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Alzheimer's disease genes and autophagy

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ABSTRACT

Autophagy is a process to degrade and recycle cellular constituents via the lysosome for regulating cellular homeostasis. Its dysfunction is now considered to be involved in many diseases, including neurodegenerative diseases. Many features reflecting autophagy impairment, such as autophagosome accumulation and lysosomal dysfunction, have been also revealed to be involved in Alzheimer's disease (AD). Recent genetic studies such as genome-wide association studies in AD have identified a number of novel genes associated with AD. Some of the identified genes have demonstrated dysfunction in autophagic processes in AD, while others remain under investigation. Since autophagy is strongly regarded to be one of the major pathogenic mechanisms of AD, it is necessary to review how the AD-associated genes are related to autophagy. We anticipate our current review to be a starting point for future studies regarding AD-associated genes and autophagy.

This article is part of a Special Issue entitled SI:Autophagy.

Contents

Abbreviations: AD, Alzheimer's disease; APP, amyloid precursor protein; Aβ, β-amyloid; PS1/2, presenilin 1/2, ApoE, apolipoprotein E; ADAM10, a disintegrin and metallopeptidase domain 10; TREM2, triggering receptor expressed on myeloid cells 2; BECN1, beclin-1; SNP, single nucleotide polymorphism; PICALM, phosphatidylinositol-binding clathrin assembly protein; CR1, complement component 3b/4b receptor 1; BIN1, bridging integrator 1; MS4A6A/E, membrane-spanning 4 domains subfamily A/E member 6A; ABCA7, ATP-binding cassette subfamily A member 7; CD2AP, CD2-associated protein; EPHA1, ephrin receptor A1; EPHB2, ephrin receptor B2; HLA-DRB5/1, major histocompatibility complex class II DRβ5/1; SORL1, sortilin-related receptor L A repeats containing; PTK2B, protein tyrosine kinase 2β; SLC24A4, solute carrier family 24 member 4; ZCWPW1, zinc finger CW-type with PWWP domain 1; CELF1, CUGBP Elav-like family member 1; FERMT2, fermitin family member 2; CASS4, Cas scaffolding protein family member 4; INPP5D, inositol polyphosphate-5 phosphatase 145 kDa; MEF2c, myocyte enhancer factor 2C; NME8, NME/NM23 family member 8; PLD3, phospholipase D3

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1. Introduction

1.1. Alzheimer's disease

Alzheimer's disease (AD), the most common neurodegenerative disease, is characterized by progressive impairment of cognitive function and memory formation. Pathological signalling in AD is largely mediated by two major characteristic components, neurofibrillary tangles (NFTs) and senile plaques (Gomez-Isla et al., 1997). Extracellular plaques are primarily composed of amyloid-β (Aβ) peptides, which are derived from amyloid precursor protein (APP) via proteolytic processing. NFTs are formed by intraneuronal accumulation of paired helical filaments composed of abnormally hyperphosphorylated TAU protein (Grundke-Iqbal et al., 1986).

1.2. Autophagy

Macroautophagy (hereafter, autophagy) is a catabolic process that sequesters cytoplasm, including aberrant organelles and macromolecules, into double-membrane vesicles and delivers this material to lysosomes for degradation and the eventual recycling of the resulting macromolecules (Castellano et al., 2011b). Under the control of various signalling and protein assemblies from certain stimuli, such as starvation, damaged organelles, or protein aggregates, the first step of autophagy begins with the formation of an isolation membrane (phagophore). The isolation membrane elongates around the molecules and organelles to be degraded, closing its inner and outer bilayers to form a double-membrane autophagosome. The autophagosome then fuses with a lysosome that degrades the autophagosome contents (Hale et al., 2013; Klionsky, 2012). Impairment or misregulation in these steps of autophagy is associated with many neurodegenerative diseases, including AD (Nixon, 2013).

1.3. Autophagy in AD

Marked accumulation of autophagosomes and late autophagic vacuoles is observed in dystrophic neurites of AD brains, animal AD model brains, and AD cellular models, suggesting impaired fusion with or degradation by lysosomes (Yoon et al., 2008; Yu et al., 2004, 2005). Nixon (2013) recently reviewed the relationship between impaired lysosomal function and autophagy in neurodegenerative diseases, including AD. In our present review, we discuss the association of AD genes with autophagy in an attempt to understand how autophagy is involved in the pathogenesis of AD and how therapeutic approaches for AD could exploit autophagic pathways.

2. Autophagy-related features and roles of AD-associated genes

2.1. Genes associated with AD

The classical genes associated with early-onset familial AD are *APP*, presenilin 1 (*PS1*), and presenilin 2 (*PS2*). Apolipoprotein E (*APOE*) is the strongest risk factor for late-onset AD (Guerreiro et al., 2013b; Karch and Goate, 2015). Recent genetic studies have identified numerous novel gene loci affecting late-onset AD (Table 1).

2.2. APP and Aβ

APP is a type I membrane protein that is sequentially cleaved by β-secretase and γ-secretase to generate Aβ peptide, a major constituent of the senile plaques of AD. More than 30 mutations in APP are associated with early-onset familial AD (Guerreiro et al., 2012; http://www.molgen.vib-ua.be/ADMutations). Autophagy has been suggested to lead to Aβ generation since the first report proposing the role of autophagy in AD because early studies demonstrated that autophagosomes accumulate within AD neurites, and APP, CTFs of APP, Aβ, and BACE were found within these autophagosomes (Mizushima, 2005; Nixon, 2007; Yu et al., 2004, 2005). However, further understanding of autophagy itself and its relationship with AD led to the identification of APP, Aβ, APP-CTFs, and BACE as autophagy substrates (Cho et al., 2014; Jaeger et al., 2010; Liu et al., 2013; Lunemann et al., 2007; Pickford et al., 2008; Tian et al., 2013; Zhou et al., 2011). In support of this view, various compounds, such as rapamycin, trehalose, carbamazepine, latrepirdine, arctigenin, temsirolimus, and curcumin, have been suggested to help protect against AD by degrading Aβ and other related pathogenic proteins via activation of autophagy (Jiang et al., 2014a; Li et al., 2013; Perucho et al., 2012; Steele and Gandy, 2013; Tian et al., 2011; Wang et al., 2014; Zhu et al., 2013).

A direct role of APP or Aβ in autophagy has not been determined yet, but AD-related mutations in APP may contribute to AD pathogenesis by producing impaired autophagy functions. Such mutations are known to generate more Aβ and aggregation-prone Aβ, which results in an overloaded autophagic pathway due to accumulated substrates. Aβ directly interacts with membranes via its hydrophobic carboxyl terminus (Masters and Selkoe, 2012), which is suggested to interfere with normal biogenesis and trafficking of intracellular organelles (Kakio et al., 2004; Murphy, 2007; Sasahara et al., 2013). This feature of Aβ may also affect the biogenesis or trafficking of autophagosomes and their fusion with lysosomes, and this possibility needs to be addressed in the future. Aβ accumulation in lysosomes results in lysosomal membrane destabilization and leakage (Ji et al., 2002; Yang et al., 1998), which may also impair autophagy and lysosomal degradation (Nixon, 2013).

2.3. Presenilin

Presenilins 1 and 2 are homologous integral membrane proteins containing nine transmembrane domains (Guerreiro et al., 2012). Presenilin 1/2 forms the γ-secretase complex with nicastrin, anterior pharynx-defective 1 (APH1A/B), and presenilin enhancer 2 (PEN2) to cleave APP into Aβ (Wakabayashi and De Strooper,