Project 3: Pathophysiological ER stress response in Tauopathies (project leader: Mireille Rossel)

Tauopathy represents another model to study ER-stress deregulation and S1R neuroprotective function in neurodegenerative diseases. Usually considered as a common neurodegenerative factor, the microtubule associated protein **Tau is functionally altered in AD and other tauopathies**. Its impact on the ER stress and UPR response seems to depend on the mutation and/or the oligomer status, and therefore needs to be clarified using in vivo models. We have already shown that S1R agonist can block Tau hyperphosphorylation in AD context. We investigate in vivo how S1R activity can modulate mutated Tau toxicity and also how Tau might trigger S1R chaperone function. Taking advantage of our Tauopathy zebrafish lines with human Tau WT and mutated (P301L and A152T), we further analyse the functional implications of Tau/S1R interaction and eventually its disruption.

Using a pharmacological approach, we have shown that the neurotrophic factor BDNF is deregulated by the overexpression of the protein hTauP301L, and that the behavioral abnormalities observed in visual motor response are repaired by the restoration of a normal level of BDNF expression (PhD thesis of C. Barbereau 2020). Moreover, these defects are not found in other models of tauopathies such as PSP.

Our goal is now to develop a neuroprotective strategy targeting the relationship between mutated forms of Tau and ER-stress dysregulation using already established zebrafish models. Our projects aim to characterize the signaling pathways deregulated in various forms of Tauopathies with overexpression of hTauWT, hTauP301L and hTauA152T.

The project also develops on a novel association of ER modulators depending on the ER stress involved. We establish a "signature" at the cellular and functional level for mutated and unmutated Tau-related neurotoxicity. A first target that has already been validated for Alzheimer's disease is the S1R protein which plays an essential chaperone role in the regulation of these signaling pathways. Our project focuses on a new combination of modulators depending on the ER stress pathway involved, thus corresponding to the validation of a neuroprotective target. The goal is to identify neuroprotective factors to rescue functionally Tau -dependent alterations.

Project staff:
Researchers: Mireille Rossel, Tangui Maurice, Jean-Charles Liévens
Supporting personel: Nicolas Cubedo

Collaborations:
Marie-Laure Parmentier (IGF, Montpellier)
Angeleen Fleming (MRC, Cambridge UK)

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