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Poster P4

Genetic and pharmacologic modulation of the ATF6 UPR-related pathway affect disease pathogenesis in CMT1B

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Background - Charcot-Marie-Tooth type 1B is a hereditary neuropathy caused by mutations in myelin protein zero (MPZ/P0). Many of these mutations trigger a canonical unfolded protein response (UPR). Here, we explore the effects of the modulation of the ATF6 pathway of the UPR in a mouse model of CMT1B.

Material and Methods - the ATF6 gene was systemically ablated in CMT1B mice (P0S63del/ATF6KO). Locomotor, neurophysiology and morphologic studies were performed, as well as transcriptomics in sciatic nerves. Selective pharmacologic activation of ATF6 through the experimental compound AA147 was assessed in explants of myelinating dorsal root ganglia (DRG). A pharmacodynamic study was also performed in mice by administering AA147 at 2, 4, and 8 mg/kg through intraperitoneal injection and verified by gene expression analysis.

Results - We observed a worsening of disease phenotype in P0S63del/ATF6KO mice, with reduced motor capacity and neurophysiology and thinner myelin observed in morphology. RNAseq analysis indicated that ablation of ATF6 leads to a strong suppression of genes related to ER protein folding, protein degradation, oxidative stress and inflammation.

In P0S63del DRG cultures, treatment with AA147 increased myelination. In WT mice, 8 mg/kg AA147 induced an increase in BiP expression 24 hours post-injection, accompanied by an increase also of XBP1s and CHOP gene expression. Interestingly, the same UPR genes showed a dose-dependent reduction in P0S63del nerves 24 hours post-injection. Instead, no significant difference in BiP expression was observed after 72 hours between placebo- and AA147-treated mice.

Conclusions - Genetic and/or pharmacologic modulation of the ATF6 pathway of the UPR may affect neuropathy severity and progression. The drug AA147 seems to exert a short-lasting but significant pharmacological activity. A pilot study of AA147 treatment at 8 mg/kg is currently ongoing to test if the compound activation could have disease-modifying effects.