Strumpellin is a novel valosin-containing protein (VCP/p97) binding partner linking hereditary spastic paraplegia to protein aggregation diseases

Mutations in the human valosin-containing protein (VCP/p97) and strumpellin genes cause inclusion body myopathy associated with Paget’s disease of bone and frontotemporal dementia (IBMPFD) and hereditary spastic paraplegia (HSP), respectively. VCP has been reported to play an important role in various cellular processes, while strumpellin is a largely uncharacterized protein. We found that strumpellin is a novel binding protein to VCP and localized in the cytosol and the endoplasmic reticulum. Strumpellin is a ubiquitous protein and an evolutionary highly conserved protein containing a “spectrin-like” domain. Our cell migration assays showed that hereditary spastic paraplegia causing mutant N471D strumpellin is functionally inactive protein, which imply a strumpellin loss-of-function pathogenesis in hereditary spastic paraplegia. Strumpellin knock-down in human cell lines revealed defects in cell migration as well as axonal outgrowth development. Morpholino based knock-down of the strumpellin ortholog in zebrafish revealed severe cardiac contractile dysfunction, tail curvature and impaired motility which are due to a loss of central and peripheral motoneuron formation. These data imply that strumpellin play an important role in cell migration, axonal outgrowth development and motoneuron formation. Our pull down assays and immunofluorescence analyses showed neither IBMPFD mutant R155C VCP nor hereditary spastic paraplegia mutant N471D strumpellin affect binding to each other. Indirect immunofluorescence showed strumpellin is a pre-synaptic protein colocalized with synaptophysin in the human central nervous system. We further identified strumpellin is a novel component of pathological protein aggregates in IBMPFD, Huntington’s disease and various myofibrillar myopathies. Beyond hereditary spastic paraplegia, our findings imply that mutant forms of strumpellin and VCP may have a concerted pathogenic role in various protein aggregation diseases, thereby interlinking motoneuron diseases, frontotemporal dementias, and protein aggregate myopathies.