Presenilin-2

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Presenilin-2 (PS2) is one of the three proteins that are dominantly mutated in familial Alzheimer's disease (FAD). It forms the catalytic core of the γ-secretase complex—a function shared with its homolog presenilin-1 (PS1)—the enzyme ultimately responsible of amyloid-β (Aβ) formation. PS2 is also involved in several functions, also independently of γ-secretase activity, ranging from Ca2+ signalling to inter-organelle communication and autophagy. FAD-linked PS2 mutations impact on multiple aspects of cell and tissue physiology, including bioenergetics and brain network excitability.

Keywords: presenilin-2 ; calcium signalling ; Alzheimer's disease mouse models ; SOCE ; mitochondria ; autophagy ; brain networks ; oscillations

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Presenilin-2 (PS2), like its homolog presenilin-1 (PS1), is a 50-kDa multi-pass membrane protein with nine helical transmembrane (TM) domains, and in humans it is encoded by a gene present on chromosome 1 (*PSEN2*)[1].

1. Introduction

Both presenilins (PSs) mainly localize to the endoplasmic reticulum (ER) and Golgi apparatus (GA) membranes but also, although less abundantly, in plasma membrane (PM) and endosomes [2]. Their mRNAs are expressed in different human and mouse tissues, with the highest levels in the hippocampus and cerebellum [3].

2. Presenilin-2 in Physiology and Pathology

Both PSs represent the catalytic core of the γ-secretase complex, the enzyme ultimately responsible for generation of Aβ peptides; they were both discovered in genetic analyses of families in which Alzheimer's disease (AD) is transmitted as an autosomal dominant trait. In fact, as of now, about 300 mutations in *PSEN1* and 58 mutations in *PSEN2* have been described (https://www.alzforum.org/mutations), the majority of which are dominant, mostly missense, and have been associated with the inherited forms of the disease (familial Alzheimer's disease (FAD)) [4][5]. Mutations in the gene for one of the substrate of the γ-secretase complex, the amyloid precursor protein (APP), are also responsible for FAD cases [6]. It has been proposed that FAD-PS mutations lead to a less precise γ-secretase cleavage of APP, in some cases decreasing the total production of Aβ but increasing the relative amount of the more amyloidogenic Aβ42 peptide, the seeding core of extracellular amyloid plaques, over the more soluble Aβ40 peptide [6].

The γ-secretase complex is part of the family of intramembrane-cleaving proteases (I-CliPs), which perform hydrolysis of protein domains embedded in the hydrophobic environment of the membrane. The family includes SP2 metalloproteases, serine proteases of the rhomboid family, and the aspartyl proteases to which γ-secretase belongs.

The γ-secretase has a central role in cellular biology, with about 150 different integral membrane proteins recognized as substrates [9]; the most studied are the Notch family of receptors, with a crucial role in signalling and cell differentiation, and APP [4][7] The γ-secretase complex is composed of four subunits: PS1 or PS2; nicastrin, an integral membrane protein concerned with substrate recognition and selection [8]; PS enhancer-2 (PEN-2) that stabilizes the PS complex and has a role in its endoproteolytic cleavage [9]; and anterior pharynx defective 1 (APH1), which interacts with nicastrin, providing the initial scaffold to which PS1/2 and PEN-2 are added [10]. In humans, APH1 is encoded by two paralogous genes (APH1A and APH1B), and each protein can interact with either PS, resulting in the existence of four different γ-secretase complexes that might have slightly different specificities [11]. After its enclosure within the complex, PS undergoes an endoproteolytic cleavage that produces N- and C-terminal fragments; the two fragments remain associated and represent the biologically active form of the complex, each carrying one of the two key aspartic acid residues on TM6 and TM7, respectively [12].

PS1 and PS2 share about 66% of amino acidic sequence; one key difference is a motif in PS2 that interacts with activating protein-1 (AP-1) complexes in a phosphorylation-dependent manner and targets PS2 to the late endosome/lysosome compartment, leading to a different subcellular distribution of PS2 and perhaps to subtly different

functions [13][14]. For example, it has been demonstrated that PS2-containing γ-secretase complexes are involved in the processing of premelanosome (PMEL) protein, which is involved in melanosome maturation and melanin deposition. Indeed, PS2-null zebrafish showed defects in skin pigmentation [15]. Importantly, melanosome biogenesis seems to be Ca^{2+}-dependent[16].

Several γ-secretase-independent functions of PSs have emerged in the recent years, enriching the overall importance of these proteins in cell biology. For example, PSs bind to glycogen synthase kinase 3β (GSK3β), a key protein of the Wnt signalling pathway, and to its substrate β-catenin, a transcription regulator [17]. The interaction of PSs with GSK3β and β-catenin is independent of γ-secretase activity [18] and influences β-catenin phosphorylation and turnover, as well as the activity of kinesin-1 and dynein and thus axonal transport of type 1 transmembrane receptors [19]. PSs have been implicated also in autophagy and protein trafficking [20].

Last, but not least, the regulation of cellular Ca^{2+} homeostasis has emerged as a key PS function with relevant implications in multiple Ca^{2+}-regulated cell processes [21][22]. FAD-linked PS2 mutations are also linked to neuronal hyperactivity [23]and alterations in spontaneous brain oscillations [24][25]. The central role played by PS2 in cellular Ca^{2+} homeostasis, and brain pathophysiology has recently summarized [26][27][28].

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