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Potential Link Between Proprotein Convertase Subtilisin/Kexin Type 9 and Alzheimer's Disease

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Abstract

Alzheimer's disease [AD] is not only the most common neurodegenerative disease but is also currently incurable. Proprotein convertase subtilisin/kexin-9 [PCSK9] is an indirect regulator of plasma low density lipoprotein [LDL] levels controlling LDL receptor expression at the plasma membrane. PCSK9 also appears to regulate the development of glucose intolerance, insulin resistance, abdominal obesity, inflammation, and hypertension, conditions that have been identified as risk factors for AD. PCSK9 levels also depend on age, sex, and ethnic background, factors associated with AD. Herein, we will review indirect evidence that suggests a link between PCSK9 levels and AD.

Keywords: Alzheimer's disease; PCSK9; LDL; Metabolic diseases.

Overview

In 2017, about 5.5 million Americans were diagnosed with Alzheimer's disease [AD] [1]. The majority of the AD patients [96%] were 65 years of age or older; only 4% were under the age of 65 [1]. About 47 million people worldwide are presently suffering from AD, a number predicted to triplicate by 2050 [2,2]. Even though all individuals with AD do not share most symptoms, many symptoms are common to all patients [4]. The more typical prime symptom of AD is short-term memory loss [4]. Over time, the person also suffers a deterioration in his/her ability to perform routine tasks, disorientation, personality changes, and inability to learn new information [4]. AD eventually prevents the person from caring for him or herself [4]. As AD progresses, other symptoms arise such as language impairment, difficulties completing complex tasks, depression, psychotic episodes, and behavioral changes [4,5]. Even with aggressive management, AD patients often live out their final months or years in a vegetative state [6]. Currently, the disease is incurable and fatal [6].

Risk factors for AD are age, familial aggregation of AD, Down's syndrome, and Parkinson's disease, late maternal age, inflammation, head trauma, and family history of dementia, depression, and hypothyroidism [7]. The incidence of AD increases with age, which seems to be the leading cause of AD, and is doubled every five to ten years [7,8]. Genetic mutations are additional contributing factor [7]. Mutations in specific genes lead to increased risk of AD development [9]. Genes with reported connections to AD development include amyloid precursor protein[APP], apolipoprotein [Apo] E4, and Tau [9-13].

Gender is another known risk factor for AD [14]. It has been shown that women acquire AD at a higher rate than men [14,15]. Ethnicity is another crucial determinant of AD [1]. Statistics reveal that African-American are more likely to get AD than Caucasian-Americans [1,16]. Hispanics are statistically the second prevalent ethnic group diagnosed with AD [2,17]. Health disparities such as diabetes, hypertension, and heart diseases are the main reasons for the ethnic differences

in the risk of developing AD [8,18,19]. It has also been shown that exposure to discrimination or poverty and not finishing school are also risk factors for AD [8,18,19].

Development of AD

The distinguishing "hallmark" lesions found in the brain of AD patients are extracellular amyloid β (Aβ) plaques (senile plaques) and intracellular neurofibrillary tangles (NFTs) of hyperphosphorylated Tau (Figure 1) [2,17,20]. No new lesions associated with AD brains have been identified since Dr. Alois Alzheimer discovered and described the disease in1906 [21].

One of the well-publicized proteins related to AD lesions is APP [20]. APP is part of a highly conserved family of type-I transmembrane proteins [10]. This protein is responsible for neuron outgrowth and survival [10]. The precursor protein is oriented with the N-terminal region towards the extracellular space of the cell and the C-terminal domain within the cytosol [10]. APP is cleaved into two different secreted proteins, Aβ or p3 [3-kD soluble peptide], depending on the enzymes available for the processing of APP [22,23]. The normal processing of APP begins with α-secretase that cuts in the middle of the Aβ sequence (Figure 2) [22,23]. The ectodomain-α [ectodomain+N-terminal region of Aβ] is released to the extracellular space while γ-secretase cuts the remaining transmembrane domain producing the secreted p3 fragment and the APP intracellular domain (AID) [22,23]. The function of p3 is currently unknown [24]. The AID has been implicated in nuclear signalling [25,26].

Aβ is a short peptide of 39-43 amino acids that could assemble into amyloid or senile plaques in response to abnormal processing of APP [22,23]. The abnormal processing occurs when APP is cleaved first by β-secretase (Figure 2) [22,23]. This cut releases the ectodomain of APP while γ-secretase cleave off the Aβ fragment from the AID [27]. Aβis then secreted into the extracellular space of the cell where it is assembled into oligomers, which are mostly soluble [28,29]. However, at a high concentration, the conformation of the Aβ oligomers can change into a β-sheet-rich tertiary structure that accumulates forming amyloid plaques around the neurons [28,29]. Highly aggregated Aβ oligomers can form complexes with plasma membrane lipids that leads to membrane disruption, pore formation, and cellular damage [30].

Tau is another crucial gene involved in the development of AD [13]. Tau is a microtubule-associated protein [MAP] mainly expressed in axons of developing and mature neurons and is crucial for neuronal function [13,31]. The primary function of tau, when phosphorylated, is to bind to microtubules (MTs) and to promote MT stabilization and polymerization [13,31,32]. Tau also stimulates neurite outgrowth, organizes axonal MTs, and is involved in kinesin-dependent axonal transport [32].

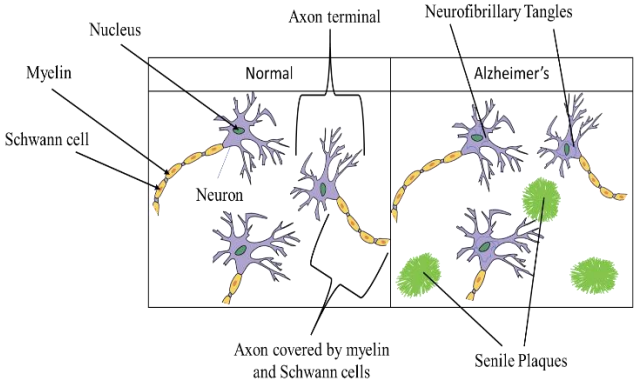

Figure 1: Schematic comparing neurons from a healthy and Alzheimer's disease (AD) brain. (A) Structure of neurons from a healthy brain. Typical structural parts of neuronal cells containing myelin are indicated. (B) "Hallmark" lesions of AD. Senile plaques are usually found extracellularly whereas neurofibrillary tangles are found intracellularly.

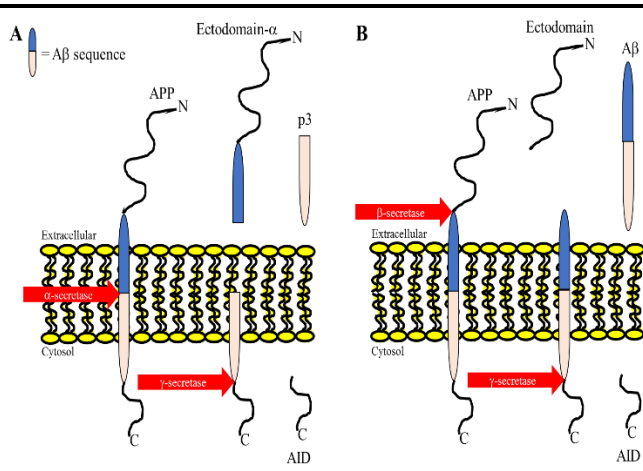

Table 2: Pathways for the processing of amyloid precursor protein (APP). (A) Normal pathway involving α and γ secretases and resulting in the formation of p3. (B) Abnormal pathway involving β- and γ- secretases and resulting in the formation of amyloid β (Aβ). AID refers to APP intracellular domain.

Tau has three main protein domains, the acidic N-terminal region, a proline-rich middle region [hinge], and a basic C-terminal region [13,31]. The N-terminal region of tau interacts with the plasma membrane

protein dynactin and with the tyrosine kinase Fyn [13,31]. The hinge region of tau influences MT spacing and inhibits kinesin-dependent axonal transport [13,31]. The C-terminal domain contains either three or four MT-binding motifs [changing tau affinity for the MTs] depending on splicing of exon 10 [31,33,34].

Tau undergoes phosphorylation at as many as eighty serine/threonine residues and five tyrosine residues [31]. Tau is crucial for establishing neuronal cell polarity and axonal outgrowth during development, and for maintaining axonal morphology and transport in mature cells [35]. Tau carries out those functions by binding directly to MTs and controlling the MT's growing and shortening dynamics [35]. Previous studies have shown that proper regulation of the MT's dynamics is imperative for cell viability. Tau activity is regulated through two mechanisms, alternative splicing, and phosphorylation [Figure 3] [35,36].

The human tau is composed of 16 exons, three of which, 2, 3, and 10, are alternatively spliced to form six Tau isoforms [37]. Exon 10 encodes the second of four imperfect MT-binding repeats in the C-terminal region of the tau protein [37]. Tau isoforms not including exon 10 have three MT binding domains (3R), whereas tau isoforms including exon 10 have four MT-binding domains (4R) [37,38]. Equal quantities of Tau 3R and Tau 4R [1:1] are expressed in adult human brain [37]. Changes in the ratio of Tau 4R to Tau 3R in the human brain have been associated with the development of neurodegenerative diseases [37]. For example, increases in the Tau 3R isoforms are associated with AD, progressive supranuclear palsy, and cortico basal degeneration [37]. Increases in Tau 4R isoforms have related to fronto temporal dementia and Pick's disease [37].

Sometimes changes in the ratio of Tau 3R and 4R do not indicate a pathological condition. For example, increases in Tau 4R are seen during neurite outgrowth, neuronal differentiation, and cell death [33]. Increases in Tau 3R, however, have been associated with neuronal proliferation and survival [33]. Tau 4R has three times more MT-stabilizing ability than Tau 3R due to the presence of the additional motif [39]. Tau 3R has been shown to inhibit Tau 4R-dependent MT assembly [33]. Thus, an equimolar ratio of Tau 4R and Tau 3R is necessary to maintain proper neuronal microtubule dynamics and to prevent abnormal filament assembly [33,39]. Changes in the ratio of Tau 4R and Tau 3R do not affect the overall levels of tau protein expression [33,39].

Tau phosphorylation is also regulated and can result in a decreased affinity of tau for the MTs [31]. Hyperphosphorylation of Tau is the primary factor involved in the formation of NFTs which trigger disintegration of MTs leading to AD [31]. NFTs are insoluble tau aggregates located within the neurons of AD patients [31]. NFTs mainly affect the cognitive [empathy, affect, social, behavior, language use, and comprehension] of the frontal and temporal cortex [31,40]. Interestingly, several studies suggest that high levels of Aβ enhance tau phosphorylation leading to the destabilization of microtubules, impaired axonal transport, and death of neurons [41-43]. Therefore, the appearance of Aβ plaques accentuates the development of NFTs.

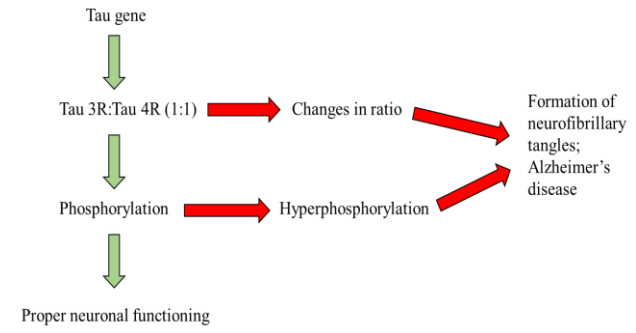

Figure 3: Proper processing of Tau and alterations in this processing leading to Alzheimer's disease.

Cholesterol

Cholesterol is a sterol compound found in most body tissues, including blood and the nervous system [44,45]. Cholesterol and its derivatives are essential ingredients of cell membranes and precursors to other steroid compounds such as bile acids, vitamin D, glucocorticoid, estrogen, progesterone, androgen and more [44,45]. However, high concentrations of cholesterol in the bloodstream promote different atherosclerotic-related diseases including heart diseases and strokes [46]. The highest amount of cellular cholesterol [about 30-50%] is found in the plasma membrane where it regulates membrane fluidity [47]. Membranes with a high content of cholesterol have a decreased fluidity, whereas membranes with low content of cholesterol have an increased fluidity [47]. Membrane fluidity is involved in different processes including signal transduction and the transport of nutrients/waste products in and out of the cell [48]. Surprisingly, the brain contains the highest amount of free cholesterol [about 25%] compared to other organs in the human body [49].

The cholesterol found in the bloodstream comes from two primary sources: de novo synthesis and the diet [50,51]. Independently of the source, serum cholesterol is lipoproteins [51,52]. Once dietary cholesterol and other lipids reach the small intestine, they are absorbed by the enterocytes and then packaged with Apo B-48 into nascent chylomicrons [54]. The enzyme responsible for the assembling of nascent chylomicrons within the enterocytes is the microsomal triglyceride (TG) transfer protein (MTP) [54]. Nascent chylomicrons are transported along the secretory pathway, where they acquire Apo E and Apo C-II by exchanging components with the high-density lipoprotein (HDL) particle, followed by secretion of the now mature chylomicrons into the lymph [54]. During their journey through the lymph, TGs contained within chylomicrons are hydrolyzed to supply fatty acids and glycerol to myocytes, adipocytes, and lactating breast tissue, leaving behind TG-depleted chylomicron remnants [54]. Hepatocytes remove chylomicron remnants from the circulation through a process mediated by the low-density lipoprotein (LDL) receptor [54]. The transport of dietary lipids through the circulation is known as the exogenous lipoprotein pathway [54].

In contrast to the exogenous pathway, the endogenous lipoprotein pathway originates in the hepatocytes [51]. Hepatic lipids, including cholesterol, are packaged into Apo B-100/Apo E-containing lipoproteins known as very low-density lipoproteins (VLDL) [55,56]. The assembling of VLDL requires the action of the MTP expressed in hepatocytes [55,56]. Upon secretion, most of the VLDL particles are quickly internalized by the action of the LDL receptor [55,56]. Those VLDL particles that escape the receptor enter the circulation [55, 56]. As for chylomicrons, VLDL acquires Apo C-II in the circulation by exchanging components with the high-density lipoprotein (HDL) [55,56]. Apo C-II allows the hydrolysis of the VLDL's TGs to provide fatty acids to muscle, adipose tissue and lactating breast. The enzyme responsible for hydrolyzing TGs from either chylomicrons or VLDL particles is lipoprotein lipase (LPL), which is activated by Apo C-II [55,56]. The hydrolysis of VLDL's TGs yields intermediate-density lipoprotein (IDL), which is also called β-VLDL or VLDL remnants. IDLs have a high affinity for the LDL receptor and are rapidly taken up by the liver. Those IDL particles that survive the receptor's internalization pathway go on to suffer further hydrolysis [55,56]. Apo E, Apo C-II, and other apolipoproteins present in IDL, except ApoB-100, are transferred back to HDL [55,56]. This process leads to the formation of LDL, which is also removed by the LDL receptor pathway, but at a reduced rate, when compared to the removal rate of IDL [55,56].

Therefore, the LDL receptor pathway is responsible for the uptake and degradation of most Apo B-containing lipoproteins of the exogenous and endogenous lipoprotein pathways [57,58]. These lipoproteins are chylomicron remnants, VLDL, and IDL, via their Apo E, and LDL, via Apo B-100 [57,58]. About 70% of the cholesterol present in the bloodstream is found in the form of LDL [59,60]. The hepatic LDL receptor is the determining factor of plasma LDL levels [57].

Cholesterol synthesis and transport in different organs

In most organs and under healthy conditions, there is a balance between de novo cholesterol synthesis and its transport in and out of the cell [61,62]. This balance is critical to prevent an over-accumulation of cholesterol within tissues [61,62]. As mentioned above, the liver is the organ responsible for the synthesis of VLDL, which transport triglycerides and cholesterol to most peripheral tissues [51,55,56]. Many of these tissues also synthesize their own cholesterol, some of which is added to LDL [61]. Several organs also transport excess cholesterol to HDL, a process that is mediated by the transporterABCA1 [61,63]. The cholesterol added to HDL is esterified and transported to the liver where the cholesterol is selectively transported into cells via the scavenger receptor class B type 1 [SR-B1] [63,64]. A significant portion of the cholesterol reaching the liver is secreted from the body either as bile acids or as free cholesterol after secretion into the bile by the action of the transporters ABCG5/8, ABCB4, and ABCB11 [63,65].

It has been proposed by many scientists that the brain has the capacity of acquiring cholesterol either by uptake of plasma lipoproteins across the blood-brain barrier or by de novo synthesis within the neurons [61,66]. In fact, high expression levels of the LDL receptor, SR-B1 and ABCA1 have been detected in brain endothelial cells [67,68]. However, several animal studies have failed to demonstrate that lipoproteins are taken up by brain cells [69-72]. Thus, it appears that the brain makes the majority of its cholesterol, and if this organ takes any lipoproteins from the blood to supplement its cholesterol pool, this contribution is undetectable by the methods utilized in those studies [69-72].

Cholesterol role in myelin formation

The axons of some nerve cells are covered by myelin, which serves as an electrical isolator [73]. The myelin

layer is essential for the functioning of the nervous system since it speeds up the signal transfer process [73]. Loss of the myelin layer either induced in animal studies or due to disease in humans leads to disruption of the signal between neuronal cells [74-77]. Although it could have different chemical components, cholesterol has been identified as an essential constituent of myelin conforming 70-85% of the myelin together with galactocerebroside [78-80]. Other components of myelin are water [40%] and myelin-specific proteins [15-30%] [78-80]. Myelin is what gives the color to the "white matter" of the brain [73].

Myelin is made of two different types of cells. In the central nervous system [CNS; the brain and spinal cord], oligodendrocytes create the myelin sheath after wrapping themselves around the axons of the neuronal cells [81]. In other parts of the nervous system, the myelin is produced by Schwann cells [Figure 1] [81]. In both cases, the function of myelin is the same.

In addition to being part of myelin, cholesterol also plays crucial roles in the synapse, dendrite formation, and axonal guidance [82-84]. Several oxidized products of cholesterol made within the brain influence critical cell functions such as regulation of cholesterol excess within this organ [66,85]. Depleting cholesterol in neurons impairs synaptic vesicle exocytosis, neuronal activity, and neurotransmission, and leads to dendritic spine and synapse degeneration [86,87]. Also, defects in cholesterol metabolism cause structural and functional CNS diseases such as Smith-Lemli-Opitz syndrome, Niemann-Pick C disease, Huntington's disease, Parkinson's disease, and Alzheimer's disease [88-91].

It is critical to discuss that in the brain, the cholesterol pathway and the prenylation of proteins are reciprocally regulated in correlation with the synthesis of Aβ [92]. In fact, it has been shown that Aβ inhibits cholesterol synthesis and protein prenylation in neuronal cells [93]. Prenylation is mainly affected due to a lack of isoprenoid from the cholesterol biosynthetic pathway, whereas cholesterol synthesis is reduced as a result of a down-regulation in sterol regulatory element binding protein-2 [SREBP-2] cleavage [93,94].

The LDL receptor gene and its family of proteins

The LDL receptor is a transmembrane glycoprotein found on the surface of cells [58,95]. As described above, this receptor plays a significant role in the removal of cholesterol-carrying Apo B-lipoproteins from the circulation [57,58]. The human LDL receptor gene, which is located on chromosome 19p 13.1-13.3, is approximately 45 kb long [96]. The LDL receptor gene is composed of 18 exons and 17 introns [96]. The promoter of the LDL receptor gene has two TATA-like sequences and three 16 bp direct repeats critical for the transcription of this gene [97]. Repeats 1 and 3 are recognized by the transcription factor Sp1 and help in maintaining basal LDL receptor transcription levels [97,98]. Repeat 2 is a sterol regulatory element that controls transcription of the LDL receptor in response to sterol levels [99].

The LDL receptor superfamily of proteins also includes the LDL receptor-related protein 1 (LRP1; also known as Apo E receptor or ApoER), LRP1b, ApoER2, LRP4, VLDL receptor, and megalin [99]. In addition to internalizing different lipoproteins, the LDL receptor seems to play a crucial role in preventing Aβ aggregation and enhancing Aβ clearance from the extracellular space of the brain [100]. ApoER is involved in intracellular signaling, lipid homeostasis, coagulation, tumor invasion, and clearance of apoptotic cells [102,103]. ApoER is also involved in the metabolism of Apo E within the brain and synapsis [104,105]. LRP1b is critical for normal cell function and development, and in brain cells, it increases expression and normal [α-secretase] cleavage of AP Producing Aβ production [106,107]. ApoER2 mediates signal transduction, endocytosis of specific ligands, embryonic neuronal migration, and postnatal long-term potentiation [99,108]. This receptor also protects against neuronal cell loss during normal aging [109]. LRP4 is a critical regulator of Wnt signaling and controls synaptic transmission and postsynaptic integration that contribute to long-term plasticity, learning, and memory [110,111]. The VLDL receptor is vital in providing cholesterol to the brain, but it is also essential for tumor growth and neuronal migration in developing brain [99,112, 113]. Like other members of the superfamily, Megalin mediates endocytosis of ligands leading to their degradation in the lysosomes, but it also forms the Heymann nephritis antigenic complex and serves as a receptor for thyroglobulin [114]. In the brain, megalin is involved in Aβ-mediated neurotoxicity and in the neurodegenerative processes that occur in AD [115]. Many of these receptors directly interact with APP in brain cells controlling the trafficking, processing, and elimination of APP, and consequently, the formation of Aβ [116]. All these receptors share similarities in their protein structures and ligand internalization pathways [99].

Structure and cycling of the LDL receptor protein

The 18 exons of the LDL receptor gene code for an 839 amino acids protein divided into five functionally distinct domains [58,117]. First, it is the ligand binding domain located at the N-terminal (292 amino acids).

This domain is composed of seven adjacent LDL receptor type-A (LA) modules or repeats (each 40 amino acids long) [58,117]. Each LA repeat uses three conserved calcium atom-binding acidic residues for protein-protein interactions [118]. Immediately next is the epidermal growth factor (EGF) precursor domain (400 amino acids). The EGF precursor domain is composed of two EGF modules or repeats (40 amino acids each), the YWTD region (280 amino acids; contains six YWTD repeats), and a third EGF module (40 amino acids) [58,117]. The YWTD region forms the six-bladed β-propeller that is implicated in the release of bound lipoproteins at low pH [118,119]. The O-linked glycosylation domain (58 amino acids) follows which is rich in serine and threonine residues that get glycosylated [120]. This region does not appear to be involved in ligand binding, internalization, and receptor recycling [120]. The following domain is the transmembrane domain (22 amino acids) that anchors the receptor to the plasma membrane [121]. The last domain is the 50-residue cytoplasmic tail (50 amino acids). The cytoplasmic tail is essential for localization within clathrin-coated pits and receptor endocytosis [122]. After its synthesis within the endoplasmic reticulum, the molecular weight of the LDL receptor is 120 kDa [95]. Upon transport through the Golgi, the LDL receptor undergoes extensive O-linked glycosylation resulting in the mature 160 kDa form found at the cell surface [95].

The LDL receptor removes lipo proteins from the circulation through a process that involves endocytosis of the lipoprotein/LDL receptor complex within clathrin-coated regions [58]. At the plasma membrane, the LDL receptor's extracellular domain is extended, exposing the ligand-binding domain [open position], which allows the lipoprotein binding [118]. The cytosolic domain of the LDL receptor contains an 823FDNPVY sequence that is necessary and sufficient for rapid clathrin-mediated endocytosis [123]. Internalization of the lipoprotein/LDL receptor complex into hepatic cells is controlled mainly by the LDL receptor adaptor protein-1 [124].

After endocytosis, the LDL receptor/lipoprotein complex is delivered to the endosome [118]. Acidification of the endosome occurs facilitating folding of the LDL receptor into the closed position releasing the lipoprotein particle [58,125]. The lipoprotein particle moves to the lysosome, where the cholesteryl esters are hydrolyzed to form free cholesterol and fatty acids, and the protein fraction of the lipoprotein is degraded into free amino acids [58].

Most receptor molecules are recycled back to the cell surface, where they can bind and internalize lipoprotein again [126]. At every round of the cycle, only a minuscule percentage of LDL receptor molecules are degraded [126]. Each LDL receptor molecule completes about 150 cycles before it is finally degraded in about 20 hours [126].

Role of Apo E in the brain

ApoE is a ligand for all members of the LDL receptor family of proteins [112]. This apolipoprotein is also found in many of the lipoprotein particles that transport lipids and cholesterol in the bloodstream [112]. In the nervous system, Apo E is produced by astroglia and microglia cells, whereas neuron cells express the receptors to uptake ApoE [112]. There are three main types of Apo E in humans, E2, E3, and E4 [112]. The main difference between these Apo E isoforms is in two amino acids, specifically residues 112 and 158 [112]. ApoE3 has a cysteine at position 112 and an arginine at position 158; ApoE4 has arginines at both sites, whereas ApoE2 has cysteines at both sites [112]. Having different residues at positions 112 and 158 affects the risk of patients to acquire some diseases [112]. For example, patients that are carriers of the Apo E4 isoform have a higher chance of developing coronary artery disease and AD than patients with the other two isoforms [127]. Inheritance of the ApoE4 allele is the most influentially known genetic risk factor that leads to the development of AD [9].

It currently unknown how having Apo E4, and not Apo E2 or E3, affect a patient's risk to develop these diseases. However, it has been proposed that it is due to the Apo E role in cholesterol transport and brain function [112]. The functions of Apo E in the brain are neuronal survival, synapse formation and plasticity, modulation of neurite outgrowth, destabilization of microtubules, Aβ clearance, and prevention of NTF formation [112,128-132]. ApoE2 and ApoE3 usually induce neurite outgrowth, whereas ApoE4 inhibits it [112,130,131]. The genotype of Apo E also influences the appearance of neuroinflammation, which has been considered as a potential early indicator of AD risk in humans [133].

Related to the formation of senile plaques, ApoE binds Aβ and contributes to its clearance and degradation in a process that requires lipoprotein receptors [134-137]. Apo E4 not only enhances the formation of senile plaques but also leads to hypercholesterolemia; Apo E2is protective against both effects [11,138,139]. The effect of Apo E4 on cholesterol levels also contributes to enhancing the accumulation of Aβ plaques by

promoting the cleavage of APP through the abnormal pathway [140].

Proprotein convertase subtilisin-kexin type 9 [PCSK9]

PCSK9 was discovered in 2003 when gain-of-function [GOF] mutations in this gene were identified as causative of familial hypercholesterolemia [FH] in an autosomal dominant manner [141]. Serum PCSK9 levels are identified as a key cause of atherosclerosis independently of other risk factors in patients without symptoms [142]. Interestingly, loss-of-function [LOF] mutations of PCSK9 have also been identified and are associated with hypocholesterolemia and substantial protection against cardiovascular diseases [143,144]. PCSK9 is expressed and secreted by multiple tissues but primarily by the liver, small intestines, and kidneys [145]. PCSK9 can also be found in cerebrospinal fluid [CSF] [146] and at the sites of atherosclerotic plaques [147]. There is a definite correlation between wild-type PCSK9 levels and atherogenic lipoproteins such large VLDL, IDL, the smallest LDL, the smallest HDL, and all remnant lipoproteins [148,149].

Structure and processing of PCSK9

The human PCSK9 gene is localized on chromosome 1p32.3 [150]. This gene is about 22-kb long and comprises 12 exons encoding a 692-amino acid glycoprotein [151]. The protein domains that comprise PCSK9 are a signal peptide, the propeptide or inhibitory prodomain, the subtilisin-like catalytic domain, a hinge region, and a cysteine-rich, histidine-rich, C-terminal domain [152,153].

PCSK9 is synthesized as a 74 kDa precursor protein that undergoes autocatalytic processing in the endoplasmic reticulum to release the propeptide (14 kDa) from the N-terminal region resulting in a processed protein of about 60 kDa [154,155]. This autocleavage is necessary to activate the convertase and to allow its departure from the endoplasmic reticulum [155,156]. After self-cleavage, the prodomain remains in the catalytic groove and obstructs the access of other proteins and peptides [157]. Then, the PCSK9/prodomain complex departs from the endoplasmic reticulum and migrates through the secretory pathway until it is secreted into the bloodstream [154,155].

The main function of PCSK9

The primary function of PCSK9 is to control serum LDL levels by promoting the degradation of the LDL receptor, especially in the liver [158,159]. The GOF mutations of PCSK9 are connected with decreased expression of LDL receptors and internalization of LDL, while the LOF mutations are associated with increased LDL receptor levels and internalization of LDL [158, 159]. After secretion into the serum, PCSK9 interacts with the EGF-A domain of the LDL receptor at the surface of cells [160,161]. Then, the PCSK9/LDL receptor complex enters the endosomal pathway [160]. Unlike the interaction between lipoprotein and receptor, the affinity of PCSK9 for the LDL receptor at the acidic pH of the endosome is increased over the affinity at the neutral pH [153,162]. PCSK9 helps to keep the LDL receptor in the open conformation preventing its recycling to the plasma membrane causing receptor degradation in the lysosome [163,164].

Other functions of PCSK9

In addition to the LDL receptor, PCSK9 also degrades the VLDL receptor, ApoER, ApoER2, the cluster of differentiation 36 [CD36], β-secretase 1 [BACE1], the epithelial sodium [NA+] channel [ENaC], and CD81 [165-171]. Due to the vast number of targets, it is expected that PCSK9 controls multiple pathways. The ENaC, for example, regulates blood pressure by modulating epithelial sodium reabsorption, and PCSK9 regulates the levels of ENaC protein expression suggesting that this convertase also has a role in blood pressure [169]. Furthermore, some rare variants in PCSK9 have been shown to influence blood pressure among African Americans [172]. Recent reports on several ethnic populations have also revealed that blood pressure is positively correlated with circulating PCSK9 levels [173-175].

PCSK9 also affects triglyceride metabolism and accumulation in visceral adipocyte tissue, and these effects are connected to the effects of this convertase on CD36 and the VLDL receptor [176]. In humans, circulating PCSK9 has been shown to be positively associated with body mass index [BMI] [173,175]. Accordingly, exercising, which is essential to regulate body weight and modulating lipid metabolism, reduces the hepatic expression and plasma concentration of PCSK9 [177,178].

PCSK9 is critical during inflammation and for the formation of atherosclerotic plaques [179,180]. Also, PCSK9 levels increase every time there is inflammation in the body [181,182]. Related to thrombosis, it has been reported that the levels of PCSK9 in the plasma are positively and strongly correlated with platelet, white blood cell count, and fibrinogen levels [183,184]. Additionally, circulating PCSK9 positively correlates with high sensitivity C-reactive protein levels [184,185]. Receptors modulated by PCSK9 that are

associated with these processed are the LDL receptor and ApoER2.

Diabetes is a metabolic disturbance that is conditioned to the levels of PCSK9. Although high circulating PCSK9 levels are positively correlated with fasting blood glucose levels and insulin resistance [173,175], having low levels of PCSK9 can also lead to diabetes. Treatment with PCSK9 inhibitors, in addition to statins, results in a cholesterol accumulation in pancreatic islets that causes diabetes [186]. In fact, diabetes is reported in 1.8% of patients that had no diabetes before starting treatment with PCSK9 inhibitors [187,188]. Other side-effects observed when using PCSK9 inhibitors are neurocognitive events, gastrointestinal disturbances, infections, and ophthalmologic events, all related to the roles attributed to PCSK9 based on the receptors that interact with this convertase [189,190].

Hormonal regulation of PCSK9

A hormone that controls the expression of PCSK9 is estrogen [191,192]. Estrogen levels are inversely correlated to circulating PCSK9 in pre-menopausal females [191,192]. Post-menopausal females have 22% more PCSK9 than pre-menopausal females [174,191]. Interestingly, females have 10% more circulating PCSK9 than males suggesting that the inverted relationship between estrogen and PCSK9 levels only applies to females [191,192]. Testosterone, on the other side, does not affect the levels of circulating PCSK9, so it is not involved in the differences in PCSK9 levels between males and females [192]. The hormone that appears to be responsible for these gender differences is growth hormone (GH) [193]. GH is also responsible for the diurnal variation of PCSK9 levels that mimics the diurnal variation of cholesterol synthesis [193].

Insulin and glucagon also regulate the PCSK9 expression [194,195]. It has been found that glucagon downregulates while insulin upregulates the expression of PCSK9 in several animal models [195-197]. Similar decreases in PCSK9 protein expression are seen in intestinal cells from Psammomys obesus with type 2 diabetes [198] and women with gestational diabetes [199]. Thyroid hormone is another hormone that regulates the expression of PCSK9 [200,201]. Thyroid hormone reduces circulating PSCK9 thereby explaining the lower plasma LDL levels seen in hyperthyroidism and the higher LDL levels characteristic of hypothyroidism [200]. In euthyroid subjects, the levels of circulating PCSK9 are positively associated with thyrotropin [TSH] [202]. Serum PCSK9 concentrations significantly increase with age, especially in females [173,203]. Interestingly, adiposity can interfere with this relationship between PCSK9 and TSH [202], which might be related to the positive correlation between BMI and PCSK9 levels overcoming the effects of thyroid hormone [203].

Potential Link between PCSK9 and AD

Age and gender are risk factors for the development of AD, and in both cases, PCSK9 seems to be the connecting factor. Thyroid hormone, which appears to be responsible for the increase in PCSK9 levels as people age [173], also controls the expression of APP and the splicing of tau exon 10 [34,36,204,205]. Thyroid hormone decreases the expression of APP which in turns results in a reduction in Aβ levels [204,205]. Changes in the splicing of tau exon 10 are known to cause AD [206].

Females suffer from hypothyroidism at a higher rate [4:1] than males [207] and also have consistently higher levels of PCSK9 than men [191,192]. Therefore, it appears that females suffer from AD more than males because of their higher levels of PCSK9 in correlation with lower levels of thyroid hormones. Some researchers have indicated that the differences in females versus males on AD risk are related to the protection that estrogens provide to the mitochondria against Aβ-toxicity preventing apoptosis of neuronal cells, and it is lost once females enter menopause [14]. However, the possibility that the age-dependent increase in PCSK9 levels, due to a decrease in both thyroid hormone and estrogen, is what enhances neuron apoptosis cannot be discarded [179]. In fact, PCSK9 is well-known to cause apoptosis in neurons, an effect that is mediated by the ApoER2 and VLDL receptors [179].

In mice, upregulation of PCSK9 is seen in response to cerebral ischemia [179,208] and whenever signs of neuronal apoptosis are seen [209]. Interestingly, it has been shown that PCSK9 is necessary for brain development, especially in the cerebellum [210], so inhibiting PCSK9 may cause problems with this function. It is important to mention that any involvement of PCSK9 on AD is questionable since PCSK9 degrades BACE1, which could prevent the formation of Aβ peptides [168]. Interestingly, one of the side effects of using PCSK9 inhibitors is an increase in neurocognitive events correlating with an adverse effect of low levels of PCSK9 in the brain [191,192].

Another important consideration is that by degrading the LDL receptor, ApoER, and ApoER2, elevated levels of PCSK9 may also help in the development of AD due to an increase in the formation of Aβ plaques [100,104,109]. Inhibiting ApoER2 could also lead to neuronal cell apoptosis [109]. Thus, variations in the

normal levels, either up or down, of PCSK9 could lead to AD. PCSK9 is detected in CSF [146] indicating that this convertase could directly affect the expression of those receptors in the brain.

The development of AD also has another major contributor that is often overlooked, cholesterol. High levels of cholesterol in the brain seems to be critical for the development of healthy neurons. Studies have shown that elevated levels of total and LDL cholesterol are associated with higher memory scores for noncarriers of the Apo E4 allele [211]. However, in another study, it was reported that high cholesterol levels could lead to AD [19]. PCSK9 works by increasing LDL concentrations in the serum, so elevated levels of this protease would cause the effects seen in the latter study [19]. Likewise, inhibition of PCSK9 which leads to low LDL levels in correlation with neurocognitive events would agree with the first study [211]. Interestingly, African-Americans, who carry LOF mutations in PCSK9 that are associated with hypocholesterolemia, are at a higher risk of developing AD than Caucasians [212], also in agreement with the first study [211].

Neuronal cells control the amount of intracellular cholesterol by converting excess cholesterol into oxidized products that serve as regulators of cholesterol synthesis, and they can be efficiently secreted out of the cells in a process that involves ABCA1 and HDL [213]. Thus, higher levels of HDL would be of great benefit because this lipoprotein could help reduce cholesterol levels in the brain. Interestingly, PCSK9 inhibition has been associated with slightly higher HDL levels [211], so low concentrations of PCSK9 would prevent neuronal damage due to excess levels of cholesterol.

In addition to the risk factors for AD mentioned above, some researchers have suggested that other factors such as diabetes mellitus, hypertension, obesity, and physical inactivity could be considered as causative of AD [18,214]. Surprisingly, the levels of circulating PCSK9 are positively associated with blood pressure and BMI [173-175], whereas changes in total PCSK9 levels, in either direction, can lead to diabetes [173,175,187,188]. PCSK9 levels also increase in response to inflammation [181,182], which is another risk factor for AD. Besides, physical inactivity has been shown to lead to higher levels of PCSK9 [177,178], which could also explain that this is a risk factor for AD.

Conclusions

Indirect evidence suggests a connection between PCSK9 levels and AD. Figure 4 summarizes the evidence discussed herein. Variations in PCSK9 levels, either up and down, seems to cause an unbalance in the amount of cholesterol required for the proper functioning of the brain and to prevent the proper processing of APP and removal of Aβ, a critical component of one of the main lesions found in AD. PCSK9 also appears to work by exacerbating several metabolic conditions that are risk factors for AD. Studies are needed to confirm this link between PCSK9 levels and AD.

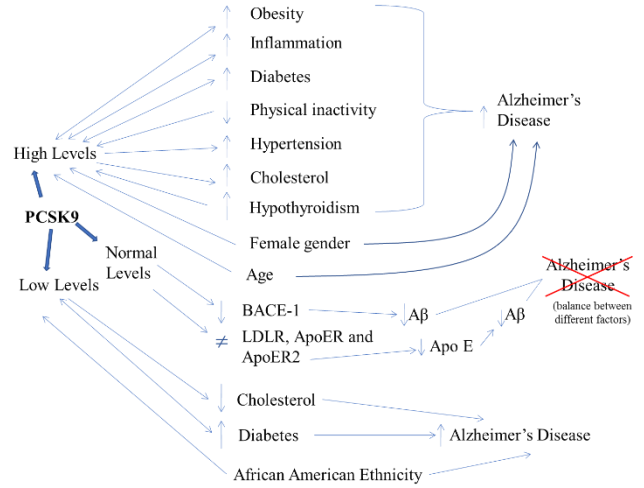

Figure 4: Schematic representation of all the factors connecting PCSK9 levels and Alzheimer's disease. Abbreviations: PCSK9, proprotein convertase subtilisin-kexin 9; BACE-1, beta-secretase 1; Aβ, amyloid beta; LDLR, low density lipoprotein receptor; ApoER, apolipoprotein E receptor.

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