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Science

Gamma-Secretase complex plays a role in Alzheimer's disease and cancer progression. The development of clinical useful inhibitors is complicated by the role of the gamma-secretase complex in regulated intramembrane proteolysis of Notch and other essential proteins. Different gamma secretase complexes containing different Presenilin or Aph1 protein subunits are present in various tissues and cell types. We showed before that these complexes have heterogeneous biochemical and physiological properties. Aph1A gamma-secretase complex is essential for Notch signalling, but no specific function could be assigned to Aph1B-γ-secretase. We demonstrated that Aph1B γ-secretase complex is highly expressed in neurons of specific brain regions. These findings prompted us to search for brain specific functions for Aph1B. Inactivation of the Aph1B gamma-secretase in the mouse led to hypersensitivity to psychotropic drugs, sensorimotor gating abnormalities, and working memory deficits, which mimic aspects of schizophrenia. Specific inactivation of the Aph1B gamma-secretase in a murine Alzheimer's disease model on the other hand led to improvements of Alzheimer's disease-relevant phenotypic features without any Notch-related side effects. Furthermore, we provided evidence that the Aph1 protein contributed directly to the proteolytic activity of the gamma-secretase complex by influencing the conformation of the catalytic Presenilin subunit. We also demonstrated that the Aph1B complex contributes to total gamma-secretase activity in the human brain.

The fact that Aph1B gamma-secretase complex deficiency leads in the mouse to problems with sensorimotor gating asks for caution, but as this is likely a

neurodevelopmental phenotype we believe that this potential side effect is not a major obstacle for the further consideration of this particular complex for therapy.

This combined work suggests that the different Aph1 gamma-secretases contribute differentially to physiological and pathological functions and make specific targeting of Aph1B-containing gamma-secretase complexes an attractive target for generating less toxic therapies for Alzheimer's disease.

It is therefore extremely important to further investigate the exact mechanism(s) underlying our findings and to evaluate Aph1B-gamma secretase as a potential drug target. To address these issues, we will focus on the following approaches:

1. We aim to screen for specific gamma-secretase inhibitors in cell-free and cell-based assays.

2. We aim to develop specific Aph1 antibodies and to evaluate these as alternative approach for specific gamma secretase inhibition.

3. We will study expression levels and patterns of the different gamma-secretases complexes and its substrates in more depth at the cellular level.

4. We will use specific knockout mice models to get more insight into the biological function of the different Aph1-gamma-secretases and the substrates involved.

We are confident that these studies will contribute to novel insights and the development of drugs with therapeutic functions in Alzheimer Disease.

Selected publications

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