A molecular genetic and cell biological analysis of neuromuscular remodelling in the kyphoscoliotic mouse (ky)

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The autosomal recessive murine muscle disease, kyphoscoliosis (ky), has muscle fibre degeneration in tonic muscles (eg. soleus) followed by regeneration. However, maturation of regenerating fibres is arrested such that muscles are smaller and weaker than controls.

The most striking histopathological differences between ky and other mutants such as mdx mice are the extreme motor axon sprouting in ky as well as the grossly abnormal distribution of acetylcholine receptor (AChR) and acetylcholinesterase (AChE) in affected muscles, reminiscent of myasthenic syndromes. There are also multiple endplates on single regenerated muscle fibres sometimes from different nerves sometimes one junction is supplied by a sprout from another nearby. We have also localized several junction-associated proteins and found that 43 kDa was associated with AChR in ky muscles but AChR could be found without 43 kDa. We have also shown that the soleus muscles of older ky mice are significantly weaker and express only the slow myosin heavy chain, presumably as a long term consequence of the abnormal neuromuscular interaction. The long term outcome of degenerative muscle disease is not simply a consequence of the relative efficiency of muscle regeneration but is a consequence of the complex interaction of genes regulating nerve and muscle differentiation and stability.

Using an interspecific backcross segregating the ky mutation we have mapped the ky locus to chromosome 9 and it is non-recombinant with the microsatellite marker D9Mit24. We have eliminated most obvious candidate proteins (AChR's, AChE, myosin, actin, 43 kDa protein, dystrophin, DRP etc.) which might otherwise have been implicated in the development of the ky disease. Based on current evidence the ky mutation would appear to lie in a gene coding for an as yet unidentified junction-associated protein.

The ky mouse is a valuable experimental system for the investigation of the molecular and cellular processes which precipitate abnormal gene expression following initial muscle fibre death.