Regulation of human muscle contraction in health and disease

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The overall objective of the research in our group is to have a detailed understanding of regulation of muscle contraction in human skeletal muscle in health and disease. The development and modifications of methods to study human muscle contraction from the whole muscle, motor unit, muscle cell and motor protein levels and most recently the three-dimensional organization of myonuclei at the single muscle fibre level have been driven by our long-standing interest in the aging-related impairment in skeletal muscle structure and function, i.e., sarcopenia. Falls are a major cause of morbidity and mortality in the growing population of elderly citizens and events after depolarization of skeletal muscle, i.e., in force-generation and contractile speed, have been shown to play a primary role for the impaired ability in old age to recover from an impending fall (Schultz *et al.*, 1997). In support of this, the decline in mobility and lower extremity disability have been reported most influential in predicting falls in the elderly (Blake *et al.*, 1988; Mahoney *et al.*, 1994; Mahoney *et al.*, 1999; Robbins *et al.*, 1989), and the predictive value of the muscle weakness is increased further when muscle force is measured at a speed of movement resembling more functional limb velocities. Specific interest has therefore been focussed on the mechanisms underlying the decreased force and speed of contraction associated with aging from the muscle to the motor protein levels.

During the past two decades the focus of our research has shifted more towards muscle diseases affecting sarcomeric proteins, primarily myosin and regulatory proteins. The coding sequence for the adult myosin isoforms is among the most heavily amplified in mammalian species. In spite of the abundance of myosin and its critical role in motor function, there are only few reports in the literature describing neuromuscular disorders where the motor protein myosin is primarily affected by the disease. However there is an increasing awareness of both acquired and hereditary myosin myopathies, *i.e.* “myosinopathies” as well as other sarcomeric protein specific diseases (Laing, 2007; Shrager *et al.*, 2000). The methods to study regulation of muscle contraction at the muscle cell and motor protein levels together with biochemical and molecular biological methods to determine protein and gene expression have proved very useful in the understanding of the mechanisms underlying the motor handicap in these patients.

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