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Review

A fast growing spectrum of biological functions of γ-secretase in development and disease☆

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ABSTRACT

γ-secretase, which assembles as a tetrameric complex, is an aspartyl protease that proteolytically cleaves substrate proteins within their membrane-spanning domain; a process also known as regulated intramembrane proteolysis (RIP). RIP regulates signaling pathways by abrogating or releasing signaling molecules. Since the discovery, already >15 years ago, of its catalytic component, presenilin, and even much earlier with the identification of amyloid precursor protein as its first substrate, γ-secretase has been commonly associated with Alzheimer's disease. However, starting with Notch and thereafter a continuously increasing number of novel substrates, γ-secretase is becoming linked to an equally broader range of biological processes. This review presents an updated overview of the current knowledge on the diverse molecular mechanisms and signaling pathways controlled by γ-secretase, with a focus on organ development, homeostasis and dysfunction. This article is part of a Special Issue entitled: Intramembrane Proteases.

Contents

1. Introduction

γ-Secretase is a promiscuous di-aspartyl protease responsible for the cleavage of a series of integral membrane proteins, almost all being type I transmembrane proteins. To date, more than 90 proteins have been identified as substrates among which the most notorious

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are Notch and Amyloid precursor protein (APP). Interestingly, γ-secretase emerged first as an enigmatic enzymatic activity with the discovery of amyloid β and APP as scientists realized at that time that proteolysis within the transmembrane domain was required to generate this peptide [1]. Now we know that γ-secretase is a multiprotein complex consisting of presenilin (abbreviated as PSEN independently of its origin), nicastrin (NCT), anterior-pharynx defective-1 (APH1) and PSEN enhancer-2 (PEN2) [2–5]. Originally discovered by geneticists as the protein products of genes mutated in families with autosomal dominant Alzheimer's disease (AD), PSEN harbors the catalytic activity of the complex ([6,7], reviewed in [8]). However, PSEN absolutely requires the co-factors NCT, APH1 and PEN2 to form a functional γ-secretase complex. Additionally, the γ-secretase complex is heterogenous in nature due to the existence of two PSEN homologues (PSEN1 & 2) and several APH1 isoforms. Different complexes are not only present in different tissues [9–11]; they have as well heterogeneous biochemical and physiological properties [12,13]. However, little is known with respect to the cell biology of these complexes and how (or whether) they might contribute to substrate and/or cleavage specificity [14]. In addition, PSEN also functions outside the γ-secretase complex, for instance, in vesicular trafficking, Ca2 + homeostasis, β-catenin stabilization and cell adhesion [5,15].

γ-Secretase created thus far a tremendous attraction through its intimate involvement in the pathophysiology of AD by catalyzing the final cleavage in the production of amyloid β peptides, thereby overshadowing its increasing involvement in major physiological processes during development as well as adulthood. In this review we summarize our current knowledge not only on the function of PSEN and γ-secretase in the broader physiological context, but also provide an updated catalogue of mutations in γ-secretase components discovered so far in human diseases.

2. Complex structure and formation

At least 19 transmembrane domains (TMD) contribute to the hydrophobicity of γ-secretase, of which nine are from PSEN and seven from APH1. PEN2 has a hairpin-like topology containing two TMDs, whereas NCT is the only type I transmembrane glycoprotein of the complex. The crystal structure of an ancestral PSEN/signal peptide peptidase (SPP) homologue has been recently revealed [16] (discussed in more detail in the article of Mike Wolfe in this review series) and remarkably confirms earlier biochemical studies on its genuine 9 transmembrane [17–19] and ring-structure topology [20]. Genetic ablation of only one component results in mislocalization (notably retention in the endoplasmic reticulum (ER)), incomplete maturation and destabilization of the remaining components, clearly indicating that inter- and intramolecular interactions are crucial in the course of assembly, transport and activation of the γ-secretase complex [14].

All γ-secretase components colocalize initially in the ER where proper posttranslational modifications and quality control systems ensure their correct folding and assembly. Their assembly is not a random process but occurs sequentially and stoichiometrically and is superimposed on transport regulation that ensures cell- and tissue-specific levels of γ-secretase activity. Most studies agree on the initial formation of an NCT–APH1 subcomplex as the first step [21,22] that is stable even in the absence of PSEN and PEN2 [23]. The formation of this intermediate NCT–APH1 scaffold is regulated by the Golgi-to-ER cargo receptor Rer1p (retrieval to ER 1 protein) [24]. Rer1p binds to the same polar residues on the NCT TMD that are essential for interaction with APH1, and thus blocks APH1 interaction with NCT during the early stages of γ-secretase complex assembly. Hence, Rer1p controls formation of γ-secretase subcomplexes and, concomitantly, total cellular γ-secretase levels and activity [14,24].

Thereafter, the sequence of events leading to the formation of a mature PSEN complex may involve direct binding of the APH1–NCT scaffold to PSEN followed by the incorporation of PEN2 [25,26]. This is thought to trigger the endoproteolysis of PSEN to form N- and C-terminal fragments (NTF and CTF) that stably associate into heterodimers. Although both fragments are part of the catalytic γ-secretase, endoproteolysis is not a requirement for activity. Alternatively, the APH1–NCT pre-complex combination may bind directly to a preformed PSEN1–PEN2 structure to generate the mature, active γ-secretase complex [23,27]. This alternative assembly process is based on the detergent-based identification of two additional intermediate complexes, NCT–APH1–PSEN1 CTF and PEN2–PSEN1 NTF; also the fact that PEN2 can bind full-length PSEN independently of NCT and APH1 supports this view [28,29].

3. Regulated Intramembrane Proteolysis (RIP)

γ-Secretase belongs to the family of intramembrane cleaving proteases (i-CLiPs) which contains in addition to the PSENs, the zinc metalloprotease site-2 protease (S2P), the signal peptide peptidases (SSP) and the rhomboid proteases. All i-CLiPs enzymatically cleave their substrate proteins within the plane of the lipid bilayer in a process termed regulated intramembrane proteolysis (RIP)([30,31]). With the exception of rhomboid proteases, RIP requires the initial ectodomain shedding of the substrate. Hence, the magnitude of RIP depends on the rate-limiting regulation of these shedding enzymes. Ectodomain shedding can be constitutive but it may also be induced by several stimuli such as ligand binding, protein kinase C (PKC) activation by phorbol esters or Ca^{2+} influx. The initial ectodomain shedding in γ-secretase-associated RIP is essentially carried out by either of two protease families, i.e. members of the 'α-disintegrin and metalloprotease' (ADAM) family commonly referred to as α-secretases (for review see [32]) and the aspartyl proteases BACE1 and BACE2 also called β-secretase [33]. The shedding results in the release of a soluble ectodomain into the extracellular environment and generation of a truncated membrane-associated carboxyl terminal fragment (CTF). The CTF is in turn cleaved by the i-CLiP that releases the intracellular domains (ICD) and a small peptide such as P3 or Aβ in case of APP.

γ-Secretase-mediated RIP may activate, turn off or switch the signaling properties of the transmembrane protein involved (Fig. 1). For instance, RIP activates signaling pathways like Notch, by allowing intracellular domains (ICD) to translocate to the nucleus where it incorporates into a transcriptional complex and regulates gene transcription (Fig. 1A) [34]. Alternatively, RIP may turn off signaling events in which the transmembrane anchored protein is responsible for signaling, and the cleavage event terminates the signal. The cleavage of Deleted in Colorectal Cancer (DCC), for instance, attenuates downstream signaling (Fig. 1B) [35]. A third possibility is that the cleavage serves as a switch between signaling modes with the uncleaved transmembrane form activating one pathway at the membrane and the soluble ICD carrying out a different function in another cellular compartment (Fig. 1C). This has been shown for various substrates including ErbB4 [36] and APP [37].

4. The most prominent γ-secretase substrates

To date more than 90 substrates have been identified for γ-secretase (reviewed in [38]). Although they are diverse in their structure, localization and physiological functions, the majority of these proteins share some common features. For instance, almost all substrates are type-I transmembrane proteins. The only exceptions identified so far are the polytopic membrane proteins glutamate receptor GluR3 and polycystin-1 as well as the type-II transmembrane protein glucosaminyltransferase (GnT-V). Typically, they contain a large ectodomain often including cell adhesion molecule-like domains, a single-pass transmembrane domain and a cytosoplasmic tail frequently capable of initiating or mediating intracellular signaling. Interestingly, the γ-secretase-mediated RIP does not depend critically on recognizing particular sequences in the transmembrane domains of its substrates but rather on the size of the extracellular domain remaining after