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Physiological and pathological roles of the γ -secretase complex

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Abstract

Gamma-secretase (GS) is an enzyme complex that cleaves numerous substrates, and it is best known for cleaving amyloid precursor protein (APP) to form amyloid-beta (A β) peptides. Aberrant cleavage of APP can lead to Alzheimer's disease, so much research has been done to better understand GS structure and function in hopes of developing therapeutics for Alzheimer's. Therefore, most of the attention in this field has been focused on developing modulators that reduce pathogenic forms of A β while leaving Notch and other GS substrates intact, but GS provides multiple avenues of modulation that could improve AD pathology. GS has complex regulation, through its essential subunits and other associated proteins, providing other targets for AD drugs. Therapeutics can also alter GS trafficking and thereby improve cognition, or move beyond A β entirely, effecting Notch and neural stem cells. GS also cleaves substrates that affect synaptic morphology and function, presenting another window by which GS modulation could improve AD pathology. Taken together, GS presents a unique cross road for neural processes and an ideal target for AD therapeutics.

Keywords

Alzheimer's disease; Gamma-secretase; Amyloid-beta

1. Background

Alzheimer's disease (AD) is a global health crisis. It is a neurodegenerative disorder characterized by amyloid plaques made of amyloid beta aggregates (A β and neurofibrillary tangles (NFT) made of hyper-phosphorylated tau protein. Symptoms include memory loss and behavioral deficits (Musiek and Holtzman, 2015), and there is no cure for this disease. This is especially troubling as the number one risk factor for AD is age, and the western world has an aging population.

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Conflict of interest

The authors declare that there are no conflicts of interest.

While NFT align more closely with disease stage (Arriagada et al., 1992; Giannakopoulos et al., 2003), researchers believe amyloid beta ($A\beta$) to be causative in the disorder, mainly because of the genetic evidence (Musiek and Holtzman, 2015). Autosomal dominant AD is caused by mutations in amyloid precursor protein (APP) or presenilin, the catalytic subunit of gamma-secretase (GS) (Ahn et al., 2010; Bettens et al., 2013), and these mutations lead to an increase in $A\beta$ and downstream dementia.

Amyloid precursor protein (APP) can be cleaved by two pathways, the non-amyloidogenic versus the amyloidogenic pathway (Zheng and Koo, 2011). In the non-amyloidogenic pathway, APP is first cleaved by alpha-secretase and then by GS. In the amyloidogenic pathway, however, the first cleavage is done by beta-secretase (BACE) then. This second pathway releases $A\beta$ of varying lengths (Fig. 1), with GS first cleaving the β -CTF into long forms of $A\beta$, either $A\beta_{48}$ or $A\beta_{49}$. GS then makes step-wise cleavages every three amino acids, preferring $A\beta_{40}$ and $A\beta_{42}$ (Barnwell et al., 2014; Li et al., 2016; Qi-Takahara et al., 2005; Takami et al., 2009). $A\beta_{42}$ production may also not relate solely to the cleavage of the longer $A\beta$ forms, but instead may depend on the dissociation rate of $A\beta_{42}$ from the complex. If it remains in the active site, it may cleave further into shorter forms (Okochi et al., 2013). APP cleavage is a more complicated process than was originally described.

Of the $A\beta$ lengths, $A\beta_{42}$ is believed to be more toxic than $A\beta_{40}$. Scientists measure the ratio of $A\beta_{42}$: $A\beta_{40}$, and when this ratio increases, like in genetic forms of AD, $A\beta$ peptides oligomerize more readily (Iwatsubo et al., 1994). After oligomerization, the $A\beta$ species then aggregate, eventually leading to downstream neurotoxicity. The original hypothesis for AD, the $A\beta$ hypothesis coined by Hardy and Higgins (Hardy and Selkoe, 2002; Hardy and Higgins, 1992) has been updated to place $A\beta$ not as the sole instigator of a direct cascade, but instead as an initiator for a series of changes, many through tau protein and inflammation, that eventually lead to neurodegeneration (Musiek and Holtzman, 2015).

Because of its role in the cleavage of $A\beta$ and the fact that many genetic forms of AD are caused by mutations in the enzyme, GS has long been a target for drug development, though previous clinical trials of Semagacestat, a GS inhibitor, have failed due to an increase in skin cancer, and a decrease in cognitive performance (Doody et al., 2013; Herrmann et al., 2011; Niva et al., 2013). GS has more than 90 identified substrates, and gamma-secretase inhibitors (GSI) block the action of GS on all of these, likely resulting in those unwanted side effects (De Strooper and Chavez Gutierrez, 2015; Henley et al., 2014). Researchers then developed a reported Notch-sparing inhibitor, Avagacestat (Gillman et al., 2010). This compound had the similar toxicity issues Semagacestat. However, multiple studies indicated that Avagacestat was actually not Notch-sparing, having a similar potency for both Notch and APP (Chavez-Gutierrez et al., 2012; Crump et al., 2012). Because of the large-scale failures, $A\beta$ as a target then fell out of favor.

Recently, there has been revitalization for $A\beta$ as a therapeutic target for two main reasons. First, Biogen has shown preliminary clinical evidence that their $A\beta$ antibody improves cognition in patients (Underwood, 2015). Second, scientists found a protective mutation in APP, showing that modulation of $A\beta$ can protect a patient from developing AD by reducing the beta cleavage of APP (Jonsson et al., 2012). With this renewed vigor, researchers are

turning their attention back to the APP cleavage pathway. By better understanding the complex regulation and modulation of GS, researchers can develop better therapeutics that reduce A β toxicity. It is also crucial to understand how GS affects other neuronal substrates, for GS-directed compounds can influence a range of pathways beyond amyloidogenesis. This review will highlight a few of the most important roles and regulators of GS, in hopes of highlighting the unique position of GS in AD pathology.

2. Gamma-secretase complex

If the goal is to create GS directed therapeutics, it is first important to understand the subunit structure and composition of this enzyme. GS is an enzyme complex, composed of 4 required sub-units that form a 1:1:1:1 heterodimer (Li et al., 2014; Sato et al., 2007): presenilin (PS), nicastrin (NCT), anterior pharynx-defective 1 (APH-1), and presenilin enhancer 2 (PEN2) (Francis et al., 2002; Goutte et al., 2002; Yu et al., 2000) (Fig. 2). It is an aspartyl protease, accountable for cleaving over 90 integral membrane proteins after they have undergone ectodomain shedding (Haapasalo and Kovacs, 2011).

Of the subunits, PS is the most important for activity and therefore the most studied. PS contains the catalytic subunit for the complex (Ahn et al., 2010; Esler et al., 2000; Li et al., 2000), with nine transmembrane helices (Doan et al., 1996; Laudon et al., 2005). The two catalytic aspartyl residues are located in transmembrane domains 6 and 7 (Wolfe et al., 1999). PS has two forms in mammals, PS1 and PS2. PS must be endoproteolysed to form the N-terminal and C-terminal fragments to become active, with the exception of the exon 9 deletion mutant PS that is active but not cleaved (Thinakaran et al., 1996). Mutations in PS lead to changes in either the ratio of A β peptides, with a shift towards more amyloidogenic forms, or an increase in the total amount of A β generated (Citron et al., 1997; Scheuner et al., 1996). These familial mutations lead to the heritable form of Alzheimer's disease (Chavez-Gutierrez et al., 2012). Of note, whether loss of or gain of function of PS1 mutations leads to AD has been questioned (Shen and Kelleher, 2007; Xia et al., 2015).

The other three subunits help form the mature enzyme. NCT, with its large extracellular domain, transmembrane helix and smaller cytoplasmic domain (Yu et al., 2000), is involved in substrate recognition. Extracellular domain antibodies disrupt NCT binding to substrates (Zhang et al., 2012), but this role is controversial (Chavez-Gutierrez et al., 2008; Dries et al., 2009; Zhao et al., 2010), as NCT is not absolutely required for GS activity (Shah et al., 2005). The final two subunits, APH-1 and PEN2, are less well studied. APH-1 helps form a scaffold, and PEN2 works in enzyme maturation (Niimura et al., 2005; Prokop et al., 2004). APH-1 has two different isoforms from two paralogous genes on chromosomes 1 (APH-1A) and 15 (APH-1B). The structure of PEN2 also presents some controversy, as biochemical studies have shown it to only have one transmembrane domain with a reentrant loop (Zhang et al., 2015), differing from previous models of a subunit with two transmembrane domains. More work is needed to fully understand the role of these two subunits in GS activity and specificity.

Even with all of the subunits present, the complex must also be correctly assembled for the enzyme to function properly. The complex is first assembled in the endoplasmic reticulum,

with NCT and APH-1 binding together. They form the initial scaffold, so full-length PS can attach itself, and finally PEN2 associates and causes the endoproteolysis of PS into the N-terminal fragment (NTF) and C-terminal fragment (CTF). The active complex is then shuttled to the Golgi where it is glycosylated (Takasugi et al., 2003). Only after the assembly of all four subunits and the glycosylation will GS become active, and even then, not all present complexes are active (Beher et al, 2003; Lai et al., 2003). The disconnect between the presenilin level and the activation of γ -secretase complex remain a large area of research for the GS community.

To help address these questions about GS structure, much work has focused on generating high-resolution structures for GS. Many groups have recently published structures using electron microscopy techniques, building on previous work giving a GS structure at a lower resolution (Lazarov et al, 2006). The group by Li et al. published a 17 Å model, showing a large base with a smaller head, and NCT's extracellular domain is in the smaller head (Li et al., 2014). This study was followed up by a 3.4 Å resolution structure that showed GS in the same shape as the previous report, with APH-1 and Pen-2 holding PS1 under the NCT extracellular domain, while leaving PS1 flexible (Bai et al., 2015; Lu et al., 2014). Other EM papers have also shown that GS exists in multiple conformations (Bai et al., 2015; Elad et al., 2015). In order to measure the distinct conformations, Bai et al. used a GSI, DAPT, to lock the enzyme in place. The sixth transmembrane helix of PS1 can exist in 3 shapes, potentially providing the range of enzyme activities. The group also found a single helix in the cavity of PS1 that does not belong to any of the subunits, and mass spectrometry identified a mixture of proteins. This mixture could include potential regulatory subunits. The structural information from the EM work will serve as a jumping off point for future rational drug design, as well as highlighting the importance of enzyme regulation.

3. Gamma-secretase regulation

An enzyme complex with such a large range of substrates and functions requires tight regulation. It is important to keep in mind that only a small fraction of GS complexes are active (Beher et al., 2003; Gu et al., 2004; Lai et al., 2003). All active complexes have all four subunits, and previously it was thought that activity cannot be increased by only overexpressing PS (Levitan et al., 2001)-all subunits must be increased (Edbauer et al., 2003). However, when these studies moved into a mouse model, overexpression of PS alone was able to increase GS activity (Li et al., 2011). This discrepancy between cells and animal models show that GS regulation in vivo is much more complicated than originally anticipated. GS is regulated by layers of control, from subunit composition to associated proteins that may regulate the complex in specific tissues or disease situations.

There are multiple GS complexes since PS and APH-1 have 2 isoforms, and APH-1 also has two splice variants, APH-1A and APH-1B (Lai et al., 2003; Shirotani et al., 2004). These variants can exist at the same time in the same tissue, and isoforms sometimes compete for substrates (Placanica et al., 2009a,b). APH-1A regulates Notch during embryogenesis (Ma et al., 2005; Serneels et al., 2005), and APH-1B contributes to the production of longer A β fragments. By targeting APH-1B, researchers can reduce aggregates without Notch-related

toxicity (Serneels et al., 2009). More work is required to fully understand how GS activity is regulated by its subunits.

GS is also regulated by associated proteins. It can form differential complexes with modulatory proteins. One example is GSAP, which complexes with GS and APP, giving preference to APP cleavage over Notch. GSAP knockdown mice reduce A β when crossed with an AD model (Chu et al., 2014; He et al., 2010), and there is a GSAP SNP associated with AD (Zhu et al., 2014). However, the precise mechanism is unknown. Recent work has also shown that GS can be regulated by Hif1 α , long known as the master regulator of hypoxia (Villa et al., 2014). Hif1 α normally acts as a transcription factor, stabilized in low oxygen conditions, and turning on several genes in response. However, Hif1 α binds directly to GS and increases its Notch activity by shifting inactive complexes to their active form, independent of Hif1 α 's ability to act as a transcription factor.

To alter GS activity, one can alter not only the active site, but also by altering its subunits and associated proteins. Because GS has a wide range of substrates and functions, it needs a wide range of controls on activity.

4. Gamma-secretase trafficking

GS activity for APP can be influenced by sub-cellular trafficking, as APP cleavage differs depending on its localization. APP is synthesized in the ER and transported to the trans-Golgi network (Annaert et al., 1999; Pasternak et al., 2003; Ray et al., 1999a; Rechards et al., 2003; Vassaretal., 1999). If it is on the cell surface, it can be cleaved by α -secretase (Parvathy et al., 1999). APP can also be internalized and cleaved by β -secretase (BACE) and GS in the ER, Golgi, and the endosomal system. The goal of some therapeutics is to shift localization to the cell surface to decrease amyloidogenic processing. Therefore, it is important to understand what factors alter APP localization.

Cholesterol and lipid metabolism can affect this trafficking. APP needs to interact with lipids and associated proteins to change its localization. For example, LRP1 binds to APP and mediates A β clearance (Deane et al., 2004; Herz and Bock, 2002; Zerbini et al., 2006). It is found near plaques (Rebeck et al., 1993) and polymorphisms are linked with increased risk for AD (Kang et al., 1997, 2000). Disrupting the interaction between LRP1 and APP decreases A β production by increasing cell surface APP (Ulery et al., 2000). LRP1 is also a GS substrate (Lleo et al., 2005), so modulating GS cleavage of LRP1 can shift APP trafficking.

SorLA is another GS substrate implicated in APP trafficking. SorLA is decreased in AD brains (Scherzer et al., 2004) and binds APP directly (Andersen et al., 2005). Its overexpression shifts the APP to the Golgi, thereby altering A β production (Offe et al., 2006). SorLA was also implicated as an AD risk gene through gene variants identified in a GWAS study (Rogaeva et al., 2007).

Finally, GS activity itself is regulated by low levels of cholesterol (Grimm et al., 2005, 2008). Shifting APP to lipid rafts increases A β , where GS is localized (Fuentes et al., 2007). Cholesterol lowering drugs decrease this interaction (Ehehalt et al., 2003; Kojro et

al., 2001). An increase in cholesterol shift PS1 to late endosomes and is associated with an increase in GS activity (Burns et al., 2003). However, the interplay between GS and cholesterol is still controversial. Modulating lipid metabolism and GS activity could provide a new therapeutic target for AD.

5. Notch and neural stem cells

Notch was the second GS substrate identified (De Strooper et al., 1999; Ray et al., 1999a,b). Importantly, Notch can act as a proto-oncogene or tumor suppressor in some cancers (Lobry et al., 2011). It is also involved in neural differentiation, which is especially crucial during neural development.

Notch must be cleaved to become active (Kopan and Goate, 2000). Ligand binding triggers the sequential cleavage, first by ADAM metalloproteases and then by GS. This releases the Notch intracellular domain (NICD), which acts as a transcription factor for a host of genes, many involved in cell survival and differentiation (Kopan and Ilagan, 2009). All four Notch receptors are GS substrates (Saxena et al., 2001), so any therapeutic that inhibits GS activity completely will also block the action of Notch.

Neural stem cells exist in both the adult and the embryonic brain, defined as any cell that can both replicate and also has the potential to differentiate into neurons or glia (Altman and Das, 1965). These neural stem cells give rise to either other neural stem cells or neural progenitors cells, which have a limited ability to divide and cannot self-renew (Bonaguidi et al., 2011). Neural progenitor cells give rise to new adult neurons, and this is correlated with improved spatial memory (Sahay et al, 2011; Stone et al., 2011). In AD, there is a decrease in neurogenesis, so understanding the complex mechanisms that regulate this process may open a new therapeutic window for the treatment of AD (Lazarov et al., 2010). Strikingly, GS and its substrates are at the heart of these pathways.

Notch signaling maintains the balance between neural stem cells and neural progenitors (Aguirre et al., 2010; Basak and Taylor, 2007; Mizutani et al., 2007). Conditional knock out of Notch causes depletion in the progenitor pool, showing that Notch is required for the maintenance of neural stem cells (Basak et al., 2012). Notch inhibits the differentiation of progenitors into neurons and promotes the differentiation of glia progenitors into astrocytes (Bai et al., 2007; Shimojo et al., 2008). Scientists, looking to accelerate neural differentiation of induced pluripotent stem cells (iPSCs), took advantage of Notch signaling. By adding a gamma-secretase inhibitor, researchers are able to drive iPSCs to neurons (Borghese et al., 2010; Chambers et al, 2012; Chen et al., 2014; Wang et al., 2015) (Fig. 3).

PS1 is also involved in adult neural stem cells. Scientists knocked down PS1 and saw a decrease in neurogenesis in the subgranular zone of the hippocampus (Gadadhar et al., 2011). Also, by knocking-in PS1 familial mutations or using a transgenic mouse expressing a chimeric human-mouse version of APP with the Swedish mutation, a severe and well studied familial mutant, researchers observed a decrease neural proliferation (Haughey et al., 2002; Wang et al., 2004). Many groups have seen a similar effect with other PS1-dependent AD mouse models, including PS1 mutants and PS1 knock downs (Bonds et al., 2015; Choi

et al, 2008; Demars et al, 2010; Donovan et al., 2006; Rodriguez et al, 2008; Wen et al., 2004; Zhang et al, 2007). Conditional knock-out of PS1 in forebrain alone is enough to reduce neurogenesis (Saura et al, 2005), highlighting the importance of PS1 in the maintenance of neural stem cells.

GS regulation is crucial to the maintenance and proliferation of adult neural stem cells, and modulating GS activity could improve cognitive outcomes based on its effect on these specific cell types. While most of the focus of GS modulators has been on its effects on A β , altering Notch signaling could also improve cognitive outcomes by maintaining neural stem cells, and Notch-focused therapies still need to be investigated.

6. Gamma-secretase in neuronal structures: beyond A β and notch

GS, through its other substrates, is involved in many neuronal processes. One such process is axonal guidance, and many GS substrates are involved. For example, the Netrin receptor, DCC, must be processed for axons to recognize midline guidance cues (Serafini et al., 1994). GS inhibition leads to an accumulation of DCC—CTF (Taniguchi et al., 2003) and increased neurites. Another GS substrate, ephrinB and its receptor are involved in spine maturation and synaptogenesis (Barthet et al., 2013). It contributes to deficits in neuronal circuits, and acts with BACE to regulate growth cone collapse and recovery in axon path finding through CHL1 processing (Barao et al, 2015).

GS is also crucial for synaptic morphology. Synaptic dysfunction precedes neurodegeneration and is crucial to brain health. GS substrates include cell adhesion molecules-neuroigin in the post synaptic membrane is involved in cell signaling (Marballi et al., 2012). Disruptions in this pathway are implicated in schizophrenia (Mei and Xiong, 2008). Finally, GS activity regulates dendritic spine density. EphrinA4 is cleaved by GS and regulates dendritic spine morphology. EphrinA4 cleavage is disrupted by FAD mutations, and its activity is increased by synaptic activity (Inoue et al., 2009).

By looking outside canonical substrates, APP and Notch, researchers could develop GS-directed therapeutics spine maturation, synaptic morphology, and dendritic spine density, all processes dysregulated in AD.

7. Conclusion

Gamma-secretase is an enzyme complex involved in multiple signaling pathways through its numerous substrates (Fig. 4). GS is best known for its role in AD, where aberrant cleavage of APP can cause neurodegeneration. Developing therapeutics that block amyloidogenic cleavage, without altering other substrates would decrease A β peptides in the brain without the negative side effects associated with other GS substrates.

However, GS as an enzyme holds more process in AD therapeutics than just canonical inhibitors and modulators. GS is regulated by its subunits and associated proteins, so drugs that influence those components can decrease A β as well. Therapeutics can also alter GS trafficking and thereby improve cognition, or move beyond A β entirely, effecting Notch and neural stem cells. GS cleavage of DCC, neuroigin, and ephrin control neuronal morphology

and function, presenting another avenue by which GS modulation could improve AD pathology. Taken together, GS presents a unique hub for neural processes and an ideal target for AD therapeutics.

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Fig. 1.

Amyloid precursor protein (APP) can be cleaved in two major pathways. If it is first cleaved by alpha-secretase, then subsequent cleavage by gamma-secretase results in the intracellular domain (AICD) and p3, a non-amyloidogenic by-product. However, if beta-secretase performs the initial cleavage, then gamma-secretase cleaves the beta-CTF at multiple sites, sequentially releasing the AICD and Aβ peptides of varying lengths, which can oligomerize. The gamma-secretase cleavage sites are referred to as ϵ , ζ , and γ , and the starting amino acid, either 48 or 49, determines the end product, either Aβ_{338/42} or 37/40.

Fig. 2. Gamma-secretase is composed of four essential subunits: presenilin (PS1), Nicastrin (Nct), Pen-2, and APh-1. Presenilin must be endoproteolysed into the N and C terminal fragments to become active, and the catalytic residues (D*) are present in this subunit.

Fig. 3. Notch is crucial to maintaining neural progenitors. Notch inhibition maintains the progenitor pool for neurons, while Notch signaling drives glial progenitors to become astrocytes. By applying gamma-secretase inhibitors (GSIs) to induced pluripotent stem cells, researchers can drive progenitors into neurons.

Fig. 4. Gamma-secretase is vital to multiple neuronal processes. Through Notch signaling, GS is involved in the balance between neural stem cells (NSC) and neurons. GS also cleaves DCC, which regulates neurite outgrowth, neuroligin, which controls synaptic adhesion, and ephrin-B, which is involved in spine maturation.