of skeletal muscles in zebrafish. Deficiencies in components of the DGC have been shown before to be involved in the cause of MD and therefore, Ilk is a potential new factor involved in MD. Interestingly, we identified an interaction between Ilk and the mechanical stretch sensor protein MLP (muscle LIM protein), suggesting a link between Ilk and the stretch sense response in skeletal muscle cells.

Role of perlecan, a heparan sulfate proteoglycan, in skeletal muscle maintenance

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Mutations in extracellular matrix molecules such as collagen VI and laminin-2 cause myopathy phenotypes. Schwartz-Jampel syndrome (SJS), which is characterized by myotonia and mild chondrodysplasia, is caused by functional mutations in the perlecan gene. Perlecan is a large heparan sulfate proteoglycan expressed in all basement membranes. Perlecan binds extracellular matrix molecules, growth factors, and receptors and is implicated in many biological functions. We have created a mouse model for SJS by rescuing the perinatal lethality of perlecan-null mice by expressing recombinant perlecan specifically in cartilage under the control of a cartilage-specific promoter. The mutant mice survived and exhibited myotonic myopathy. The mutant mice also developed muscle degeneration and hypertrophy, and changes in the proportion of muscle fiber types. These results suggest that perlecan is required not only for adult muscular function, but also to maintain muscle homeostasis.