Analysis of the cellular functions of strumpellin

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Mutations of the human VCP gene cause three autosomal-dominantly inherited diseases, inclusion body myopathy associated with Paget disease of bone and frontotemporal dementia (IBMPFD), amyotrophic lateral sclerosis with frontotemporal dementia (ALS14), and a complex form of hereditary spastic paraplegia with Paget disease of bone. We had identified strumpellin, a component of the WASH-complex, as a novel direct VCP binding partner. Strumpellin mutations have been reported to cause a pure motor form of hereditary spastic paraplegia (SPG8). Strumpellin knock-down in human neuroblastoma cells and zebrafish resulted in a significant reduction of axonal outgrowth and a lack of motoneuron formation, respectively. For additional studies of the basal cellular functions of strumpellin we have generated *Dictyostelium discoideum* strains lacking strumpellin or over-expressing GFP- and RFP-tagged wild-type and mutant strumpellin. Strumpellin knock-out cells display defects in growth and development. Moreover, we observe a mis-regulation of proteins of the WASH-complex in the *Dictyostelium* strumpellin knock-out strain, in mice haploinsufficient for VCP, and in human SPG8 specimens. We will employ our models for the investigation of the intracellular localization of strumpellin and its cell biological and biochemical functions. We will focus on main cellular processes some of which are known to be affected in hereditary spastic paraplegia, i.e. mitochondrial function, membrane trafficking, proteasomal activity, and autophagy.