Sacsin

Loss of sacsin, a large 520 kDa multidomain protein, causes autosomal recessive spastic ataxia of the Charlevoix-Saguenay, one of the most common childhood-onset recessive ataxias. A prominent feature is abnormal bundling of neurofilaments in many neuronal populations. This study shows the direct involvement of sacsin domains in regulating intermediate filament assembly and dynamics and identifies important domains for alleviating neurofilament bundles in neurons lacking sacsin. Peptides encoding sacsin internal repeat (SIRPT) 1, J-domains, and ubiquitin-like domain modified neurofilament assembly in vivo. The domains with chaperone homology, the SIRPT and the J-domain, had opposite effects, promoting and preventing filament assembly, respectively. In cultured Sacs-/- motor neurons, both the SIRPT1 and J-domain resolved preexisting neurofilament bundles. Increasing expression of heat shock proteins also resolved neurofilament bundles, indicating that this endogenous chaperone system can compensate to some extent for sacsin deficiency [1)].

1)
Gentil BJ, Lai GT, Menade M, Larivière R, Minotti S, Gehring K, Chapple JP, Brais B, Durham HD. Sacsin, mutated in the ataxia ARSACS, regulates intermediate filament assembly and dynamics. FASEB J. 2018 Oct 17:fj201801556R. doi: 10.1096/fj.201801556R. [Epub ahead of print] PubMed PMID: 30332300.