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New pathway links γ -secretase to inflammation and memory while sparing Notch

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γ -secretase is comprised of a $\sim 10^6$ Dalton complex of four integral proteins which, together, form the aspartyl proteinase that underlies the phenomenon of “regulated intramembranous proteolysis (RIP; for review, see ^{1–3}). Twenty years ago, the idea that a proteinase could somehow bring water molecules into the hydrophobic lipid bilayer of a biological membrane in order to hydrolyze the transmembrane domains of integral proteins was considered cell biological heresy. Initial formulations of APP processing at that time raised the possibility that membrane damage was required for A β generation, but that was set aside in 1992 when amyloidogenic processing of APP to A β was found to be a normal, physiological event⁴.

In 1995, early onset familial Alzheimer disease (EOFAD) was linked to a polytopic protein christened “presenilin 1” (PS1) because mutations in PS1 were found to underlie most presenile (or early onset) FAD (also abbreviated EOFAD)⁵. Mutagenesis strategies subsequently revealed that PS1 contained the catalytic subunit of γ -secretase including the critical aspartates that form the enzyme’s active site⁴. EOFAD mutations in PS1 lead to subtle changes in A β generation, enhancing the proportion of A β that is 42 aminoacids in length and highly aggregatable⁶. Studies in transfected cells and transgenic mice revealed that PS1 is initially synthesized as a zymogen which is processed to N- and C-terminal fragments that remain associated in a complex and adopt the proper conformation for supporting catalysis⁷.

Overexpression of PS1 in transgenic mice revealed that PS1 activity is under tight control at the level of processing of the zymogen holoprotein into the cleaved, active PS1 complex⁷. Overexpressing higher and higher levels of PS1 caused the inactive zymogen to accumulate and caused the PS1 complex to be replaced by fragments derived from the transgene. However, levels of the cleaved, active complex and levels of PS1/ γ -secretase catalytic activity remained at levels close to normal⁷. This accumulated information suggested that lowering levels of PS1/ γ -secretase might lower A β generation, but until now, strategies for such an approach have been lacking.

In the current issue, Prático and colleagues⁸ reveal that expression of not just PS1, but of all four members of the γ -secretase complex (the other three being the cofactors nicastrin, APh1 and PEN2) are under the control of the transcription factor cAMP-response element binding (CREB) protein. CREB is best known as a “key point of control for long-term memory (LTM) formation”, with loss-of-function manipulations impairing LTM while leaving short-term memory (STM) intact⁹. Gain-of-function mutations in CREB reduce the amount of training required to produce maximal LTM⁹. Prático demonstrates that CREB

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modulation of expression of the γ -secretase quartet is linked to the leukotriene pathway of inflammation. This pathway is proven using either a pharmacological strategy employing 5-hydroxy-6,8,11,14-eicosatetraenoic acid (5-HETE) or a mouse genetic strategy that targeted the 5-lipoxygenase (5-LO) enzyme. Moreover, knocking 5-LO out of the mouse genome reduced generation of both A β 40 and A β 42 while leaving Notch processing unperturbed. This is somewhat surprising since at least some hypomorphic EOFAD PS1 mutations impair γ -secretase function while also selectively enhancing A β 42 generation¹⁰. Presumably the coordinated expression of the stoichiometry of the quartet and/or the structure of the quartet complex that Prático observes with 5-LO signaling is responsible for maintaining the stoichiometry of the A β 42 and A β 40 reaction products.

The immediate implication is that we have here a new pathway for lowering A β generation while sparing Notch processing. This is especially welcome news coming on the heels of the recent clinical failure of Lilly's γ -secretase inhibitor, semagacestat¹¹, to slow the cognitive decline of mild AD. The problems with this compound were complex, since subjects on drug declined more rapidly than those taking placebo, and they were also more likely to develop skin cancer. This latter issue may be attributable to inhibition of Notch processing¹², and the new 5-LO/CREB preserves normal Notch processing. The reasons for the accelerated decline of subjects taking semagacestat remain unclear. Brain plaque burden data for subjects and controls have not been released, so the efficacy of semagacestat at lowering brain amyloid burden remains unknown. Herms has reported that γ -secretase cleavage of APP is required for maintenance of dendritic spine morphology and that semagacestat disrupts dendritic spines¹³. If confirmed, this could explain the accelerated decline in semagacestat-treated subjects via mechanism-based toxicity that will be difficult to avoid with classical γ -secretase inhibitors. Luckily for those invested in targeting γ -secretase, three more γ -secretase modulatory strategies were reported in the past few months in addition to the 5-LO/CREB approach reported here^{14–16}. However, the potential clinical benefits of all these late-breaking strategies remain to be assessed. In addition, it is worth noting that Prático reports no behavioral data on his 5-LO knockout mice. Given the integral role of CREB in the physiological modulation of memory function, this will be important to investigate before 5-LO modulators can move forward into the clinic.

Does the Prático paper tell us more about how nonsteroidal anti-inflammatory (NSAID) use might lower AD risk? This, too, remains to be clarified. At the basic science level, the NSAID link to AD has been suggested to be related to allosteric modulation of γ -secretase^{17,18}; yet, the apparent clinical benefit of NSAIDs has been reported to be independent of their γ -secretase modulatory activities¹⁹. Indomethacin, ibuprofen, and aspirin lower 5-HETE levels in leukocytes²⁰, but whether this is meaningful for lowering the coordinated expression of PS1, nicastrin, A β 1, and PEN2 in brain remains to be clarified. Furthermore, NSAIDs are pleiotropic in action, and unraveling their potential benefits remains challenging. Perhaps NSAID action in AD is attributable to a complicated summation of their CNS penetration and their multiple actions and targets (5-LO and cyclooxygenase 1 and 2 activities, γ -secretase constituent expression levels and allosteric modulation, nuclear factor kappa B, peroxisome proliferator activated receptors) acting in concert²¹.

While this expanding list of targets and activities is extremely encouraging, there remains the likely scenario that no anti-amyloid or anti-A β strategy will succeed unless initiated pre-symptomatically²². The prospect of designing affordable prevention trials for AD has been daunting, but recent efforts of the Alzheimer's Prevention Initiative (API)²³ and the National Institute on Aging's Dominantly Inherited Alzheimer's Network (DIAN)²⁴ are finally bringing the enormous challenge of prevention trials closer to reality by focusing on

populations with either deterministic mutations (i.e., *APP*, *PS1*, *PS2*) or other populations highly enriched in apolipoprotein E ϵ 4 alleles^{23,24}.

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Figure 1.

Catalytically active γ -secretase requires assembly of four transmembrane proteins: presenilin 1 (or 2), nicastrin, APH-1, and PEN-2 (Reprinted with permission from Gandy S. The role of cerebral amyloid beta accumulation in common forms of Alzheimer disease. *J Clin Invest.* 2005 May;115(5):1121-9. PubMed PMID: 15864339; PubMed Central PMCID: PMC1087184).