PRINCIPE FELIPE
CENTRO DE INVESTIGACION

Seminario CIPF

A Drosophila model to study the Charcot-Marie-Tooth neuropathy caused by mutations in GDAP1

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Abstract:

Our goal is to develop a Drosophila model of the forms of CMT caused by mutations in the GDAP1 gene. The fly homolog of GDAP1 is the CG4623 gene. We have investigated the effect of altering CG4623 expression on neuromuscular function in order to achieve a better understanding of the pathophysiology of the disease, to advance towards a better diagnosis through the use of biomarkers based in the physiological hallmarks, and to develop a tool for drug discovery.

We have used tissue-specific drivers to express wild type CG4623 or an RNAi construct against the gene in order to increase and reduce the gene function, respectively. Using the retina-specific GMR-Gal4 driver we have found out that both overexpression and silencing of CG4623 induce neuronal death. We used the Mhc-Gal4 driver to direct expression in the muscle. In this tissue we have also observed that overexpression and silencing of CG4623 induce degeneration of the muscle fibers, and mitochondrial defects which are consistent with the CG4623 function: mitochondrial fragmentantion upon overexpression and fusion upon interference. Moreover, the defects caused by RNAi can be rescued by co-expression of human GDAP1.

Retinal and muscle degeneration are age-dependent, being much more accused in 35-day old flies than in young ones, so they represent a genuine degeneration rather than a developmental defect. We are also conducting physiological studies on the affected tissues to define the hallmarks of the cellular degeneration. Our preliminary results indicate a possible increase of oxidative stress.

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