γ-Secretase: From Aβ Production to Neuroinflammation

March 24

Tuesday, 12:30 pm

Billings Building—Rosedale Room

SPEAKER:

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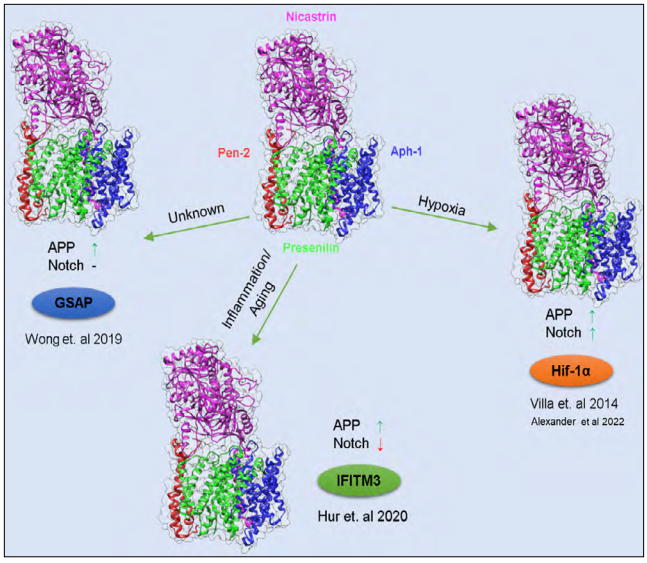
Abstract



γ-Secretase is a transmembrane aspartyl protease that cleaves the amyloid precursor protein (APP) in the final step of proteolysis to generate Aβ peptides. This enzyme is distinguished by several unique features—including intramembrane catalysis, a multi-protein transmembrane complex, and numerous substrates—that have long made it an enigmatic target of study. Adding to the complexity, only a small fraction of γ-secretase complexes are catalytically active, leaving the role of the inactive pool largely unexplored. To address this gap, we have developed new tools and approaches to probe the regulation and activation of γ-secretase. Our studies show that its activity is modulated by non-essential subunits, termed γ-secretase modulatory proteins (GMSPs), such as HIF1α under hypoxia and IFITM3 during neuroinflammation. These GMSPs associate with the γ-secretase complex in a context-dependent manner. Our findings suggest that the inactive pool of γ-secretase functions as a reservoir, enabling rapid adaptation of enzymatic activity through conversion into active complexes in response to cellular and environmental cues. This activation process appears to involve transient interactions with GMSPs, thereby providing temporal control of γ-secretase function. Importantly, while this adaptive plasticity may be beneficial under physiological conditions, aberrant activation of γ-secretase occurs in pathophysiological contexts such as cerebrovascular and cardiovascular disease, aging, and neuroinflammation. Such dysregulation contributes to neurodegenerative processes, including the progression of AD. A deeper understanding of γ-secretase plasticity in response to cellular stressors and environmental changes not only elucidates the mechanisms of disease progression but also informs the development of targeted therapeutic strategies for AD.

Publications:

1. Alexander C, Li T, Hattori Y, Chiu D, Frost GR, Jonas L, Liu C, Anderson CJ, Wong E, Park L, Iadecola C, Li YM. *Hypoxia Inducible Factor-1alpha binds and activates gamma-secretase for Abeta production under hypoxia and cerebral hypoperfusion.* Molecular psychiatry. 2022;27(10):4264-73. PMCID: PMC9722522.

2. Nie P, Kalidindi T, Nagle VL, Wu X, Li T, Liao GP, Frost G, Henry KE, Punzalan B, Carter LM, Lewis JS, Pillarsetty NVK, Li YM. *Imaging of Cancer gamma-Secretase Activity Using an Inhibitor-Based PET Probe.* Clin Cancer Res. 2021;27:6145-55. PMCID: PMC8610083.

3. Hur JY, Frost GR, Wu X, Crump C, Pan SJ, Wong E, Barros M, Li T, Nie P, Zhai Y, Wang JC, Tcw J, Guo L, McKenzie A, Ming C, Zhou X, Wang M, Sagi Y, Renton AE, Esposito BT, Kim Y, Sadleir KR, Trinh I, Rissman RA, Vassar R, Zhang B, Johnson DS, Masliah E, Greengard P, Goate A, Li YM. *The innate immunity protein IFITM3 modulates gamma-secretase in Alzheimer's disease.* Nature. 2020;586:735-40. PMCID: PMC7919141.

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