Sarcomeric proteins and disease

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My laboratory has identified muscle diseases associated with mutations in a number of sarcomeric proteins. These include mutation of slow α-tropomyosin in autosomal dominant nemaline myopathy, the first known cause of nemaline myopathy (Laing *et al.*, 1995), mutations in nebulin (Pelin *et al.*, 1999), skeletal muscle α-actin (Nowak *et al.*, 1999), slow-skeletal/β-cardiac myosin (Meredith *et al.*, 2004), cofilin (Agrawal *et al.*, 2007), β-tropomyosin (Lehtokari *et al.*, 2007) and filamin (Duff *et al.*, 2011). Other labs have identified mutations in other sarcomeric proteins. Mutations in sarcomeric proteins cause a large range of diseases, from congenital myopathies resulting in almost complete paralysis at birth, through limb girdle muscular dystrophies, to distal myopathies (Laing & Nowak, 2005). Finding these disease genes has helped families through accurate diagnosis, accurate genetic counselling, prenatal diagnosis and to some extent prognosis. Many unanswered questions remain however. These include how mutations in sarcomeric proteins, fundamental to muscle contraction, expressed in either every muscle fibre in the body (Hackman *et al.*, 2002), or in every muscle in the body (Meredith *et al.*, 2004), cause distal myopathies, muscle diseases which preferentially affect specific muscles in specific patterns and result in characteristic distributions of muscle weakness. Another unanswered question is how to treat these diseases. In our own work we have shown that cardiac α-actin, the fetal α-actin isoform in skeletal muscle, can replace skeletal muscle α-actin in skeletal muscle actin knock-out mice. Skeletal muscle α-actin knockout mice normally die by nine days after birth, mimicking the generally severe phenotype of recessive skeletal muscle actin disease in humans, which is characterized by absence of skeletal muscle actin. Transgenic expression of cardiac actin in skeletal muscle after birth rescued the mice to old age (the longest survivors lived greater than two years) (Nowak et al., 2009). We have thus shown that cardiac actin is a target for therapy for the skeletal muscle actin diseases. These results also raise questions of why during normal development, cardiac actin is expressed in fetal skeletal muscle, but is switched off before birth and replaced with skeletal muscle actin (lkovski *et al.*, 2005), when, from our results, cardiac actin function in skeletal muscle is compatible with normal life span.

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