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REVIEW PAPER

# Role of Microglia in Regulating Cholesterol and Tau Pathology in Alzheimer's Disease

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## Abstract

Cholesterol, a principal constituent of the cell membrane, plays a crucial role in the brain by regulating the synaptic transmission, neuronal signaling, as well as neurodegenerative diseases. Defects in the cholesterol trafficking are associated with enhanced generation of hyperphosphorylated Tau and Amyloid-β protein. Tau, a major microtubule-associated protein in the brain, is the key regulator of the mature neuron. Abnormally hyperphosphorylated Tau hampers the major functions related to microtubule assembly by promoting neurofibrillary tangles of paired helical filaments, twisted ribbons, and straight filaments. The observed pathological changes due to impaired cholesterol and Tau protein accumulation cause Alzheimer's disease. Thus, in order to regulate the pathogenesis of Alzheimer's disease, regulation of cholesterol metabolism, as well as Tau phosphorylation, is essential. The current review provides an overview of (1) cholesterol synthesis in the brain, neurons, astrocytes, and microglia; (2) the mechanism involved in modulating cholesterol concentration between the astrocytes and brain; (3) major mechanisms involved in the hyperphosphorylation of Tau and amyloid-β protein; and (4) microglial involvement in its regulation. Thus, the answering key questions will provide an in-depth information on microglia involvement in managing the pathogenesis of cholesterol-modulated hyperphosphorylated Tau protein.

**Keywords** Alzheimer's disease · Amyloid-β protein · Tau hyperphosphorylation · Cholesterol · Microglia

## Abbreviations

| | |
|---|---|
| AD | Alzheimer's disease |
| Aβ | Amyloid-β |
| FAD | Familial Alzheimer's disease |
| APP | Amyloid precursor protein |
| PS-1 & 2 | Presenilin-1 & 2 |
| CNS | Central nervous system |
| BBB | Blood–brain barrier |
| HMG-CoA | 3-Hydroxy-3-methylglutaryl-CoA |
| ABCA1 | ATP-binding cassette transporter |
| CERP | Cholesterol efflux regulatory protein |
| NPC | Niemann–Pick type C |
| ACAT1/SOAT1 | Acyl-coenzyme A: cholesterol acyltransferase-1 |
| 24- OHC | 24-Hydroxycholesterol |
| LXR | Liver X receptor |
| CaMKII | Calcium and calmodulin-dependent protein kinase- II |
| TLR4 | Toll-like receptor-4 |
| CX3CR1 | CX3C chemokine receptor-1 |
| PI3K | Phosphoinositide 3-kinase |
| ITAM | Immunoreceptor tyrosine-based activation motif |
| SORL1 | Sortilin-related receptor 1 |
| ER | Endoplasmic reticulum |
| APOE | Apolipoprotein E |
| SREBPs | Sterol regulatory element-binding proteins |
| LDL | Low-density lipoprotein |
| VLDLR | Very low-density lipoprotein receptor |
| LRP1 | LDL receptor-related protein 1 |
| GWAS | Genome-wide association studies |
| TREM2 | Triggering receptor expressed on myeloid cells 2 |

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| | |
|---|---|
| RCT | Reverse cholesterol transport |
| MAP | Microtubule-associated protein |
| PHFs | Paired helical filaments |
| GSK-3 | Glycogen synthase kinase-3 |
| cdk5 | Cyclin-dependent protein kinase-5 |
| PKA | Protein kinase A |
| SIGLEC | Sialic acid-binding immunoglobulin-type lectins |
| BIN1 | Bridging integrator 1 |
| CME | Clathrin-mediated endocytosis |
| LOAD | Late-onset AD |
| HSPG | Heparin sulfate proteoglycan |
| FAK | Focal adhesion kinase |

## Introduction

Cholesterol, a structurally important component of cellular membrane and myelin sheath, is the principal constituent of the brain. In comparison to the whole body, the brain contains 20% of the body's total cholesterol (Björkhem et al. 2006). Glycerophospholipids, sphingolipids, and cholesterol are the three major brain lipid components (Korade and Kenworthy 2008). Neurons and glia (astrocytes, microglia, and oligodendrocytes) are helping to regulate the cholesterol concentration to achieve healthy brain development. The critical functions of the brain cholesterol include synapse, dendrite formation, and axonal guidance. Along with this, brain cholesterol also contributes in precursor activity, steroid hormones, and bile acid synthesis (de Chaves et al. 1997; Radhakrishnan et al. 2007; Fester et al. 2009; Wong et al. 2014). Bile acids are the amphipathic end products of cholesterol metabolism. It plays a significant role in cell signaling by binding to cell membrane and nucleus. Also, it has been reported to interact with receptors involved in neurotransmission (McMillin and DeMorrow 2016). The impairment of synaptic vesicle exocytosis, neuronal activity and neurotransmission, dendritic spine, and synapse degeneration due to cholesterol depletion in neurons causes Alzheimer's, Parkinson's, Niemann–Pick C, and Huntington's diseases (Block et al. 2010; Linetti et al. 2010; Di Paolo and Kim 2011; Wang et al. 2011). Alzheimer's disease (AD), one of the multifactorial neurodegenerative diseases, is characterized by pathological features of cerebral atrophy, extracellular amyloid-β (Aβ) plaques, intracellular neurofibrillary tangling, neurovascular dysfunction, and neuronal cell death (Sato and Morishita 2014; Ramanathan et al. 2015). The population suffering from AD have a progressive decline in memory, thinking, language, and learning capacity (Duthey 2013). Nearly 8–10% of the population over the age of 65 suffer from AD, and in every 5 years, the number is getting doubled (Cummings 2004; Bertram and Tanzi 2005). Most of the patients suffering from AD are sporadic, whereas 5% or less are familial with an early-onset issue (Kang and Rivest 2012). The early-onset form of FAD is linked with mutations in Amyloid Precursor Protein (APP), presenilin-1 (PS-1), and presenilin-2 (PS-2) affecting APP processing which results in increased production of insoluble Aβ plaques. The overproduced Aβ plaques, in turn, cause pathogenic Tau hyperphosphorylation which leads to neurodegenerative diseases (Selkoe and Hardy 2016; Szaruga et al. 2017). Sporadic AD being the late-onset AD (LOAD) appears mainly due to genetic and environmental factors including aging that impair the brain's ability to clear Aβ and Tau protein (Wildsmith et al. 2013; Pereira et al. 2019). Hence, based on the prevalence, AD is considered as one of the most significant health and socio-economic problems (Wong et al. 2014). Initially, full-length APP localized in the plasma membrane, as well as several organelles like mitochondria, endoplasmic reticulum (ER), and Golgi apparatus, was considered as the primary reason for the development of AD. Thus, anti-amyloid strategies have been the primary focus of AD drug development for the last 10 years. But recently, more and more evidence has demonstrated the crucial role of Tau abnormalities in AD neurodegeneration (Gong and Iqbal 2008; Busche et al. 2019). This review aims to explore the detailed molecular mechanisms of Taupathy in AD and its regulation via microglial uptake.

### Tau Protein

Tau, a microtubule-associated protein (MAP) present in the central nervous system (CNS), is associated with several functions related to neuronal cells. Tau gene is located at chromosome 17q21, comprising 16 exons, among which 1, 4, 5, 7, 9, 11, 12, and 13 are constitutive, whereas 2, 3, and 10 undergo alternative splicing. The dysregulation of alternative splicing process especially in exon 10 contributes to neurodegeneration (Andreadis 2005; Liu and Gong 2008). Axonal transportation, neurotransmission and assembly, and stability of microtubules are some of the major functions of Tau protein (Iqbal et al. 2005a). Tau undergoes various posttranslational modifications like phosphorylation, glycosylation, and ubiquitinylation (Morris et al. 2015; Avila et al. 2016; Wang and Mandelkow 2016; Sonawane and Chinnathambi 2018). Hyperphosphorylation of Tau hampers its microtubule assembly activity as well as binding capability (Lindwall and Cole 1984; Alonso et al. 1994). Among several reasons, cholesterol metabolism in the brain is one of the major causes of Tau hyperphosphorylation (Rahman et al. 2005; Michikawa 2006; Maccioni et al. 2010). Tau is hypothesized to get released from its intracellular localization into extracellular space. The extracellular released Tau is reported to cause severe damage due to its interaction with neighboring cells, such as neurons or glia (Luo et al. 2015; Hu et al. 2016; Bolós et al. 2017b). Thus, regulating

these hydrophilic soluble proteins (Tau) is of major concern. Microglia, the macrophages of the brain, are the resident immune cells constituting about 15% of cell population in CNS (Lawson et al. 1992). It was discovered between 1919 and 1921 by a Spanish neuroscientist, Pío del Río Hortega, and was hypothesized to undergo morphological changes, proliferate, and migrate with respect to change in microenvironment (Pérez-Cerdá et al. 2015; Perea et al. 2018). Microglia are reported to play a major role in interacting, internalizing, and regulating the pathological Tau (Luo et al. 2015; Perea et al. 2018; Hopp et al. 2018). Thus, the current review article is focused on emphasizing the mechanism of Tau pathology due to cholesterol metabolism and their regulation via microglia in managing the AD condition.

## Cholesterol Biosynthesis in Neurons and Astrocytes

Cholesterol, an indispensable component of biological membranes, acts as precursor for various signaling molecules. Except brain, its provision and disposal in all other organs of the mammalian body rely upon dietary intake, on de novo synthesis in every organ, and lipoprotein-mediated transport via the blood circulation (Pfrieger and Ungerer 2011). But, the cells in the brain are cut off from this process due to blood–brain barrier (BBB) and thus they have adopted their own specific way to handle cholesterol turnover. Therefore, the necessary cholesterol in the brain is synthesized de novo within CNS (Gamba et al. 2015). Brain cholesterol, considered as a distinct pool from body cholesterol, is majorly composed of non-esterified cholesterol with small amounts of desmosterol and cholesteryl ester (Dietschy and Turley 2001; Björkhem and Meaney 2004). The amount of cholesterol in the brain is high (15–30 mg/g tissue) compared to other tissues of the body (2–3 mg/g tissue) (Dietschy 2009). The importance of brain cholesterol has been described in early 1834's as "un element principal" of the CNS (Couerbe 1984). Brain cholesterol is found in two major forms, myelin sheath and plasma membrane of neurons and glial cells. The smaller portion of cholesterol constitutes to produce plasma membrane of neurons (10%) and glial cells (20%) and have relatively fast turnover rates of 5–10 months, and 8 mg/g half-life. However, myelin sheath, a protective outer membrane of the neurons, constitutes the major portion of cholesterol (70–80%) that is composed of oligodendrocytes have slower turnover number (half-life ~ 5 years, 40 mg/g). These are reported to maintain the morphology and synaptic transmission (Dietschy and Turley 2004). Once the myelin sheath encircles the neurons, the majority of brain cholesterol accumulates between perinatal and adolescence period (Orth and Bellosta 2012). After myelination, very low turnover and loss is observed in the adult brain (Morell and Jurevics 1996). Brain cholesterol is more stable than the peripheral with the turnover rates of 1% (Andersson et al. 1990). The half-life of adult brain cholesterol is between 6 months to 5 years, whereas the plasma cholesterol is only for few days (Dietschy and Turley 2004; Björkhem et al. 2006).

The de novo biosynthesis of cholesterol in the brain is a complex and intense process. Acetyl CoA, a primary precursor molecule, is converted to 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) by 3-hydroxyl-3-methylglutaryl-CoA synthase (HMG-CoA synthase). HMG-CoA is further reduced to mevalonate by HMG-CoA reductase. The same is considered as the rate-limiting and irreversible step in cholesterol synthesis. After a series of nearly 20 enzymatic reactions, cholesterol formation is observed (Zhang and Liu 2015). The other important metabolites along with cholesterol include mevalonate, farnesyl pyrophosphate, squalene, and lanosterol (Bae et al. 1999). The necessary enzymes involved in de novo synthesis occur primarily in the ER, which are further transferred to the plasma membrane (DeGrella and Simoni 1982; Gaylor 2002). The redistribution of cholesterol in the subcellular compartments is accomplished by two ATP-driven processes, i.e., vesicles-mediated inter-organelle transport and protein-mediated monomeric transport/non-vesicular transport (Kaplan and Simoni 1985; Heino et al. 2000). The energy-dependent vesicular transport contributes to cholesterol flux between ER, plasma membrane, and endocytic vesicles (Litvinov et al. 2018). However, the non-vesicular transport along with carrier proteins or membrane contact between mitochondria and lipid droplets helps in the circulation of cholesterol in the outer surface (Kallen et al. 1998). Since cholesterol is water-insoluble, the amount of unbound cholesterol in the cytosol is minimal. Thus, most of the cholesterol exists as protein-bound in the cytosol as apolipoprotein E (APOE) (Zhang and Liu 2015). There are two cholesterologenic pathways in the brain, sterols in the neurons are synthesized via the Kandutsch–Russell pathway, and astrocytes contain precursors from the Bloch pathway (Leoni and Caccia 2015). The post-squalene ancestor, and lanosterol obtained during the cholesterol synthesis in the brain, acts as a precursor molecule for the cholesterol synthesis in astrocytes and neurons (Zhang and Liu 2015).

The Kandutsch–Russell pathway employed in the neurons converts the precursor molecule, lanosterol, into 24, 25-dihydroxylanosterol. Further reduction in 24, 25-dihydroxylanosterol is reported to generate cholesterol. In case of Bloch pathway, astrocytes convert the post-squalene component, lanosterol, into 32-hydroxylanosterol. The later consecutive reduction steps with various enzymes end up in the generation of cholesterol from desmosterol. Astrocytes meet neuronal cholesterol demand by secreting APOE–cholesterol complexes, which are then transported to the neurons for their development and function (Swathi Parasuraman 2013). Figure 1 delineates the de novo synthesis of cholesterol in

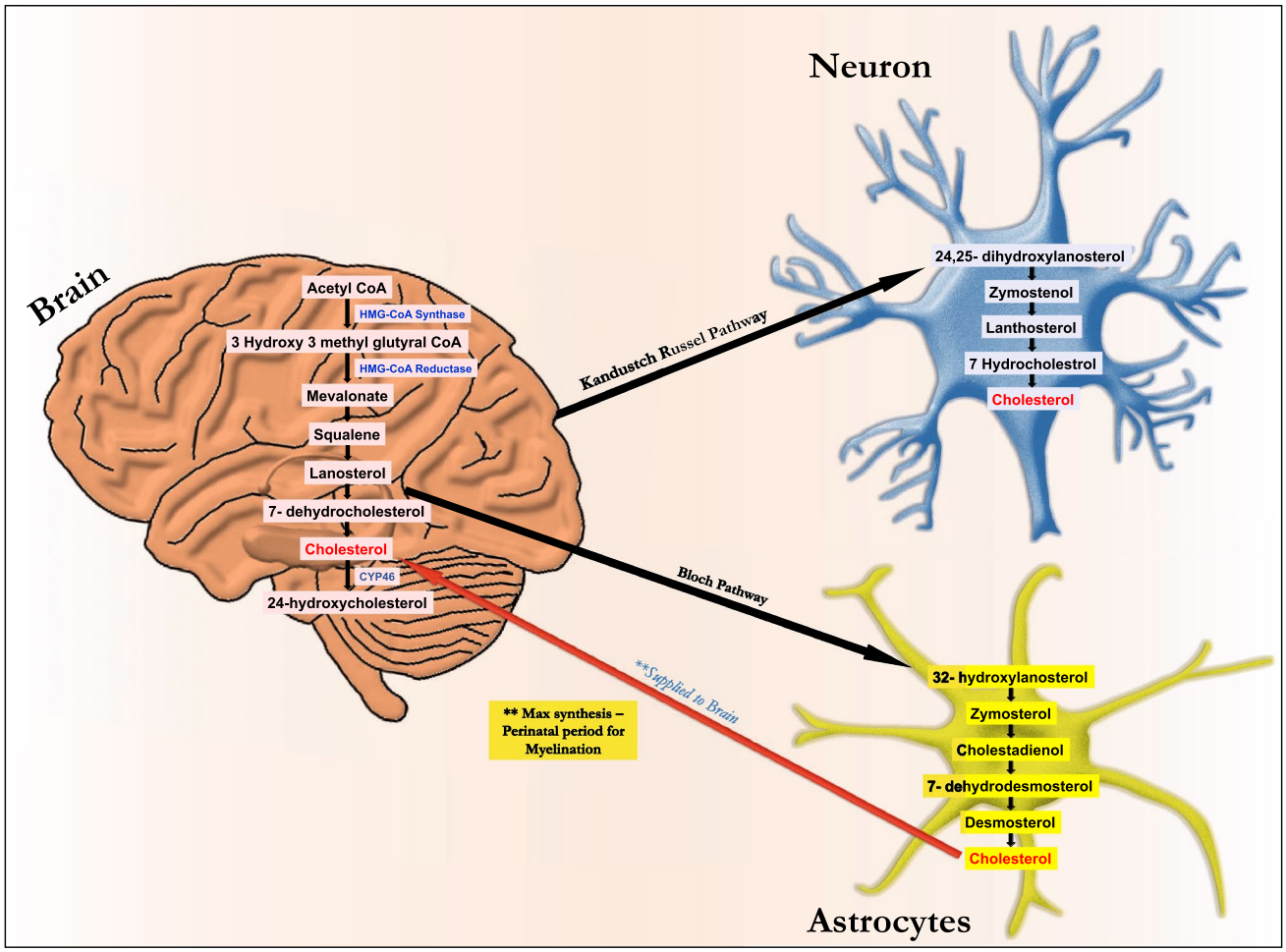


**Fig. 1** Cholesterol synthesis in the brain, neuron, and astrocytes. Cholesterol in the brain is primarily synthesized from the precursor molecule acetyl-CoA by a series of enzymatic steps. Initially, acetyl-CoA gets transformed into 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) via a catalyzed reaction by HMG-CoA-synthetase and then by HMG-CoA reductase to mevalonate. 3-hydroxy 3-methyl-glutaryl-CoA reductase (HMG-CoA reductase) acts as rate-limiting step for mevalonate pathway. This is followed by a series of enzymatic reactions in converting mevalonate into squalene, lanosterol, and other products. In the final step, 7-dehydrocholesterol is converted to cholesterol by the enzyme 7-dehydrocholesterol reductase. Finally, the hydroxylated derivative of cholesterol, 24-hydroxycholesterol, produced by CYP46, acts as the only molecule capable of crossing the BBB. The maximum production of brain cholesterol is observed during the perinatal period, mainly for myelination. The post-lanosterol steps of cholesterol synthesis are divided into Bloch and Kandutsch–Russell pathways. Cholesterol in neurons is primarily biosynthesized through Kandutsch–Russell pathway by consecutive reaction steps involving 24, 25-dihydroxylanosterol, zymosterol, lanosterol, 7-dehydrocholesterol. In case of astrocytes, the Bloch pathway utilizes the precursor molecule lanosterol from the brain, hence converting to 32-hydroxylanosterol, zymosterol, cholestadienol, 7-dehydrodesmosterol, desmosterol, and cholesterol. Further, the excess cholesterol synthesized from astrocytes is supplied to the brain to maintain the cholesterol turnover

brain and its adaptive pathways to manage its turnover via neurons and astrocytes.

## Cholesterol Trafficking Between Astrocytes and Neurons

Neuronal cells regulate the cholesterol content by balancing the biosynthesis, import, and excretion via the feedback mechanism. The biosynthesis of cholesterol occurs in the ER and further transferred to the Golgi apparatus and plasma membrane (Rogers et al. 2015; Xu et al. 2018). The membrane-bound transcription factors such as sterol regulatory element-binding proteins (SREBPs), SREBP1 and SREBP2, act as a tool in helping the cells to balance the cholesterol content by regulating the transcription of genes encoding enzymes related to cholesterol, fatty acid biosynthesis, as well as lipoprotein receptors (Eberlé et al. 2004). The maximum amount of cholesterol within CNS is associated with the cell membrane, thus leaving behind a minimal amount in the intercellular space and the cerebrospinal fluid. APOE that is highly expressed in the intercellular space of the CNS helps in associating the unbound cholesterol, thus

regulating its metabolism, as well as genetic risk factors related to sporadic AD (Ashford 2004). Also, the astrocytes or the glial cells present in the brain are reported to help cholesterol recycling in the peripheral nervous system. The lipoprotein particles secreted by astrocytes are also composed of APOE, APOA1, and lipids (Orth and Bellosta 2012). A 32 kDa APOE gene residing on chromosome 19 contains three major form of alleles, i.e., $\varepsilon 2$ (5–10%), $\varepsilon 3$ (65–70%), and $\varepsilon 4$ (15–20%) (Orth et al. 1999; Bu 2009; Holtzman et al. 2012). Other than astrocytes, oligodendrocytes, microglia, and ependymal layer cells are also reported to be the major sources of APOE (Mahley et al. 2006). The APOE-containing lipoproteins secreted by glial cells, lipids, and other macromolecules act as ligands for numerous lipoprotein receptors of low-density lipoprotein (LDL), very low-density lipoprotein receptor (VLDLR), and LDL receptor-related protein 1 (LRP1) family (Liu et al. 2007b; Pottier et al. 2012). Since APOE is the major exporter of extracellular cholesterol and other lipids, dynamic exchange of APOE has been reported among cells (Lahiri 2004). APOE2 defectively binding to LDL receptor is responsible for type III hyperlipidemia. APOE3 and APOE4 are also reported to be highly associated with LDL receptor (Mahley 2016). Chances of developing LOAD are high in individuals with one ε4 allele than with those without the ε4 allele. And people having ε2 allele are reported to be at lower risk in developing LOAD compared to ε3 allele (Corder et al. 1993). The in vivo study conducted on mice expressing P301L mutant human Tau with no apoE and P301L mice with wild-type ApoE fed with cholesterol-enriched diet or control diet for 15 weeks showed enhanced ongoing Tau pathology only in wild-type mice, thus contributing to AD pathology (Glöckner et al. 2011). In addition to APOE, genome-wide association studies (GWAS) have identified novel risk genes of AD. Triggering receptor expressed on myeloid cells 2 (TREM2) in the brain is expressed primarily by microglia. It is reported to promote microglial survival, proliferation, and phagocytosis of excess cholesterol (Wolfe et al. 2019). The most common TREM2 mutant, R47H (arginine to histidine at position 47), impairs ligand binding and increases the risk of developing AD by approximately fourfold (Guerreiro et al. 2013a; Jonsson et al. 2013). Other than this, some of the identified genes are reported to be associated with lipid metabolism. Also, diabetic patients affected from glucose-energy metabolism are reported to be significantly at higher risk of developing AD (Maher and Schubert 2009; Matsuzaki et al. 2010; Hollingworth et al. 2011). Other signaling pathways like ATP-binding cassette transporter (ABCA1), also known as a cholesterol efflux regulatory protein (CERP) with the MAP-kinase system, are also active in microglia and neurons (Witzlack et al. 2007). ATP-binding cassette (ABC) transporters, namely ABCA1, ABCG1, and ABCG4, expressed in neurons and astrocytes mediate sterol efflux at the plasma membrane (Tarr and Edwards 2008; Kim et al. 2008). Among them, ABCA and ABCG play a major role in regulating the lipid homeostasis (Puglielli et al. 2003). Expression of ABCA1 has been reported in both neurons and glial cells, whereas a higher level is in neurons, thus contributing to cholesterol efflux via APOA1.

The excess cholesterol is released from APOA1-containing lipoproteins to LRP1/LDLR receptor located in neurons (Gosselet et al. 2009). In comparison to LRP1, LDLR is highly expressed in glial cells than neurons (Rebeck et al. 1993), whereas the highly expressed LRP1 in neurons contributes to the transportation of APOE-associated cholesterol from astrocytes (Li et al. 2001). Downregulation of ABCA1 and LRP1/LDLR expression reduces the cholesterol efflux. However, increased level of the receptors maintains the excess cholesterol either by esterification or hydroxylation process catalyzed by acyl-coenzyme A: cholesterol acyltransferase-1 (ACAT1/SOAT1) present primarily in the ER (Wüstner et al. 2005; Minagawa et al. 2009). The externally uptaken excess cholesterol enters subcellular endosomal membrane compartments like Niemann–Pick type C1 (NPC1) & NPC2 (Vanier 2015). The transmembrane protein NPC1 is associated with the sterol-sensitive domain, whereas NPC2 being an intraluminal component binds to cholesterol (Carstea et al. 1997; Soccio and Breslow 2004). The dysfunction of either the protein causes accumulation of unesterified cholesterol, thus causing pathological changes in neurons and glial cells (Reid et al. 2004). Also, the presence of excess unesterified cholesterol contributes to the excessive movement of cholesterol between the plasma membrane and ER, as well as genetically impairs the ACAT1/SOAT1 gene (Wollmer et al. 2003; Hutter-Paier et al. 2004; Karten et al. 2006).

The surplus amount of esterified cholesterol in neurons is stored as lipid droplets or excreted out from the brain as 24-hydroxycholesterol (24-OHC) via hydroxylation process at the rate of 6–12 mg/day (0.02–0.04% of the total cholesterol turnover) (Dietschy 2009; Bryleva et al. 2010). The cholesterol 24-hydroxylase enzyme catalyzing the above reaction is located in somata, dendrites of neurons, as well as in the glial cells of the brain. Thus, the major cholesterol turnover is observed in the brain than astrocytes (Ramirez et al. 2008). The hydroxylated product, 24-OHC, is reported to up-regulate the expression of ABCA1 via activated liver X receptor (LXR) in astrocytes and neurons (Gabbi et al. 2014; Korach-André and Gustafsson 2015). LXR acts as a cholesterol sensor by protecting the cell from excess internal cholesterol by suppressing cholesterol biosynthesis via cholesterol efflux by feedback process (Wang et al. 2008; Kang and Rivest 2012), stimulates reverse cholesterol transport (RCT) from peripheral tissue, activates the conversion of cholesterol, and decreases intestinal cholesterol

absorption (Baranowski 2008). Hyperphosphorylation of Tau protein due to impaired cholesterol accumulation caused by overexpression/mutation in the functioning of cell-surface receptors such as ATP-binding cassette transporters, LRP1/LDLR, and endosomal membrane compartment-NPC1/2 leads to neurodegenerative disorders (Akram et al. 2010; Rodrıguez-Rodrıguez et al. 2010; Liu et al. 2010; van der Kant et al. 2019). Thus, cholesterol homeostasis between astrocytes and neurons plays a crucial role in modulating the pathogenesis in brain (Fig. 2).

## Tauopathies

The normal function of mature neurons is accomplished by some of the major MAPs like Tau, MAP1 (A/B), and MAP2. The primary role of these three MAPs is towards the promotion of assembly and stability of microtubules in the neurons. In spite of its importance, neurons can compensate for the loss of function of one MAP with the other two MAPs. According to Teng et al., healthy development in adult life was observed in both tau and MAP2 knockout transgenic mice. However, double knockout of Tau and MAP2, as well as MAP2 and MAP1B in transgenic mice, shows defects in axonal elongation and neuronal migration (Takei et al.

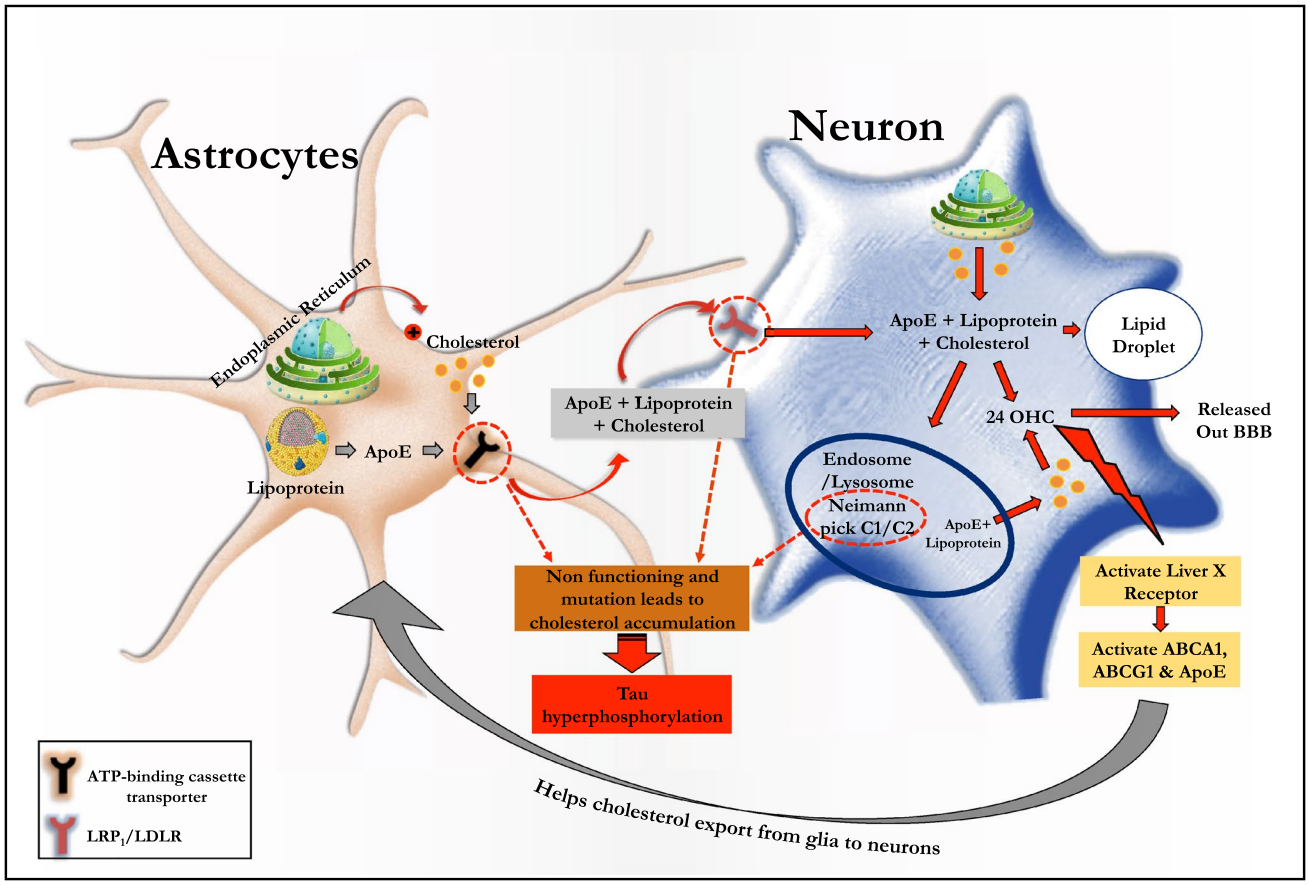


**Fig. 2** Cholesterol homeostasis in astrocytes and neurons, correlation with Tau protein hyperphosphorylation. Although neurons are capable of synthesizing cholesterol, it has been suggested that neurons rely on astrocytes for cholesterol delivery in the adult state. The major input of cholesterol into the brain comes from in situ synthesis in the ER of astrocytes. Lipoprotein particles, including apolipoprotein E (APOE) assembled in the ER and the newly synthesized cholesterol, are transported from the ER to extracellular space by non-vesicular mechanism via ATP-binding cassette transporter (ABCA1). The cholesterol-rich APOE particles interact with neuronal receptors LRP1/LDLR and undergo internalization by receptor-mediated endocytosis or routed to late endosomes/lysosomes internalization into neurons. Endosome/lysosome in assistance of NPC1/C2 leads to the generation of free cholesterol. The obtained free cholesterol is converted to 24-ortho-hydroxy cholesterol (24-OHC), which can pass through the BBB. Binding of 24-OHC to the cytoplasmic liver X receptors triggers expression of ABCA1, ABCG1, and APOE genes involved in cholesterol trafficking from astrocytes to neurons. The excess cholesterol in the neurons is stored as lipid droplets in the neurons. Although the BBB is not permeable to plasma cholesterol, BBB endothelial cells make possible cholesterol flux across via ABC transporters and LRP1 receptors. Non-functioning or mutation in ATP-binding cassette transporter, LRP1/LDLR, and Niemann–Pick C1/C2 genes leads to the excess cholesterol accumulation, in turn causing Tau hyperphosphorylation

2000; Teng et al. 2001). Also, chemical or genetic activation of microglia in the Tau mouse model of Tauopathy is reported to significantly contribute Tau pathology (Bhaskar et al. 2010). The major biological activity of Tau protein is regulated by the degree of phosphorylation. The optimal activity of Tau protein is achieved by 2–3 mol phosphate/mol of the protein (Köpke et al. 1993). The abnormally hyperphosphorylated Tau protein (~three to fourfold higher) is reported to be accumulated as interneuronal tangles of paired helical filaments (PHFs), twisted ribbons, or straight filaments in AD (Wegmann et al. 2010), thus leading to neurofibrillary degeneration and dementia due to reduced microtubule assembly and binding capability (Brier et al. 2016). Phosphorylated Tau protein in AD is a substrate for several protein kinases (Singh et al. 1994; Johnson and Hartigan 1999). Exogenous cholesterol, glycogen synthase kinase-3 (GSK-3), cyclin-dependent protein kinase-5 (cdk5), protein kinase A (PKA), calcium and calmodulin-dependent protein kinase- II (CaMKII), mitogen-activated protein kinase ERK 1/2, and stress-activated protein kinases are the major contributors for abnormal Tau hyperphosphorylation (Pei et al. 2003). Tau phosphorylation at different sites has shown the disparate impact on its biological function and pathogenesis. According to an in vitro study, Tau phosphorylation at Ser262, Thr231, and Ser235 inhibits its binding to microtubules by ~ 35%, ~ 25%, and ~ 10%, respectively (Sengupta et al. 1998). However, the in vitro kinetic studies related to the binding of hyperphosphorylated and normal Tau suggest that phosphorylation at sites, Ser199/Ser202/Thr205, Thr212, Thr231/Ser235, Ser262/Ser356, and Ser422 sequesters normal MAPs from microtubules (Alonso et al. 2004). Further self-aggregation of Tau into filaments is promoted by phosphorylation at Thr231, Ser396, and Ser422 sites. Also, mutation of Tau at Ser396 and Ser404 into Glu to mimic phosphoserine converts it to be more fibrillogenic (Abraha et al. 2000). According to the reports, increased propensity of Tau protein aggregation is observed due to the mutation at Ser422 to Glu (Haase et al. 2004).

The major contributors of Tau hyperphosphorylation are exogenous cholesterol and the increased serum cholesterol. The NPC2 characterized by the accumulation of exogenous cholesterol in lysosomes due to defective sorting/trafficking mechanism is reported to be associated with Tau hyperphosphorylation (Fan et al. 2001). Also, defective assembly of cholesterol and phospholipids within APOE due to mutated ABCA1 leads to Tau hyperphosphorylation (Akram et al. 2010). The two major lipoprotein receptors LRP1 and LRP2 bind and internalize extracellular ligands for degradation in lysosomes. The lipoprotein receptors also mediate the cholesterol uptake into the neuron. Malfunction of the receptors impairs intracellular signaling as well as storage and/or release of cholesterol in neurons. Thus, the impaired cholesterol metabolism due to LRP1 inactivation also contributes to Tau hyperphosphorylation (Spuch et al. 2012). Proline-directed protein kinases are also reported for its contribution in abnormal hyperphosphorylation of Tau (Liu et al. 2007a). As reported by Iqbal et al., GSK-3β, cdk5, and ERK ½ are the three major proline-directed protein kinases associated with Tau phosphorylation at specific sites in AD (Iqbal et al. 2005b). Also, as reported in a triple transgenic mouse model of AD, inflammation via toll-like receptor-4 (TLR4) ligand contributes to hyperphosphorylation of Tau (Kitazawa et al. 2005). The attenuation or exacerbation of Tau pathology has been reported through blockage or activation of interleukin-1 signal (Kitazawa et al. 2011). In addition to damaging neurons through phagocytosis of synapses and worsening of Tau pathology, microglia can also react to protein aggregates and inflammatory mediators. Other contributors to Tau hyperphosphorylation include TNF-α, IL-1β, inflammatory cytokines produced from activated TLRs and NLRP3 inflammasome (Heneka et al. 2013, 2015).

CX3CR1, a CX3C chemokine receptor-1, also known as fractalkine receptor or G-protein-coupled receptor 13 plays a major role in the microglial migration and phagocytosis in the CNS (Paolicelli et al. 2011). The deficiency of CX3CR1 is reported to result in the acceleration of Tau pathology in a hTau mouse model (human Tau-containing transgenic mice) (Bhaskar et al. 2010; Cho et al. 2011). CX3CL1 produced extensively in the neurons binds to the receptor CX3CR1, which is expressed on the surface of microglia (Kim et al. 2011; Zhan et al. 2014). Tau protein has also been reported binding to CX3CR1, thus increasing its internalization by microglia. Hence, increased competition has been observed between Tau and CX3CL1 in binding to the receptor (Bolós et al. 2017a). Deletion of microglial protein CX3CR1 in transgenic Tau model has shown genetic enhancement in the microglial activation and progression of Tau pathology. Thus, the reduced microglial phagocytic activity induces Tau hyperphosphorylation (Bhaskar et al. 2010; Maphis et al. 2015; Perea et al. 2018). The abnormally hyperphosphorylated Tau has been reported to develop resistance to proteolysis by the calcium-activated neutral proteases, thus leading to tauopathy in AD patients due to its lower turnover number (Khatoon et al. 1992; Wang et al. 1996; Poppek et al. 2006). Similarly, according to Maphis et al., a significant accelerated onset and progression of tau pathology, cognitive dysfunction, and neurodegeneration were observed in hTau CX3CR1$^{-/-}$ mice due to genetic enhancement of microglia-specific neuroinflammation. The microglial activation contributed to the spread of tau pathology through anatomically connected neurons of the hippocampus. Also, the adoptive transfer of purified microglia from hTau CX3CR1$^{-/-}$ mice to non-transgenic mice showed Tau hyperphosphorylation, thus indicating the role of microglia and its receptor, CX3CR1, in the dissemination of Tau pathology in the brain (Maphis et al. 2015).

As previously described, TREM2 functioning similar to APOE ε4 is reported to regulate inflammatory responses of microglia and phagocytosis of cellular debris (Li and Zhang 2018). Mutation in the TREM2 cell-surface receptor at R47H position impairs TREM2-mediated microglial activation of phagocyting hyperphosphorylated Tau protein (Guerreiro et al. 2013b; Jonsson et al. 2013; Jay et al. 2017; Ulrich et al. 2017). Also, TREM2-deficient microglia shows reduced uptake of Tau–cholesterol complex, thus leading to enhanced accumulation and risk of AD (Yeh et al. 2016). The impact of TREM2 deficiency investigated in the brain of young and aged mice using RNA-sequencing reported the pathogenesis of AD due to disrupted immune response (Carbajosa et al. 2018).

Some of the other factors influencing the Tau pathology include insulin resistance (Starks et al. 2015). Glucose uptake and metabolism impairment have been reported in AD brain (Hoyer 2004). The impaired glucose uptake/metabolism causes deregulation of Tau phosphatases and decreased Tau O-GlcNAcylation, thus facilitating abnormal hyperphosphorylation of Tau protein in many diabetic animal models (Gong et al. 2006; Jolivalt et al. 2008; Ke et al. 2009; Qu et al. 2011).

GSK-3, a proline-directed serine/threonine kinase, is reported to play a pivotal role in the pathogenesis of both sporadic and familial forms of AD (Hooper et al. 2008). The activity of GSK-3 is reported to be regulated by insulin and Wnt signaling pathways. Insulin signaling leads to the activation of PI3-kinase, which in turn activates Akt protein. According to the reported studies, the activated Akt phosphorylates free cytoplasmic GSK3β and GSK3α at serine (Ser) residues 9 and 21, respectively (Saltiel and Kahn 2001; Lizcano and Alessi 2002). Both GSK-3 α and β analogs play a major role in the hyperphosphorylation of Tau protein, memory impairment, increased production of Aβ, and inflammatory response (Hooper et al. 2008). Attenuation of phosphoinositide 3-kinase/Akt (PI3k/Akt) signal was observed in the brain due to diet-induced insulin resistance. The increased GSK-3α activity observed by attenuating GSK-3β phosphorylation from insulin resistance resulted in increased Aβ production (Ho et al. 2004). Insulin resistance together with oxidative stress causes inhibition of Wnt signaling, which in turn is reported to activate GSK-3β (Manolopoulos et al. 2010). The inhibited Wnt thus promotes the pathogenesis of Aβ and Tau protein hyperphosphorylation (Phiel et al. 2003; Rankin et al. 2007). In addition to its role in increasing Aβ production, insulin resistance is reported to reduce Aβ clearance by decreasing the expression and activities of insulin-degrading enzyme (IDE) (Ho et al. 2004). Thus, by regulating the activity of IDE, Aβ concentration can be reduced. The overview of the influencing parameters involved in the hyperphosphorylation of Tau protein, as well as Aβ accumulation, is summarized in Fig. 3.

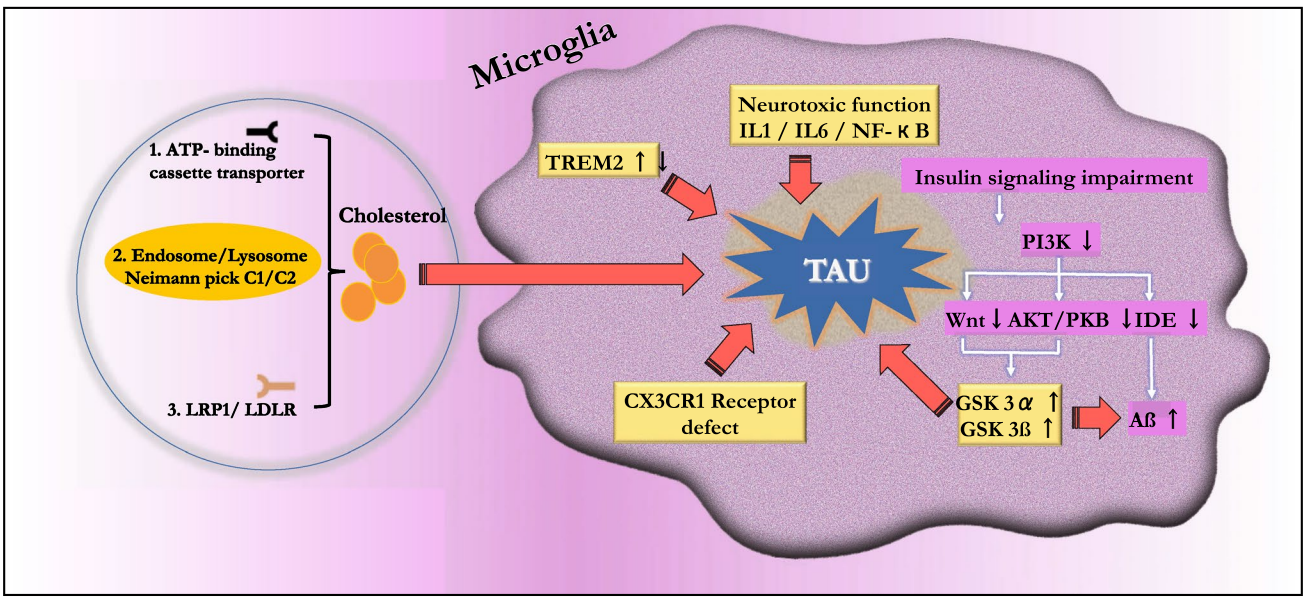


**Fig. 3** Parameters involved in the hyperphosphorylation of Tau protein in microglia. Microtubule-associated protein, Tau, involved in the microtubule dynamics, treadmilling, cargo transport, and axonal out growth, becomes aggregated into senile plaques in the brain under diseased conditions. Tau hyperphosphorylation is associated with impairment of cholesterol metabolism via non-functioning and mutations of ATP-binding cassette transporter, LRP1 receptor, Niemann–Pick C1/C2 genes, surface receptor CX3CR1, triggering receptor expressed on myeloid cells 2 (TREM2 involved in regulating microglia and phagocytosis), inflammatory cytokine, NF-κB activation, as well as glycogen synthase kinase-3 (GSK-3) activation via insulin signaling impairment

## Molecular Mechanisms of Microglial Uptake of Cholesterol, Tau, and Amyloid-β protein

Microglia are involved in the normal development, function, and repair of CNS. During injury or other pathological conditions, microglia migrate to lesion sites and initiate the immune response and resolve the particular insults in both human and transgenic murine models of AD (Nayak et al. 2014; Colonna and Butovsky 2017). As per previous reports, neurodegenerative diseases such as AD and Parkinson's are associated with abnormal intracellular accumulation of Tau protein (Ballatore et al. 2007; Goedert and Spillantini 2011; Arendt et al. 2016). The normal function of Tau, i.e., promoting and stabilizing microtubules is disrupted to form aggregates and neurofibrillary tangles due to hyperphosphorylation (Iqbal et al. 2009; Medeiros et al. 2011). The mice with mutant human Tau are reported to be associated with high levels of cellular cholesterol, thus leading to Tau hyperphosphorylation (Maccioni et al. 2010; Glöckner and Ohm 2014). The hyperphosphorylated accumulated Tau protein gets released outside the cells into the extracellular space, thus interacting with other cells and causing the cell-to-cell transfer (Simón et al. 2013; Medina and Avila 2014; Bolós et al. 2016). Microglia, the brain macrophages, play a major role in regulating the excess cholesterol and hyperphosphorylated Tau by activation/phagocytosis function (Hansen et al. 2017). The living neurons with Tau inclusions from P301S-Tau mice were reported to be phagocytized by BV2 cells or primary microglia cells (Brelstaff et al. 2018). Recently, direct internalization of Tau protein by microglia was observed in an in vitro study. The phagocytosis of newly synthesized full-length Tau oligomer $hTau40^{WT}$ was evidenced with $A11^{+}$ $Iba1^{high}$ microglial activation (Das et al. 2020). Similarly, the microglial engulfment of insoluble Tau protein obtained from homogenate of post-mortem AD brain tissue was observed in both in vitro and in vivo studies (Bolós et al. 2016). In the last decade, human genetic studies, especially GWASs using single-nucleotide polymorphisms (SNPs), have identified over 20 genetic loci that are robustly associated with AD risk (Lambert et al. 2013; Karch et al. 2014). A cell-surface transmembrane receptor protein TREM2 of the immunoglobulin superfamily is reported to be highly expressed both by the microglia in the brain, as well as by certain myeloid cells in the periphery (Guerreiro et al. 2013b; Jonsson et al. 2013). It acts as a cell-surface receptor via its interaction with the activating adaptor protein DAP12 (encoded by TYROBP gene). Various moieties activating the signaling pathways reported to be associated with TREM2 include lipopolysaccharides, phospholipids, HDL, LDL, APOE, APOJ, apoptotic neurons, Tau protein, and Aβ protein (Wolfe et al. 2019). Also, the stimulated TREM2 initiates various signal transduction pathways related to microglial chemotaxis, phagocytosis, survival, and proliferation (Mazaheri et al. 2017; Zheng et al. 2017). The cholesterol and hyperphosphorylated Tau protein are more efficiently taken up by microglia only when complexed with lipoproteins such as LDL, APOE, and CLU/apoJ (Terwel et al. 2011; Yeh et al. 2016). Besides TREM2, many other genes such as CD33, INPP5D, MS4A6A, and PLCG2 are also expressed in the microglia.

TREM2 is involved in the recruitment of tyrosine kinase SYK, which in turn phosphorylates immunoreceptor tyrosine-based activation motif (ITAM) of DAP12. The phosphorylated ITAM motif thereby activates downstream effectors such as PI3K and $Ca^{2+}$ signaling. Potential-dependent $Ca^{2+}$ channels and synaptic vesicles fuse with the presynaptic membrane to exocytosis excess cholesterol and hyperphosphorylated Tau protein (Zefirov and Petrov 2010). Another gene INPP5D, which encodes for lipid phosphatase SHIP1, is expressed in the microglia and this enzyme interacts with ITAM of DAP12 and dephosphorylates phosphatidylinositol (3,4,5)-trisphosphate (PIP3) to phosphatidylinositol (3,4)-bisphosphate (PIP2) at the plasma membrane, thus altering the outcomes of PI3K activation (Peng et al. 2010; Boucrot et al. 2015). PIP3 acts as a secondary messenger in phosphorylating and activating AKT (serine/threonine protein kinase B), which in turn helps in regulating cell apoptosis, promoting protein synthesis as well as inhibiting FOXO protein (Manna and Jain 2015). Some of the inhibitory receptors, like CD33, a member of sialic acid-binding immunoglobulin-type lectins (SIGLEC) family receptors, are reported to inhibit the activity of ITAM and SYK (Malik et al. 2013; Raj et al. 2014), whereas the protective SNP alters CD33 mRNA splicing, thus restoring the TREM2-ligand binding, ITAM signaling, and phagocytosis activity (Griciuc et al. 2013; Bradshaw et al. 2013).

The Bridging Integrator 1 (BIN1) located on 2q14.3 chromosome is reported to be key epigenetic regulator within the cell. BIN1-amphiphysin2 plays a key role in mediating cell processes such as from endocytosis to membrane recycling and cell cycle progression to apoptosis (Prokic et al. 2014). It is regarded as the second most important genetic risk factor for LOAD after APOE ε4 (Naj et al. 2011). Low expression of BIN1-amphiphysin2 observed in the diseased brains is reported to promote Tau pathology, whereas overexpression inhibits the above process by promoting endocytosis process (Tan et al. 2013; Calafate et al. 2016). It is reported to modulate Tau pathology in addition to Aβ protein by co-localizing and interacting with RIN3 (a guanine nucleotide exchange factor for Rab5 and Rab31) (Kajiho et al. 2011; Chapuis et al. 2013; Holler et al. 2014; Zhou et al. 2014). In humans, totally 1–7 isoforms are reported to specifically get expressed in brain, isoform 8 in skeletal muscles, and isoforms 9 and 10 are ubiquitous (Ellis et al. 2012; Prokic et al. 2014). The BAR domain expressed with many proteins involved in membrane dynamics in the cells

acts as the key modulators for all BIN1 isoforms to bind dynamin through the SH3 domain. But, only the neuronal isoforms of BIN1 containing a CLAP domain mediate the interaction of clathrin and AP2, and help clathrin-mediated endocytosis (CME) of Tau protein in the brain (Ramjaun and McPherson 1998; Slepnev et al. 2000). An adapter protein CD2AP, discovered as a ligand protein, interacts with T-cell-adhesion protein-CD2. It helps in membrane trafficking during endocytosis and cytokinesis (Wolf and Stahl 2003; Ma et al. 2010). CD2AP present between membrane proteins and actin cytoskeleton interacts with SHIP1 and RIN3, and regulates the microglial endocytosis of Tau protein (Bao et al. 2012; Rouka et al. 2015). The loss of CD2AP function has been reported to enhance Aβ metabolism, Tau-induced neurotoxicity, abnormal neurite structure modulation, and reduced BBB integrity (Shulman et al. 2014; Qing-Qing et al. 2018) (Fig. 4a).

Similarly, the extracellular peptide Aβ observed due to mutations within the genes encoding for PS-1 and PS-2 is cleared from the peripheral circulation via chaperone-mediated transport across the BBB (Shibata et al. 2000). Remarkably, wide varieties of genes are associated with Aβ processing or trafficking as well as myeloid cell-mediated Aβ clearance (Malik et al. 2015). LOAD risk genes related to increased complement activation and inflammation (*APOE, INDPP5D, CR1, TREM2, MS4A*), complement activation (*CLU, CR1*), the human leucocyte antigen (HLA) gene complex (*HLA-DRB1, HLADRB5*), myeloid cell-mediated Aβ proteolysis (*ACE, CD2AP*), and phagocytosis (*APOE, BIN1, INPP5D, CR1, ABCA7, TREM2)* are some of the important functions of the genes associated with Aβ protein (Karch and Goate 2015; Malik et al. 2015). The fundamental mechanism of Aβ clearance is either by removal to peripheral blood and lymphatic system or degradation within CNS tissues. Aβ reaches peripheral circulation via various mechanisms such as chaperone-mediated transport across the BBB (Shibata et al. 2000), perivascular drainage (Weller et al. 2008), or through the lymphatic system (Iliff et al. 2012; Iliff and Nedergaard 2013). The overexpressed small GTPases Rab5 and Rab7 promote the transfer of Aβ into lysosomes by regulating vesicle fusion (Li et al. 2012). The activated immune cells, mainly brain-resident microglia and infiltrating blood-borne monocyte-derived macrophages, play a crucial role in the physiological clearance of Aβ (Simard et al. 2006; Koronyo-Hamaoui et al. 2009). Transport across BBB requires special molecular chaperons belonging to LDLR family, such as LRP1 and ABC transporters (Tarasoff-Conway et al. 2015). LRP1 is the major clathrin-dependent endocytic receptor, located on the abluminal surface of brain endothelial cells. They stimulate the endocytosis of Aβ protein either by binding to APOE–Aβ complex or Aβ alone (Deane et al. 2004; Spuch et al. 2012). Once Aβ gets contained within the endothelial cells, the luminal transport protein ABCB1 facilitates the removal of Aβ into the vascular lumen via lysosomal degradation (Elali and Rivest 2013; Kanekiyo et al. 2013). Pharmacological inhibition of dynamin-mediated endocytosis leads to the prevention of transneuronal transmission of Aβ (Song et al. 2014). Receptor-associated protein (RAP), a chaperone and antagonist of LRP1, is also reported to interact with Aβ and facilitate its cellular uptake through heparin sulfate proteoglycan (HSPG) (Kanekiyo and Bu 2014). HSPG mediates the entry of various molecules including exosomes, cell-penetrating peptides, polycation-nucleic acid complexes, viruses, lipoproteins, growth factors, and morphogens into cells (Christianson and Belting 2014). It facilitates the initial binding of Aβ on the cell surface and further LRP1 mediates the endocytosis process by forming LRP1–HSPG complex (Wilsie and Orlando 2003; Kanekiyo et al. 2011). LRP1 also regulates Rac1 and RhoA activities in Schwann cell, which influences cell migration and adhesion (Mantuano et al. 2010). According to Yu et al., Aβ42 oligomers get internalized through a dynamin-dependent and RhoA-mediated endocytic pathway in neuronal cells. But no reports are available to describe the exact mechanism involved by LRP1 in activating RAC1 and RhoA (Yu et al. 2010). According to literature reports, LRP1 controls the cytoskeleton architecture by modifying PI3K/extracellular signal-regulated kinase (ERK) and/or focal adhesion kinase (FAK)/paxillin pathways. Thus, it has been predicted that the process mentioned above might contribute in regulating Rac1 and RhoA (Dedieu and Langlois 2008). The phosphatidylinositol binding clathrin assembly protein functions as an adaptor protein for the transcytosis of Aβ–LRP1 complex across BBB (Carrasquillo et al. 2010; Tian et al. 2013). Sortilin-related receptor 1 (SORL1) (also known as SorLA and LR11) are reported to be involved in the intracellular transport and processing of APP, thus resulting in decreased production of Aβ peptide (Andersen et al. 2005; Fjorback et al. 2012). Disruption of SORL1 influences the Aβ pathway and Tau-related cellular processes by mediating their endocytic pathways (Aβ and Tau) (Offe et al. 2006; Capsoni et al. 2013). A similar action was also reported for the CD33 gene (Bradshaw et al. 2013). Also, macropinocytosis or phagocytosis is said to take up larger size Aβ aggregates (Mayor and Pagano 2007). Thus, by regulating the amount of aggregated Tau and Aβ protein, the prevalence of neurodegenerative diseases can be regulated (Fig. 4b).

## Conclusion

In conclusion, Tau pathology and cholesterol metabolism appear to play a pivotal and primary role of neurodegeneration in AD and several other Tauopathies. Many studies have focused on cholesterol metabolism and its impact on amyloid-β protein. Now since Tau protein is considered

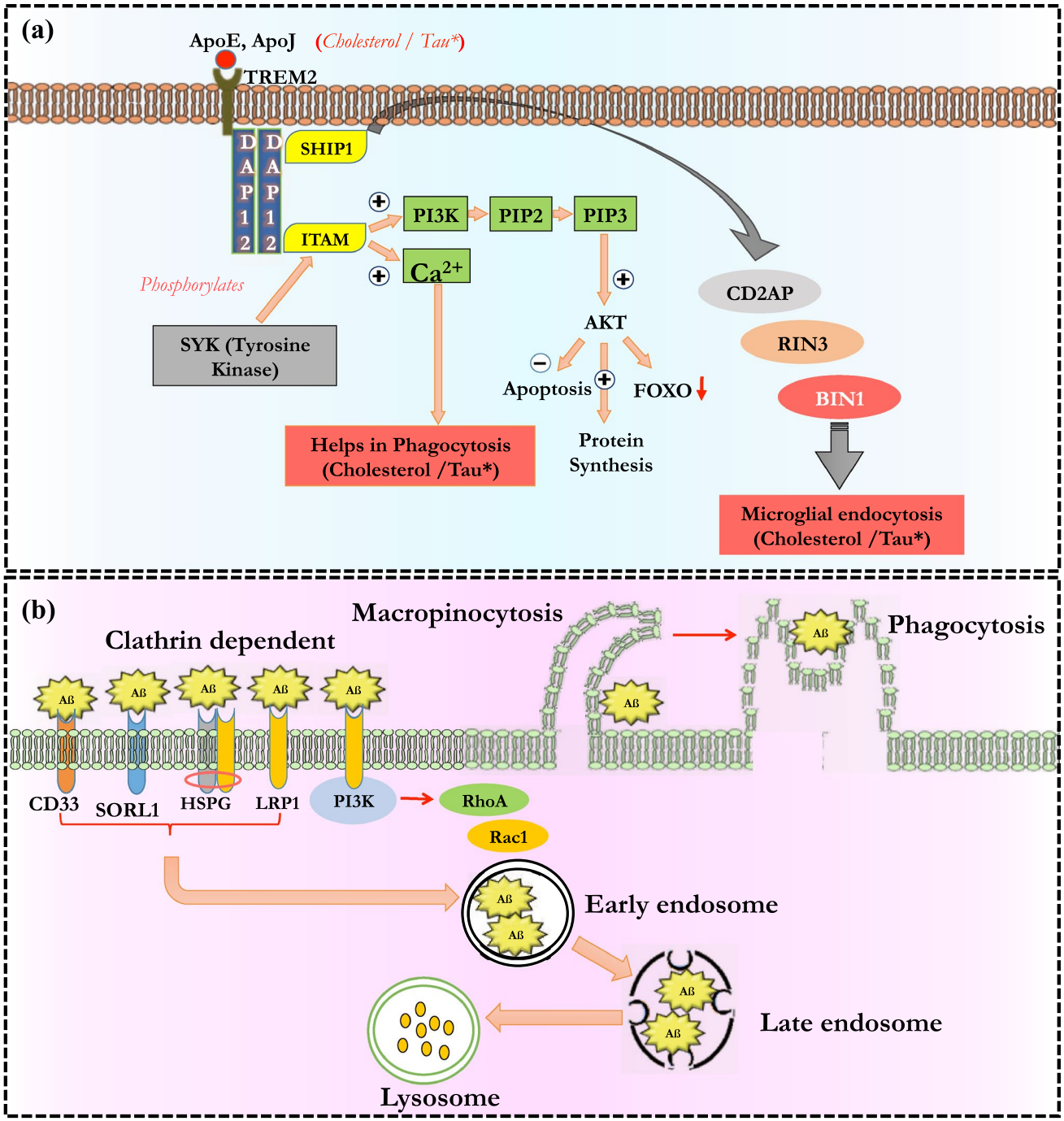


**Fig. 4** Molecular mechanisms of microglial uptake of cholesterol, Tau, and amyloid-β protein. **a** Lipoproteins containing APOE or apoJ carrying cholesterol in association with Tau protein bind to TREM2. The ligand-activated TREM2 interacts with immune receptor tyrosine-based activation motifs (ITAMs), which leads to recruitment of spleen tyrosine kinase. The ITAM/SYK mediates the activation of phosphoinositide 3-kinase-AKT pathway and $Ca^{2+}$ signaling. Through $Ca^{2+}$-dependent channels, synaptic vesicles fuse with presynaptic membrane and thus exocytosis excess cholesterol and hyperphosphorylated Tau. SH-2-containing inositol 5′ polyphosphatase 1 (SHIP1) expressed on microglia interacts with ITAM and modulates CD2AP, RIN3, and BIN1 adaptor protein in regulating microglial endocytosis of Tau protein. **b** Regulation of Aβ protein occurs via binding to clathrin-dependent receptors, including CD33, SORL1, LRP1, and LRP1/HSPG-mediated uptake. The internalized Aβ traffics to lysosomes for subsequent degradation. LRP1 also controls the cytoskeleton by modifying PI3K regulation of RhoA and Rac1 in causing Aβ cellular uptake and degradation by macropinocytosis or phagocytosis process

equally important in the pathogenesis of neurodegenerative disease, especially Alzheimer's, it is important to know the molecular mechanisms involved in its hyperphosphorylation. As per the earlier reports, cholesterol turnover in the brain contributes majorly in regulating Tau phosphorylation and pathogenesis. The article provides an overview of the molecular mechanism involving microglia and the genes in controlling the concentration of APOE-containing cholesterol and Tau protein. Hence, to the best of our knowledge the review article provides a strong background to fully elucidate the role of microglia in modulating the Tau pathology and cholesterol metabolism in the brain.

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## Compliance with Ethical Standards

**Conflict of interest** The authors declare no conflict of interest.

**Research Involving Human Participants and /or Animals** This article does not contain any studies with human participants or animals performed by any of the authors.

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