RAB6 FUNCTION DURING ER STRESS IN ALZHEIMER'S DISEASE

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Introduction: Our lab has shown that the unfolded protein response (UPR) of the ER is activated in the early stages of Alzheimer's disease (AD). The UPR aims to restore homeostasis after perturbations that lead to protein misfolding in the ER lumen. The ER is intricately connected to intracellular transport which is regulated by Rab proteins. Rab6 is involved in the retrograde transport from the Golgi to the ER and is upregulated in the early stages of AD in strong correlation with the increased UPR activation. Interestingly, Rab6 is not an UPR responsive gene.

Aim: In this study we aim to characterize the function of Rab6 on the UPR in relation to the pathogenesis of Alzheimer's disease.

Methods: Western blotting, qPCR, Immunofluorescence, subcellular fractionation.

Results: Overexpression of Rab6 reduces the induction of the UPR stimulated by tunicamycin, a classical UPR inducer, in different cellular models. Tunicamycin treatment induces perinuclear Rab6 clustering opposed to a more diffuse localization in untreated SK-N-SH cells. The autophagic marker LC3 partly colocalizes with Rab6 clusters upon tunicamycin treatment, colocalisation is enhanced by bafilomycin. Rab6 accumulates in the membrane fraction of MEF Atg5⁻/⁻ cells.

Conclusion: Our results show that Rab6 function attenuates UPR activation. We also observe that Rab6 expression and localization have a correlation with autophagy. We are currently working under the hypotheses that Rab6 is a substrate for autphagic degradation and that Rab6 directly interferes in UPR signaling. We hypothesize that impaired autophagy increases the Rab6 pool, enabling it to interfere in the UPR.