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Thesis title :

Role of Usher syndrome proteins at the auditory and vestibular hair cell ribbon synapses

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Abstract

The main objectives are to characterize the molecular mechanisms by which auditory and vestibular hair cells control transmitter release at their ribbon synapses, in normal and pathological conditions. Our project will investigate the role of otoferlin and its interaction with some of the Usher Syndrome proteins, such as harmonin and SANS (scaffold proteins) and clarin-1 (a four-transmembrane domains protein close to the synaptic protein stargazin). It is worth recalling that Usher syndrome, with various mutations affecting independently 10 different genes, is the most frequent cause of deaf-blindness in humans.

To determine the cellular and sub-cellular expression of each otoferlin isoform, specific antibodies will be designed and produced. High resolution confocal microscopy will be used to image the sub-cellular distribution of each isoform. Furthermore, by using a viral rescue approach in Otof-/- mice lacking otoferlin, we will explore the recovery of the hearing function produced by each isoform (independently or combined). In each of these different rescue models, by using time-resolved patch-clamp capacitance measurements, we will also characterize the recovery of synaptic vesicle exocytosis directly at the level of the inner hair cells. Furthermore, protein-protein interactions between the different isoforms of otoferlin and Usher syndrome proteins will be studied.

Qualification required

Good knowledge in Neurobiology.