

NCK PROTEINS CONTRIBUTE TO MUSCLE DEVELOPMENT AND FUNCTION

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BACKGROUND: The intracellular NCK adaptor proteins, NCK1 and NCK2, function to control actin polymerization downstream of activated tyrosine kinases. Since a number of tyrosine kinases have been implicated in muscle development, and actin is a major component of muscle development and function, we utilized homologous recombination technology to restrict the loss of NCK proteins to developing muscle to study the importance of NCK proteins in muscle development.

METHODS: Homologous recombination technology was employed to delete the individual genes and generate a muscle specific deletion of both genes. *In vitro* nerve muscle preparations were developed to measure muscle force, and molecular and cellular studies were used to follow the expression of muscle specific proteins during development.

RESULTS: Mice lacking NCK proteins in the developing muscle die at birth and show morphological defects consistent with muscular dystrophy including deterioration of muscle fibers and loss of myosin expression. To identify whether NCK1 or NCK2 is more critical for muscle development, we analyzed the single mutants. Both NCK1 and NCK2 mutant mice showed normal muscle weights compared to control mice; however, they both showed defects in stimulated force contractions and tetanic force contractions. Both mutant mice showed defects in the expression of muscle specific proteins. Finally, we have shown that NCK1 is not expressed in differentiated muscle, but is highly expressed in a subset of satellite cells implicating a role for NCK1 in proliferation and muscle regeneration.

CONCLUSION: Taken together, these results revealed a novel role of NCK in muscle tissue and showed the importance of NCK to maintain muscle function integrity and development.