Talk

Identification of compounds and genes that affect neurodegenerative diseases in Caenorhabditis elegans.

Bellido-Alcolea N, Pérez-Jiménez MM, y Muñoz MJ

Genética/CABD Universidad Pablo de Olavide, Ctra. de Utrera, Km 1, 41013 Sevilla

Keywords: sul-2; ssu-1; steroid hormone, sulfotransferase

ABSTRACT

Motivation: Neurodegenerative diseases have become a global health problem that need more research to find a solution. Our group has described in the organism model Caenorhabditis elegans that the loss of function of the sul-2 gene, which encodes a steroid hormone sulfatase homologous STS human, improvement the symptoms of neurodegenerative diseases. Likewise, the compound STX64, an inhibitor of steroid hormone sulphatases activity, mimics the lack of sul-2 function. It has been described that ssu-1, the only C. elegans gene orthologous to human steroid hormone sulfotransferase, is expressed in ASJ amphids neurons. The initial hypothesis is to see if the improvement of the symptoms of neurodegenerative diseases in the sul-2 mutant and with the STX treatment is due to the accumulation of sulfated hormone, or on the contrary, to the decrease of the non-sulfated hormone.

Methods: To analyze the expression of the ssu-1 gene in the absence of sul-2, was generated sul-2 (gk1187) V; vzEx29 [(Pssu-1::GFP) + prF4 (role-6)]. To analyze the effect of the absence of sulfated hormones in the Alzheimer's model, strain GMC101, the genetic crossing between GMC 101 and ssu-1 (fc73) generated ssu-1 (fc73) V; dvls100 [unc- 54p :: A-beta-1-42: unc-54 3'UTR + mtl-2p: GFP].

Results: In the cross the strain sul-2(gk187);Pssu-1::GFP the fluorescence intensity of the ASJ amphids neurons was measured, thus quantifying the expression of the Pssu-1::GFP control as in the sul-2 mutant background. The results showed a reduction in the expression of Pssu-1 in a sul-2 mutant background, with respect to the control. While in the cross the strain ssu-1 (fc73); GMC 101 a paralysis test was carried out, seeing the percentage of paralyzed in the GMC 101 control as in the mutant with ssu-1 (fc73). The results showed no significant differences between the control and the mutant.

Conclusions: The reduction of the expression of the ssu-1 gene in a sul-2 mutant, suggests that the accumulation of sulfated hormones could inhibit the sulfotransferase ssu-1. This fit with a product inhibition model. On the other hand, no significant differences were observed between the GMC 101 control and the ssu-1(fc73) mutant, because the fc73 allele has a loss of sulfotransferase function, which suggests that it is the presence of sulfated hormones that have the beneficial effect.

REFERENCES

Carroll, B.T., et al., Sulfated signal from ASJ sensory neurons modulates stomatin-dependent coordination in Caenorhabditis elegans. J Biol Chem, 2006. 281(47): p. 35989-96.

McColl, G., et al., Utility of an improved model of amyloid-beta (Abeta(1)(-)(4)(2)) toxicity in Caenorhabditis elegans for drug screening for Alzheimer's disease. Mol Neurodegener, 2012. 7: p. 57.

Pérez-Jiménez, M.M., et al., Steroid hormones sulfatase inactivation extends lifespan and ameliorates age-related diseases. bioRxiv, 2019: p. 541730.