Novel therapeutic avenues in hereditary peripheral neuropathies

Davide Pareyson – Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy

The therapeutical scenario for hereditary neuropathies is changing. A lethal disease such as hereditary transthyretin related amyloidosis (ATTRv) is now treatable with gene silencers (iRNA, ASO) and TTR stabilisers. RNAi is available also for Acute Hepatic Porphyrias. Unfortunately, there is still no effective drug treatment for Charcot-Marie-Tooth disease (CMT). The challenge is to find disease-modifying therapies. Several approaches, including gene silencing (by means of ASO, siRNA, shRNA, miRNA, CRISPR-Cas9 editing) to counteract the *PMP22* gene overexpression in the most frequent CMT1A type are under investigation. PXT3003 was the compound in the most advanced phase for CMT1A, but a second phase-III trial has just finished and seems not to have reached the primary endpoints. Gene therapy to substitute defective genes (particularly in recessive forms associated with loss-of-function mutations) or insert novel ones (e.g., *NT3* gene) are being developed and tested in animal models and in still exceptional cases have reached the clinical trial phase in humans. Novel treatment approaches are also aimed at developing compounds acting on pathways important for different CMT types. Modulation of the neuregulin pathway determining myelin thickness is promising for both hypo-demyelinating and hypermyelinating neuropathies; intervention on Unfolded Protein Response seems effective for rescuing misfolded myelin proteins such as P0 in CMT1B. HDAC6 inhibitors improved axonal transport and ameliorated phenotypes in different CMT models. Other potential therapeutic strategies include targeting macrophages, lipid metabolism, and Nav1.8 sodium channel in demyelinating CMT and the P2X7 receptor, which regulates calcium influx into Schwann cells, in CMT1A. Further approaches are aimed at correcting metabolic abnormalities, including the accumulation of sorbitol caused by biallelic mutations in the sorbitol dehydrogenase (*SORD*) gene and of neurotoxic glycosphingolipids in HSN1: clinical trials are ongoing for both diseases.