Progress in Neurobiology 93 (2011) 149–164

Contents lists available at ScienceDirect

Progress in Neurobiology

journal homepage: www.elsevier.com/locate/pneurobio

Presenilin mouse and zebrafish models for dementia: Focus on neurogenesis

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ARTICLE INFO

Article history:
Received 28 June 2010
Received in revised form 27 October 2010
Accepted 31 October 2010
Available online 5 November 2010

Keywords:
Presenilin
Mouse model
Zebrafish model
Neurodegeneration
Neurogenesis
Alzheimer's disease

ABSTRACT

Autosomal dominant mutations in the presenilin gene *PSEN* cause familial Alzheimer's disease (AD), a neurological disorder pathologically characterized by intraneuronal accumulation and extracellular deposition of amyloid-β in plaques and intraneuronal, hyperphosphorylated tau aggregation in neurofibrillary tangles. Presenilins (PS/PSENs) are part of the proteolytic γ-secretase complex, which cleaves substrate proteins within the membrane. Cleavage of the amyloid precursor protein (APP) by γ-secretase releases amyloid-β peptides. Besides its role in the processing of APP and other transmembrane proteins, presenilin plays an important role in neural progenitor cell maintenance and neurogenesis. In this review, we discuss the role of presenilin in relation to neurogenesis and neurodegeneration and review the currently available presenilin animal models. In addition to established mouse models, zebrafish are emerging as an attractive vertebrate model organism to study the role of presenilin during the development of the nervous system and in neurodegenerative disorders involving presenilin. Zebrafish is a suitable model organism for large-scale drug screening, making this a valuable model to identify novel therapeutic targets for AD.

Contents

Abbreviations: AD, Alzheimer's disease; PSEN, presenilin; APP, amyloid precursor protein; Aβ, β-amyloid; FAD, familial forms of AD; SVZ, subventricular zone; SGZ, subgranular zone; DG, dentate gyrus; NSCs, neural stem cells; DCX, doublecortin; NPC, neural progenitor cell; RMS, rostral migratory stream; NTF, N-terminal fragment; CTF, C-terminal fragment; AICD, APP intracellular domain; NICD, Notch intracellular domain; hESC, human embryonic stem cells; CNS, central nervous system; MO, morpholino antisense-oligonucleotides.

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doi:10.1016/j.pneurobio.2010.10.008

1. Introduction

1.1. Alzheimer's disease

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most common cause of dementia in the aged population. In 2005, it was estimated that 24.3 million people world-wide suffer from AD (Ferri et al., 2005). In the US alone, $237 billion is spent annually to provide care for the 5 million Americans suffering from AD (Alzheimer's Association, 2009). Given that age is the most important risk factor to develop AD, the number of patients is expected to rise dramatically in the coming years with each year 4.6 million new cases worldwide. Currently, there is no effective therapy to prevent, delay or reverse the disease process of AD (Roberson and Mucke, 2006).

In postmortem brain tissue of AD patients, numerous extra- and intracellular deposits of misprocessed, misfolded and aberrant proteins are found, such as amyloid-β (Aβ), hyperphosphorylated tau and ubiquitinated proteins, which accumulate during the course of the disease (Bertram and Tanzi, 2008; Hol et al., 2005; LaFerla et al., 2007). The genetic familial forms of AD (FAD), comprising a few percent of all demented cases, indicate that misprocessing of amyloid precursor protein (APP) and/or altered regulation of intraneuronal amyloid is involved in AD pathogenesis (Roberson and Mucke, 2006). These familial forms have further provided important information on the regulation of APP processing by presenilins (PSEN1 and PSEN2, also often referred to as PS1 and PS2) and their role in amyloid plaque formation. However, in the large population of the more common, non-inheritable "sporadic" cases of AD, the main risk factors are age and the ApoE-genotype (Bu, 2009).

The α-helical Aβ peptide, the main constituent of AD plaques, is cleaved from the type I membrane glycoprotein APP by the consecutive activity of β- and γ-secretases, resulting in the secretion of Aβ into the extracellular space. Different isoforms of Aβ are produced varying in length between 38 and 42 amino acids, each having distinct aggregation characteristics (Haass and Selkoe, 2007). Also shorter C-terminal truncated Aβ fragments have been identified, of which Aβ isoforms $A\beta_{1-14}$ to $A\beta_{1-16}$ result from APP processing by β-secretase and α-secretase (Blennow et al., 2010; Portelius et al., 2009). In AD, the levels of $A\beta_{42}$ are increased and the ratio of $A\beta_{42}$/$A\beta_{40}$ is elevated. When extracellular Aβ levels reach a threshold concentration, Aβ will undergo conformational changes and aggregate. Especially $A\beta_{42}$ has a high propensity to aggregate and form extracellular deposits in the brain of AD patients. In the amyloid hypothesis of AD, accumulation of Aβ is seen as the main underlying cause of AD pathology (Hardy and Selkoe, 2002). The current consensus among Alzheimer researchers is that the oligomeric forms of Aβ are the real culprit (Haass and Selkoe, 2007; Lansbury and Lashuel, 2006), while intraneuronal Aβ accumulation has attracted considerable interest as well (LaFerla et al., 2007; Wirths et al., 2009). In that sense, formation of extracellular amyloid plaques may, in fact, represent a defense mechanism of the brain to eliminate toxic Aβ-oligomers from the cell.

1.2. Neurogenesis in Alzheimer's disease

Given the profound memory deficits and prominent hippocampal pathology in AD, the role of adult neurogenesis, a process occurring selectively in the adult hippocampus and ventricular zone, has attracted considerable attention in the AD field. In contrast to the general post-mitotic state of the adult nervous system, new cell birth and ongoing neurogenesis does occur in restricted regions of the brains of adult rodents and primates, including humans. The identification of these stem cells in the adult brain has nurtured the hope to recruit these cells to facilitate repair of damaged neural tissue.

Adult neurogenesis occurs in two distinct locations; the subventricular zone (SVZ) and subgranular zone (SGZ), located in the lateral ventricle wall and hippocampal dentate gyrus (DG), respectively (Ming and Song, 2005; Zhao et al., 2008) while in a few other brain regions limited cytogenesis and/or neurogenesis may occur under specific conditions (Gould, 2007). The SVZ and SGZ are unique zones as they contain neural stem cells (NSCs) that retain the capacity to proliferate, migrate, and differentiate into new, fully functional neurons in a mature environment. The addition of newly born neurons to an existing circuit by means of adult neurogenesis represents a novel and unique form of structural plasticity that not only allows adaptation for the longer term, but also may constitute an endogenous cell replacement mechanism. As such, adult neurogenesis may determine "neural reserve" in selective brain regions (Kempermann, 2008; Zhao et al., 2008).

Neurogenesis occurs throughout the lifespan of many bird, rodent and primate species, indicating an important role that is conserved throughout evolution (Gould, 2007). Numerous studies have further identified factors that modulate production and survival of the newborn hippocampal neurons during adulthood; e.g. voluntary exercise, anti-depressant treatment and environmental enrichment increase the number, survival and *in vivo* fate of newborn cells, whereas (early) stress exposure or aging decreases neurogenesis (Heine et al., 2004; Kempermann et al., 2002; Kuhn et al., 1996; Leuner et al., 2007; Lucassen et al., 2010a,b; Marlatt and Lucassen, 2010; Oomen et al., 2007, 2010; Rao et al., 2006).

Although the number of new neurons directly incorporated into the adult or aged DG may be low, this ongoing phenomenon holds a potential for adaptation, as the NSCs in the adult brain are multipotent and can differentiate into neurons, astrocytes or oligodendrocytes *in vitro* (Garcia et al., 2004; Sanai et al., 2004). Interestingly, hippocampal sprouting, cyto- and neurogenesis in adult or aged individuals is potently increased in response to various types of hippocampal insults or damage, as e.g. occurs during ischemia, epilepsy or head injury, but the effects on hippocampal circuit properties and on the progress of AD are poorly understood (reviewed by Castellani et al., 2007; Kuhn et al., 2007; Marlatt and Lucassen, 2010). Assuming that a neurogenic response to damage in human brain could one day be utilized, neurogenesis may constitute a potential endogenous mechanism to replace lost or damaged cells, provided that also the affected local environment can be made "permissive" to these new cells.

Regarding AD, it has e.g. been shown that Aβ itself is toxic to neural progenitors (Donovan et al., 2006; Haughey et al., 2002a; Jin et al., 2004a; Li and Zuo, 2005; Lopez-Toledano and Shelanski, 2004). In addition, changes in hippocampal cytogenesis and neurogenesis have been reported in AD brain and in selective mouse models for dementia with the direction of the effect depending on the development and progression of the pathology (Boekhoorn et al., 2006; Ekonomou et al., 2010; Jin et al., 2004b; Kuhn et al., 2007; Li et al., 2008; Thompson et al., 2008; Yu et al., 2009).