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A DYNC1H1 MUTATION IN AUTOSOMAL DOMINANT SPINAL MUSCULAR ATROPHY SHOWS THE POTENTIAL OF PHARMACOLOGICAL INHIBITION OF HISTONE DEACETYLASE 6 AS A TREATMENT FOR DISEASE ASSOCIATED CELLULAR PHENOTYPES

Green RL¹, Simoes FA¹,², Reyes-Aldasoro CC³, Rossor AM⁶, Scoto M⁵, Barri M¹, Greensmith L⁴,⁵, Muntoni F⁵,⁶, Reilly MM⁶, Hafezparast M¹. ¹Neuroscience Centre, School of Life Sciences, University of Sussex, Brighton, United Kingdom; ²Medical Research Building, Brighton and Sussex Medical School, University of Sussex, Brighton, United Kingdom; ³Tait Building, City University London, Northampton Square, London, United Kingdom; ⁴Sobell Department of Motor Neuroscience and Movement Disorders, Queen Square, London, United Kingdom; ⁵Dubowitz Neuromuscular Centre, UCL Institute of Child Health, London, United Kingdom; ⁶MRC Centre for Neuromuscular Diseases, UCL Institute of Neurology, London, United Kingdom.

Spinal muscular atrophy with lower extremity predominance (SMA-Led) is an autosomal dominant congenital form of motor neuron disease. The most common cause of SMA-Led are mutations in dynein cytoplasmic 1 heavy chain 1 (DYNC1H1), which encodes the largest subunit of the retrograde motor cytoplasmic dynein 1. As is typical in other cases of SMA-Led, patients harbouring the DYNC1H1 p.R399G mutation exhibit lower limb weakness as a consequence of muscle atrophy and also show a degree of cognitive impairment. However, the underlying molecular pathogenesis remains unknown. In addition to its characteristic function in retrograde trafficking, the dynein complex is increasingly understood to be involved in other cellular processes including growth cone dynamics and regulation of the Golgi apparatus. Here, we show that fibroblasts with the DYN1C1H1 p.R399G mutation exhibit a striking loss of Golgi apparatus integrity as measured by increased fragmentation, which correlates with increasing zygosity of the mutation. Importantly, we also see a decrease in the localisation of the dynein complex to the Golgi cisternae and a significant decrease in the acetylation of microtubules in the perinuclear region. Excitingly, the treatment of mutant fibroblasts with tubacin, an HDAC6 inhibitor, caused a striking amelioration of the Golgi apparatus integrity by increasing microtubule acetylation. This highlights for the first time a perturbed dynein-mediated regulation of microtubule acetylation and the fragmentation of the Golgi apparatus as a contributory factors in the pathogenesis of SMA-Led. Importantly, these data also illustrate that ameliorating the microtubule acetylation is sufficient to rescue the Golgi integrity, thereby providing a potential therapeutic target for this pathology.