PRINCIPE FELIPE
CENTRO DE INVESTIGACION

Seminario CIPF

Role of laforin and malin in Lafora disease

Speaker: Marcos Lahuerta
Intracellular Protein Degradation and Rare Diseases
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Abstract: Lafora progressive myoclonus epilepsy (Lafora disease) is a fatal autosomal recessive neurodegenerative disorder. It is characterized by the presence of glycogen-like intracellular inclusions, called Lafora bodies, in neurons and in other cells from organs such as liver, heart or skeletal muscle. The disease is caused, in the vast majority of cases, by mutations in either the *EMP2A* or the *EMP2B* genes, encoding respectively laforin, a dual phosphatase, and malin, an E3 ubiquitin ligase. Since the precise physiological role of both proteins is not fully understood and alterations in macroautophagy and in mitochondrial activity have been described, we have studied here two aspects.

First, whether in Lafora disease, the previously observed impairment in intracellular protein degradation by macroautophagy and by proteasomes is more general, by studying if another proteolytic lysosomal function such as endocytosis and a non-lysosomal, non-proteasomal protein degradation mechanism (calpains) are also altered. In addition, we have investigated if the mitochondrial disfunction associated to Lafora disease is caused by an impaired specific degradation of damaged mitochondria by autophagy (mitophagy). Briefly, we have observed, in cellular models of the disease, a decrease in: 1) receptor mediated endocytosis and, especially, in fluid phase endocytosis, 2) calpain activity, and 3) selective degradation of damaged mitochondria by autophagy. These results, together with the impairment in macroautophagy and in the ubiquitin-proteasome system previously described, suggest a general alteration of the intracellular protein degradation machinery in Lafora disease.

Second, we have provided new data about the cellular functions of these proteins by studying their localization and identifying laforin protein partners. Specifically, we have observed in different cell lines that the localization of malin and laforin is mostly nuclear and cytosolic, respectively. However, in the absence of glucose the laforin localization becomes nuclear through a reversible transport and we have also identified different nuclear proteins that interact with laforin. These results, together with the colocalization of laforin and malin with markers of stress granules and P-bodies by fluorescence microscopy, suggest a new role for both proteins, different from those previously proposed in the cytoplasm, in the transcriptional regulation and processing of some mRNAs, probably related with glycogen metabolism.

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