Rab6 in Alzheimer's disease: a response to misfolded proteins?

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The focus of our research is how changes in protein trafficking can lead to the formation of protein aggregates in Alzheimer's disease (AD), and what the response of the cell to the presence of these aggregates is. In this study we analysed a protein involved in trafficking in the ER/Golgi, the small GTPase Rab6. We were particularly interested in Rab6, because it had been shown by others to affect APP processing (1). Dominant negative Rab6 inhibits the formation of Aβ, most likely due to decreased vesicular transport to the ER, resulting in decreased substrate availability for the γ-secretase activity here.
Another indication of a link between Rab6 and AD was our observation that, as we have previously observed for RabGDI (2), Rab6 membrane association was decreased in Presenilin 1 deficient cells. In addition, we could show that the regulation of Rab6 membrane association by phosphorylation is dependent on Presenilin 1 (3).
To study more directly whether Rab6 is involved in the pathogenesis of AD, we used post-mortem brain material. Rab6 is predominantly expressed in the pyramidal neurons in the temporal cortex and hippocampus. Interestingly, Western blot analysis of a panel of AD and control patients shows that Rab6 is upregulated in AD brain.
Quite recently it was shown that Rab6 is involved in a novel transport route from the Golgi back to the ER (4). Therefore, a unique Rab6-mediated retrograde route exists that is used by only a subset of proteins. We hypothesise that this involves a quality control mechanism, by which aberrant proteins that have escaped to the Golgi are transported back to the ER. Currently we are studying the involvement of Rab6 in protein quality control in the ER.

References

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