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Chapter 7

The Mevalonate Pathway in Alzheimer's Disease — Cholesterol and Non-Sterol Isoprenoids

Amany Mohamed, Kevan Smith and Elena Posse de Chaves

Additional information is available at the end of the chapter

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1. Introduction

The brain is a lipid-rich organ, with approximately 50% of its dry mass constituted by lipids [1]. The main lipid in the brain is cholesterol. The human brain represents only 2% of the total body mass but contains 25% of the total body cholesterol [2, 3]. Therefore, it is not surprising that lipids have important functions in the brain and that dysregulation of brain lipid metabolism has been linked to brain diseases, in particular Alzheimer's disease (AD). The interest in understanding the link between lipids and AD pathology has increased dramatically since the 1990s, when it was discovered that the isoform 4 (ε4) of the cholesterol transport protein apolipoprotein E, is a major risk factor for AD development [4]. Since then an important body of evidence derived from genetic, epidemiological, and biochemical studies has identified the role of cholesterol in many critical aspects of AD neuropathology. The finding that a number of genes involved in cholesterol homeostasis represent susceptibility loci for sporadic or late-onset AD (reviewed in [5-9]), and the evidence that alterations in cholesterol homeostasis are significant in regulation of Aβ production, formation of amyloid plaques, tau hyperphosphorylation, Aβ toxicity, and other mechanisms (reviewed in [5, 10-12]) highlight the importance of the dysregulation of cholesterol homeostasis in AD. [7, 9, 13-20]. Cholesterol homeostasis disturbances in AD may be both consequences of the neurodegenerative process and contributors to the pathogenesis.

2. Cholesterol homeostasis in the brain

Cholesterol homeostasis is the balance between synthesis and uptake, and efflux and metabolism. In the brain, this process acquires peculiar characteristics because of differences in the ability of neurons and glia to perform each of these processes (Figure 1).

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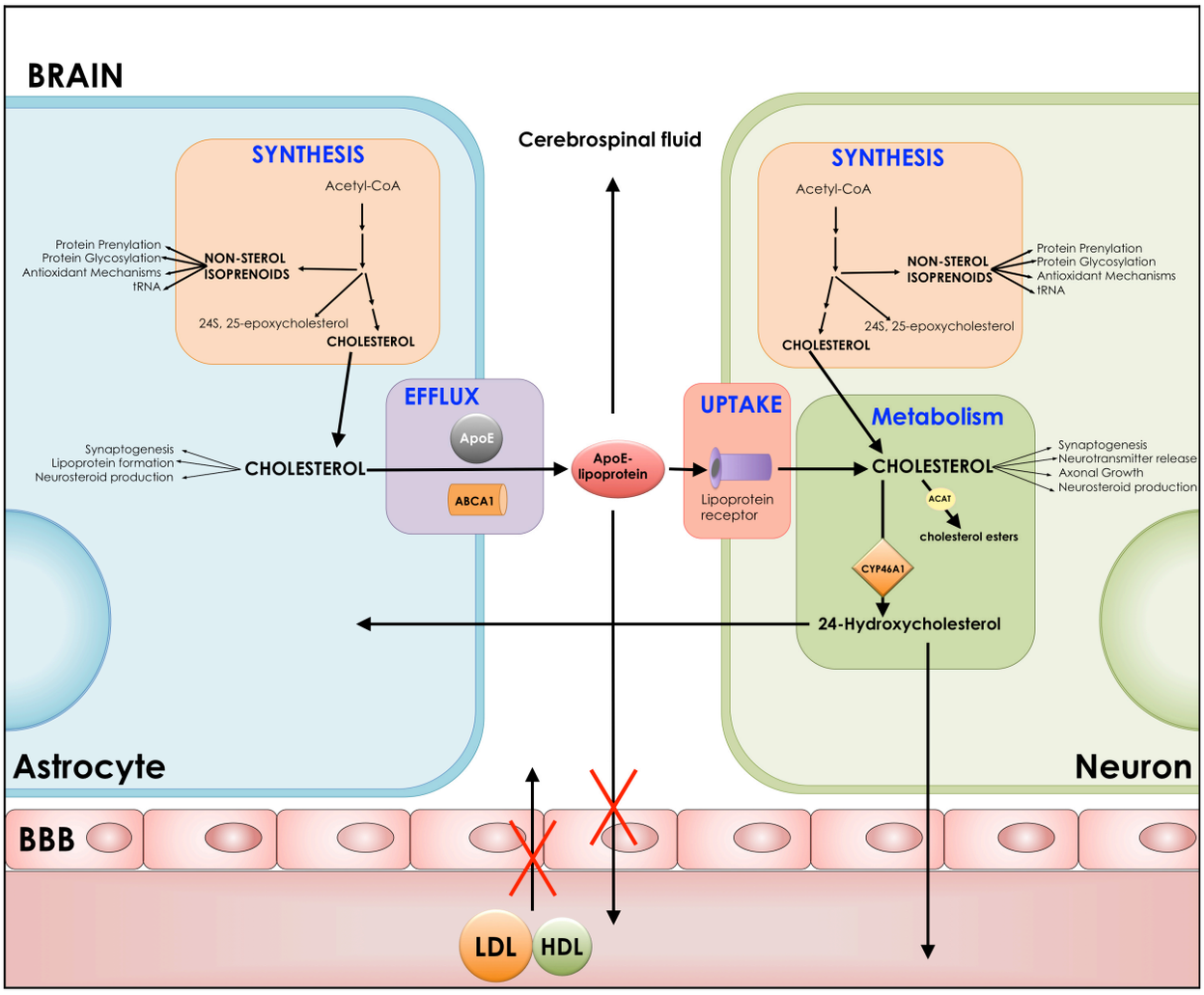


Figure 1. Cholesterol homeostasis in the brain. Cellular cholesterol is synthesized from acetyl-CoA in a multistep mevalonate pathway. Cholesterol and Apo-E synthesized in astrocytes are secreted in an ABCA1-dependent process, forming discoidal lipoprotein particles, which can be further lipidated. Brain lipoproteins are delivered to the CSF. Apo-E is a ligand for LDLR family members, which mediate neuronal lipoprotein uptake, thereby providing a supply of cholesterol to neurons. Excess cholesterol is metabolized to 24-hydroxycholesterol, which crosses the BBB and passes into the circulation. A small part of cholesterol (~1%) is esterified by ACAT. Only insignificant amounts of plasma HDL or LDL cross the BBB under normal conditions.

Cholesterol synthesis is crucial in the brain because the brain is separated from the peripheral pool of cholesterol by the blood brain barrier (BBB), which, under normal conditions, is impermeable to plasma lipoproteins [2, 3]. Thus, brain cholesterol originates almost exclusively from *de novo* biosynthesis through the mevalonate pathway. Cholesterol synthesis *in situ* in the brain is very active in order to meet the brain demands. Cholesterol is essential for normal synaptogenesis and plays important roles in axonal development, neurotransmitter release and neurosteroid production [2, 21]. Brain cholesterol synthesis is sufficient to meet the demands during development and in adult life, although this local synthesis decreases with age [22]. Genetic defects in enzymes involved in cholesterol synthesis cause severe neurological abnormalities underscoring the importance of endogenous cholesterol synthesis

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for normal brain function [23, 24]. The identity of the cells responsible for cholesterol synthesis in the adult brain is still a matter of debate. Neurons have a lower rate of cholesterol synthesis than astrocytes [25] and outsource cholesterol from astrocytes to form and maintain axons, dendrites and synapses [21, 26, 27]. In fact, based on the discovery that suppression of cholesterol synthesis in vivo in adult cerebellar neurons did not affect the viability of the neurons or the shape and density of synapses [28], it was suggested that neurons do not require autonomous cholesterol synthesis and are minor contributors to adult brain cholesterol synthesis [28]. However, *in situ* hybridization demonstrated that transcripts of several enzymes involved in cholesterol synthesis localize specifically to neurons in pyramidal and granular layers of mouse hippocampus [29], indicating that some adult neurons maintain the ability to synthesize cholesterol. Yet, there is ample evidence that brain neurons utilize cholesterol derived from astrocytes. Astrocytes provide cholesterol to neurons via apolipoprotein-mediated efflux and formation of HDL-like particles containing apoE [27]. Adenosine triphosphate-binding cassette (ABC) transporters, mainly ABCA1, mediate lipidation of nascent lipoproteins [30]. Neurons import cholesterol via lipoprotein receptor-mediated endocytosis [31]. Astrocyte-secreted lipoproteins are delivered to the CSF but they don't cross the BBB [32, 33].

Neurons convert excess cholesterol into a more polar metabolite that crosses the BBB, 24 (S) hydroxycholesterol (24-HC) by the enzyme cholesterol 24-hydroxylase (CYP46A1) [34, 35]. CYP46A1 is selectively expressed in the brain [36], in particular in pyramidal neurons of the hippocampus and cortex and in Purkinje cells in cerebellum, but not in astrocytes [25, 37]. 24-HC is a very important regulator of the mevalonate pathway (Section 3). In addition, 24-HC regulates cholesterol efflux in astrocytes [38]. Cholesterol also undergoes esterification catalyzed by the enzyme acyl CoA-cholesterol acyltransferase (ACAT) [39]. Although cholesterol esterification is not a major metabolic process in the brain, and cholesterol esters represent only 1% of the total cholesterol content in brains of human [40] and mice [41], ACAT has been identified as a crucial enzyme in AD [42].

Cholesterol-related genes that have been associated with AD encode primarily, components of the glia/neuron cholesterol shuttle processes, including apoE [4, 43], the apolipoprotein clusterin [44], ABCA1 [45-48], CYP46A1 [49-52], several members of the LDL receptor family [53-55], and ACAT [56]. Much less information is available with respect to the genetic association of AD with genes of enzymes of the mevalonate pathway. The few studies available did not provide strong associations. Thus, it is likely that changes in the mevalonate pathway identified in AD are a consequence of the disease. Here we focus on the evidence that indicate that the mevalonate pathway "per se" is affected in AD.

3. The mevalonate pathway in the brain and in AD

The brain produces cholesterol and a number of non-sterol isoprenoids such as farnesylpyrophosphate (FPP), geranylgeranylpyrophosphate (GGPP), ubiquinone and dolichol, exclusively through the mevalonate pathway. The mevalonate pathway comprises successive

enzymatic reactions that convert acetyl-CoA into the different final sterol and non-sterol products [57, 58]. For the purposes of the discussion we have separated the mevalonate pathway in components: pre-squalene pathway, post-squalene pathway, shunt pathway and non-sterols isoprenoids pathway (Figure 2). The kinetics of the enzymes involved in the mevalonate pathway have been thoroughly studied [58, 59]. Enzymes of the mevalonate pathway are expressed in the brain of rodents and humans [29, 60] and the expression of many of them is developmentally regulated in the brain [61, 62]. Inborn defects in enzymes of the mevalonate pathway result in structural abnormalities of the brain and may be accompanied by neurodevelopmental/behavioral defects [63].

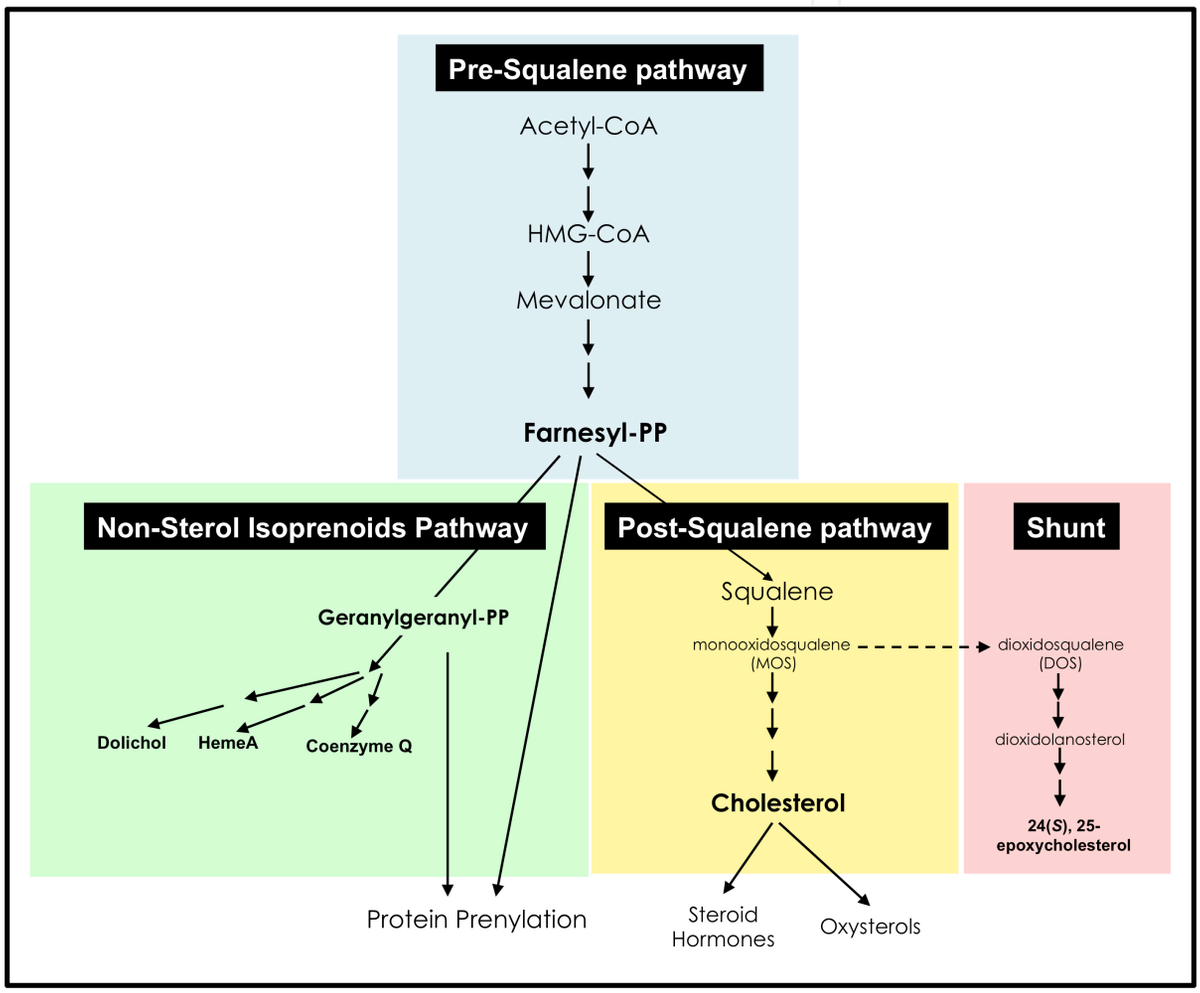


Figure 2. The mevalonate pathway. The mevalonate pathway has been divided in different components to facilitate the understanding of its regulation.

There is only limited information of changes in the mevalonate pathway enzymes and lipid intermediates in AD brains, although certain exceptions exist. The lipid products of the mevalonate pathway seem to be regulated highly individually in AD, likely through post-translational modifications of the enzymes and/or changes in levels of substrates. Most of the studies on the mevalonate pathway in AD have focused on cholesterol, although more recent

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work has also paid attention to the non-sterol isoprenoid branch of the pathway. In this chapter we focused on studies performed in brains and brain cells although there is important evidence that changes in plasma cholesterol levels may be relevant to AD development and/or progression [64]. The interest in understanding the role of the mevalonate pathway in AD increased with the reports that patients taking statins had lower incidence of AD than the general population [13-17, 65]. More recent prospective studies have produced conflicting results on the matter [15-19]. This is still an area of intense research and debate.

The mevalonate pathway is tightly regulated at the transcriptional and post-transcriptional levels to avoid accumulation of cholesterol while maintaining proper supply of non-sterol isoprenoids.

3.1. Regulation of the mevalonate pathway by SREBP-2 and LXR

Transcriptional regulation of the mevalonate pathway is mediated by two main transcription factors namely sterol-regulatory element binding protein type-2 (SREBP-2) and liver X receptors (LXR). SREBP-2 belongs to a family of membrane-bound transcription factors that regulate cholesterol and fatty acid homeostasis. Studies in knockout and transgenic mice demonstrated that cholesterol synthesis is preferentially regulated by SREBP-2 [66, 67]. SREBP-2 is synthesized and inserted in the endoplasmic reticulum (ER) as an inactive precursor (P)SREBP-2 [68]. (P)SREBP-2 has two transmembrane helices with the N- and C- terminals projecting into the cytosol [68]. The C-terminus of (P)SREBP-2 interacts with C-terminus of SREBP cleavage-activating protein (SCAP), a sterol-regulated escort protein. SCAP has eight transmembrane helices, of which transmembrane helices 2-6 are defined as a sterol sensing domain [68, 69]. (P)SREBP-2-SCAP complex has to be transported into coat protein complex II (COPII) vesicles that bud from the ER and travel to the Golgi complex [70]. Mice with haploinsufficiency of SCAP in the brain had reduced SREBP-2 processing and reduced SREBP-2 expression. Consequently, reduced SCAP level resulted in decreased expression of many enzymes in the mevalonate pathway and 30% reduction in cholesterol synthesis leading to impaired synaptic transmission and cognitive deficits [71]. At the Golgi, sequential proteolytic cleavage of (P)SREBP-2 by Site-1-protease (S1P) [72] and Site-2-protease (S2P) [73] releases the N-terminal /mature/nuclear SREBP-2 ((M)SREBP-2) that enters the nucleus to regulate gene transcription [66, 68, 74]. In the nucleus, (M)SREBP-2 binds to sterol regulatory elements (SREs) in the promoter of target genes in order to regulate gene expression [68]. SREBPs alone are relatively weak activators of gene expression. Transcriptional activities of SREBPs are highly enhanced by other cofactors such as nuclear factor Y(NF-Y) [75] and specificity protein-1 (sp-1) [76] or by the presence of two SRE motifs as in genes encoding enzymes such as 3-hydroxy-3-methylglutarylCoA reductase (HMGCR), squalene synthase [75] and 24-dihydrocholesterol reductase (DHCR24) [77]. (M)SREBP-2 increases the expression of most enzymes involved in the mevalonate pathway and the expression of LDLR involved in exogenous cholesterol uptake [66, 67]. In addition, SREBP-2 increases the expression of miR33a (encoded by an intron of SREBP-2) and miR128-2. miR33a and miR128-2 block ABCA1 and ABCG1 expression reducing cholesterol efflux [78-84]. High level of (M)SREBP-2 were detected in pyramidal neurons in hippocampus and cerebral neocotex of normal rat brain [85]. The main regulator

of SREBP-2 proteolytic processing is cholesterol. When ER cholesterol falls below 5% of total ER lipids (molar basis), SREBP-2 cleavage is activated [86]. On the other hand, when cholesterol accumulates at the ER, it binds to SCAP inducing a conformational change that promotes SCAP binding to ER integral membrane proteins Insulin-Induced gene-1 or 2 (Insig-1 and Insig- 2) [87, 88]. Once bound to Insigs, SCAP is unable to bind to COPII and the SCAP-(P)SREBP-2 complex is not transported to the Golgi leading to reduced SREBP-2 processing [89]. In vitro experiments revealed that cholesterol, and the cholesterol precursors desmosterol and 7-DHC, but not lanosterol or oxysterols are able to change SCAP conformation [87]. Desmosterol and cholesterol bind to SCAP in a similar manner [88, 90, 91]. Oxysterols also reduce SREBP-2 processing but they do so by binding directly to Insigs and not to SCAP [92]. SREBP-2 positively regulates its own expression via binding to SRE in the promoter of its own gene [93]. It also increases expression of specific miRNAs for negative SREBP-2 regulators such as miR-182, which reduce expression of Fbxw7, an E3 ubiquitin ligase involved in nuclear SREBP-2 degradation and miR-96, which targets Insig-2 [94]. Therefore, miR-182 and miR-96 increase SREBP-2 processing, reduce its degradation and consequently enhance its transcriptional activity.

LXRs (LXRα and LXRβ) also play a role in the regulation of the mevalonate pathway by activating or inhibiting expression of enzymes of the mevalonate pathway (reviewed in [95]). LXR are ligand-activated transcription factors belonging to the nuclear hormone receptor superfamily [96, 97]. Expression level of LXRα in the brain is much lower than in the liver, however, LXRβ is highly expressed in the brain compared to the liver [98]. SREBP-2 and LXR work in harmony in order to regulate the mevalonate pathway. SREBP-2 activation will enhance cholesterol production and consequently oxysterol production, leading to LXR activation and LXR targets expression [99]. On the other hand, LXRs activation enhances cholesterol efflux, reduces cellular cholesterol uptake [100, 101] and suppresses the expression of some enzymes in the post-squalene mevalonate pathway [102]. Consequently, LXR activation will reduce cellular cholesterol level leading to SREBP-2 processing and activation. In accordance, synthetic LXR agonist GW683965A significantly increased SREBP-2, LDLR, and HMGCR expression in astrocytes by indirect mechanims [38]. Moreover, significantly reduced number of SREBP-2 and HMGCR transcripts were detected in brains of LXRα and β null mice [103].

3.1.1. Transcriptional regulation of the mevalonate pathway by SREBP-2 in AD

Transcription factor profiling showed no difference in SREBPs between non-demented and AD brain cortical samples [104], however it was not discriminated if the probe was for SREBP-2 or SREBP-1. In autopsied hippocampus of patients with incipient AD, SREBF-1 was found to be elevated [105]. Haploinsufficiency of Scap, a key regulator of SREBP-2, in mice brain resulted in impaired synaptic transmission, as measured by decreased paired pulse facilitation and long-term potentiation; and was associated with behavioral and cognitive changes [71], suggesting that down-regulation of the mevalonate pathway may play an important role in the increased rates of cognitive decline in AD. Studies at the subcellular level suggest that SREBP-2 may be posttranslationally regulated in AD. We demonstrated that o$A\beta_{42}$ inhibit

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SREBP-2 maturation in cultured neurons [106]. We also discovered that the levels of (M)SREBP-2 are reduced in the frontal cortex of the AD CRND8 mouse [107], suggesting that the negative regulation of SREBP-2 may also occur *in vivo* in AD. Recently, it was reported that APP also controls neuronal cholesterol synthesis through the SREBP pathway [108]. These studies showed that APP levels inversely correlate with SREBP in mice and man, and demonstrated that inhibition of the mevalonate pathway by APP impairs neuronal activity. The interaction of APP and SREBP-1 in the Golgi prevented the release of mature SREBP-1 and the translocation of SREBP-1 to the nucleus. Our data, on the other hand, indicated that $A\beta_{42}$ did not affect the enzymatic cleavage of SREBP-2 "per se" nor did it block mature SREBP-2 translocation to the nucleus, but impaired the delivery of SREBP-2 to the Golgi preventing cleavage of (P)SREBP-2 [107]. Interestingly, the regulation of SREBP by APP takes place preferentially in neurons. In astrocytes, APP and SREBP1 did not interact nor did APP affect cholesterol biosynthesis, but neuronal expression of APP decreased both HMGCR and cholesterol 24-hydroxylase mRNA levels leading to inhibition of neuronal activity [108].

3.2. Pre-squalene pathway

The pre-squalene mevalonate pathway is depicted in Figure 3. Acetoacetyl Co-A is formed from two moles of acetyl Co-A in the presence of acetoacetyl Co-A thiolase. 3-hydroxy-3-methylglutaryl (HMG) Co-A is formed from one mole of acetyl Co-A and acetoacetyl Co-A in the presence of HMG Co-A synthase (HMGS). HMGCR converts HMG Co-A to mevalonic acid [109]. The rate-limiting enzyme of the pathway is HMGCR [110], one of the most highly regulated enzymes in nature [111]. In human brains HMGCR expression was demonstrated in both neurons and glia [112]. Studies in adult mouse brain tissue showed HMGCR expression within cortical, hippocampal, and basal forebrain cholinergic neurons [29, 60]. HMGCR protein and activity are localized in the ER and peroxisomes in the CNS [113] and in other organs. Due to the critical function of this enzyme early in the mevalonate pathway, there are no human syndromes known to be associated with HMGCR loss of function, and mouse embryos homozygous for the Hmgcr knockout allele do not progress beyond the blastocyst stage. On the other hand mice heterozygous for the Hmgcr mutation showed normal development, gross anatomy, and fertility (reviewed in [114]). HMGCR is the target of statins.

The product of HMGCR, mevalonic acid, is phosphorylated sequentially to 5-phosphomevalonate by the enzyme mevalonate kinase (MK) and to 5-pyrophosphomevalonate by phosphomevalonate kinase (PMK). MK is the second essential enzyme of the isoprenoid/cholesterol biosynthetic pathway [115]. Inherited mutations in human MK are correlated with two diseases characterized by neurological dysfunction namely mevalonic aciduria and Hyper-IgD syndrome (reviewed in [114, 116]).

5-Pyrophosphomevalonate is converted to isopentenylpyrophosphate (IPP) by mevalonate diphosphate decarboxylase. IPP is required for synthesis of all further products of the mevalonate pathway [117]. IPP is isomerized to dimethylallyl pyrophosphate (DMPP) in the presence of IPP isomerase (IPPI) [58, 118].

IPP and/or DMPP are required for isopentenylation, which is an essential modification of specialized tRNA that transfers the amino acid selenocysteine ($tRNA^{Sec}$) [119, 120]. Selenopro-

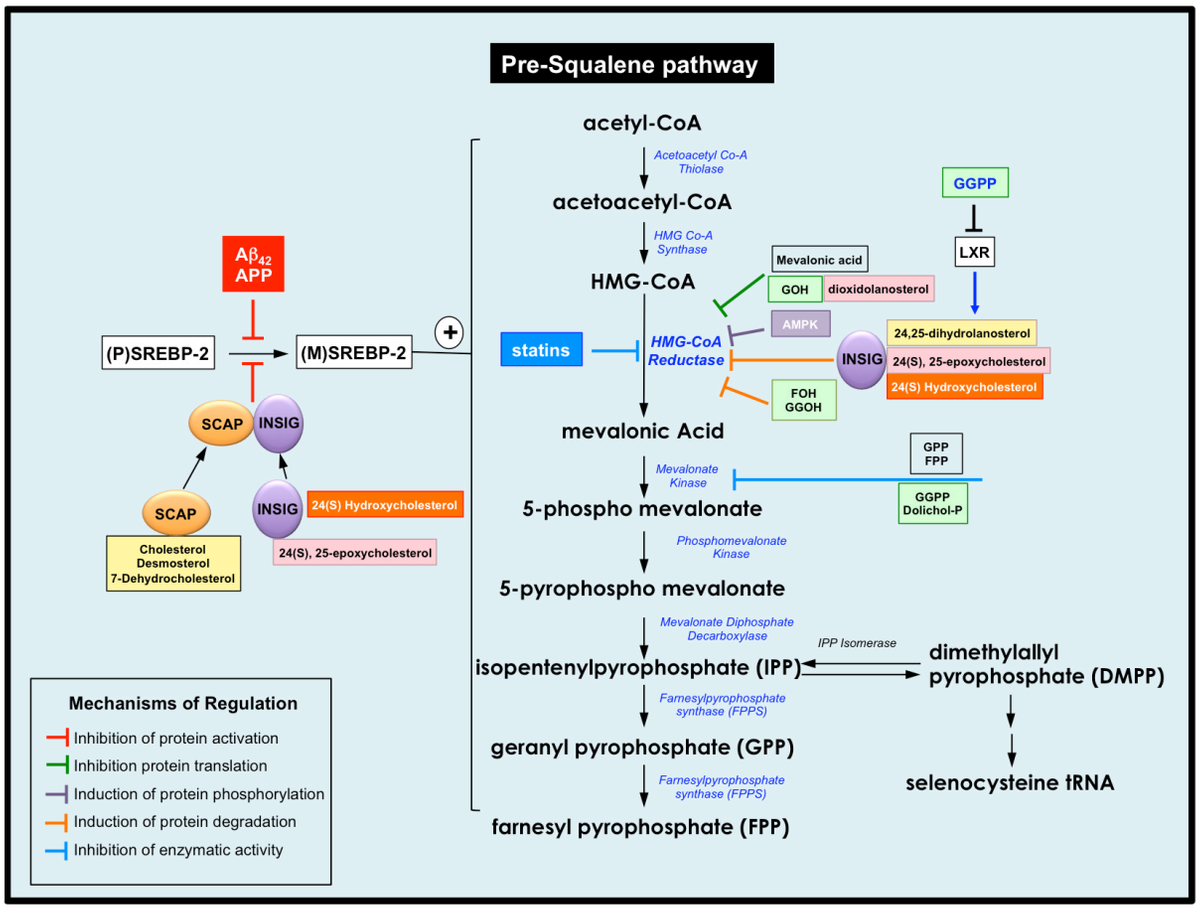


Figure 3. The pre-squalene pathway. Schematic representation of the pre-squalene mevalonate pathway and key enzymes regulating FPP synthesis. The rate-limiting enzyme of the pathway is HMGCR. Several regulatory feedback mechanisms exist at the level of many enzymes of the pathway.

teins have been implicated in protein folding, degradation of misfolded membrane proteins, and control of cellular calcium homeostasis, all processes known to be dysfunctional in neurodegenerative diseases [121, 122]. Moreover, neuron-specific ablation of selenoprotein expression causes a neurodevelopmental and neurodegenerative phenotype affecting the cerebral cortex and hippocampus [123]; and impaired expression of selenoproteins in the brain triggers striatal neuronal loss leading to coordination defects in mice [124]. Statins, by reducing production of IPP, interfere with the enzymatic isopentenylation of $tRNA^{Sec}$ and prevent its maturation to a functional tRNA molecule, resulting in the reduction of the expression of selenoproteins [125]. Other functions of IPP include its antinociceptive effect, mediated by inhibition of transient receptor potential (TRP)-channels, TRPV3 and TRPA1 [126]. Interestingly, DMPP has effects on TRP- channels opposites to those of IPP, inducing enhanced acute pain behavior [127].

IPP combines with DMPP to form geranyl pyrophosphate (GPP); and GPP is condensed with another molecule of IPP to yield farnesylpyrophosphate (FPP). GPP and FPP syntheses are catalyzed by farnesylpyrophosphate synthase (FPPS), a prenyltranferase [128-130]. FPP initiates the branches of the pathway that generate cholesterol and non-sterol isoprenoids.

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3.2.1. Regulation of enzymes of the pre-squalene pathway

HMGCR is the rate-limiting enzyme of the mevalonate pathway. HMGCR is transcriptionally activated by SREBP-2 [131]. The presence of two SRE motifs in HMGCR promoter leads to a higher level sterol-dependent regulation [75]. Gene regulation by the SREBP pathway is slow and its down-regulation requires several hours to effectively decrease mRNA of target genes [132]. In order to accomplish a rapid (within 1 h) switch off of cholesterol synthesis HMGCR is extensively regulated at the translational and posttranslational levels (Figure 3). HMGCR is post-transcriptionally regulated by alternative splicing/skipping of exon 13 leading to production of a shorter unproductive transcript that encodes an inactive enzyme. In the liver, HMGCR alternative splicing is regulated by sterols (cholesterol and 25-hydroxycholesterol), so sterol accumulation increases the proportion of shorter transcript and vice versa. Interestingly, sterol-mediated alternative splicing of HMGCR occurs faster than sterol-mediated transcriptional inhibition of HMGCR [133]. Mevalonate and certain downstream derivatives such as dioxidolanosterol (a shunt pathway intermediate) and GOH regulate HMGCR mRNA translation reducing its rate of synthesis [134-137]. Mevalonate has been shown to change polysome distribution of HMGCR mRNA leading to inhibition of HMGCR translation at the initiation step [138]. HMGCR is post-translationally regulated via phosphorylation and ubiquitin/proteasomal degradation. Short-term regulation of HMGCR is mediated via phosphorylation by AMPK and dephosphorylation by PP2A (protein phosphatase 2A). HMGCR exists in the cell in both unphosphorylated (active) and phosphorylated (inactive) states [139-141]. As a master regulator of cellular energy homeostasis, AMPK phosphorylates HMGCR to inhibit cholesterol synthesis, an energy intensive process. The implications of AMPK-mediated regulation of HMGCR are controversial. In mutant Drosophila lacking functional AMPK, higher activity of HMGCR and consequent higher rate of the mevalonate pathway were associated with progressive neurodegeneration [142]. On the other hand, activation of AMPK by quercetin reduced HMGCR activity, cholesterol synthesis and enhanced cognitive functions in high cholesterol fed old mice [143]. The best understood mechanism of HMGCR post transcriptional regulation is the sterol-mediated ubiquitination and proteasomal degradation. This mechanism requires binding of HMGCR to Insig-1 or Insig-2 and recruitment of Ring-finger ubiquitin ligases, Gp78, Trc8, and MARCH6 [144-146]. Insig binds to the sterol-sensing domain in HMGCR [147]. HMGCR share many sequence similarities in the sterol-sensing domain with SCAP, thus Insigs can bind with both HMGCR and SCAP [148]. The binding of Insigs has radically different consequences for SCAP and HMGCR. Upon binding Insig, HMGCR is ubiquitinated and degraded [147, 149], whereas, as indicated above SCAP is retained in the ER [89]. Both processes inhibit the mevalonate pathway. The oxysterols 25-EC (synthesized by the shunt pathway, Section 3.3.1.) and 24-HC; and the post-squalene intermediate 24, 25-dihydrolanosterol (Section 3.3.0), but not cholesterol, bind to Insigs and induce HMGCR degradation [91, 150-152]. Indeed, it is the accumulation of 24, 25-dihydrolanosterol the mechanism by which LXRα enhances HMGCR [102]. Adding an additional level of regulation, the non-sterol isoprenoid GGPP antagonizes LXR, blocking HMGCR degradation [153, 154]. Studies in vitro suggested that two metabolites of the non-sterol isoprenoids pathway namely farnesol (FOH) and geranylgeranyol (GGOH) enhance HMGCR degradation beyond the effect elicited by sterols. FOH and GGOH do not target the

interaction between Insigs and HMGCR but seem to rely on protein prenylation [147, 155-158]. Consequently, a GGPP synthase (GGPPS) inhibitor, and a geranylgeranyl transferase I (GGTaseI) inhibitor prevented the enhancement of HMGCR degradation [155].

MK is regulated transcriptionally by SREBP-2 through an SRE in its promoter (Horton 2002). MK activity is post-translationally reduced by GGPP, FPP, GPP and dolichol phosphate via competitive inhibition at ATP binding site [159, 160]. GGPP is the strongest inhibitor of MK activity.

3.2.2. Pre-squalene mevalonate pathway in AD

Information on the status and regulation of HMGCR in AD is very limited. HMGCR is the most important enzyme of the pre-squalene mevalonate pathway. No changes in gene expression of HMGCR were found in AD brain in humans and in a mouse model of AD [161]. Genetic association of HMGCR was found in patients under the age of 75 [162], and HMGCR promoter polymorphisms alone or with polymorphisms in other proteins of cholesterol homeostasis were associated with AD risk and cognitive deterioration in some studies [163, 164], but not in all populations [165]. The AlzGene meta-analysis for HMGCR is negative [7]. Poirier's group identified HMGCR as a genetic modifier for risk, age of onset and mild cognitive impairment (MCI) conversion to AD. In their recent study they found that carriers of a specific variant of HMGCR display a protective effect that resembled in size and gender to what has been reported for APOE2 in humans [166]. Information on protein HMGCR levels and activity in the carriers' brains is expected to be available soon. Age- and sex-dependent dysregulation of HMGCR occurs in the liver [167], but to our knowledge similar mechanisms have not been reported in the brain. Studies showed high levels of the HMGCR mRNA in all areas of the brain but no obvious differences were found between AD and controls [168]; similarly levels and gene expression of HMGCR were comparable in AD and control samples in another study [169].

FPPS is the last enzyme of the pre-squalene pathway. In two small samples, polymorphisms of FPPS or their haplotypes were associated with AD [8]. But in other samples FPPS variants were not related to AD risk. The AlzGene meta- analysis for FPPS polymorphisms is negative [7].

3.3. Post-squalene pathway

The post-squalene mevalonate pathway is depicted in Figure 4. FPP is converted to squalene by the action of squalene synthase (farnesyl diphosphate farnesyl transferase 1) [170]. Squalene synthase is the first enzyme in the mevalonate pathway whose product, squalene, is committed to cholesterol synthesis. The lack of reports indicating genetic disorders linked to mutations in squalene synthase suggest that this enzyme may be essential in embryonic development (discussed in [114]). In fact, deletion of squalene synthase is embryonic lethal in mice [171]. Squalene synthase is inhibited by zaragozic acid.

Squalene is converted to monooxidosqualene (MOS), which can be further converted to lanosterol and dioxidosqualene (DOS). Formation of both MOS and DOS requires the action of the enzyme squalene monooxygenase (SM) (also called squalene epoxidase). Lanosterol is

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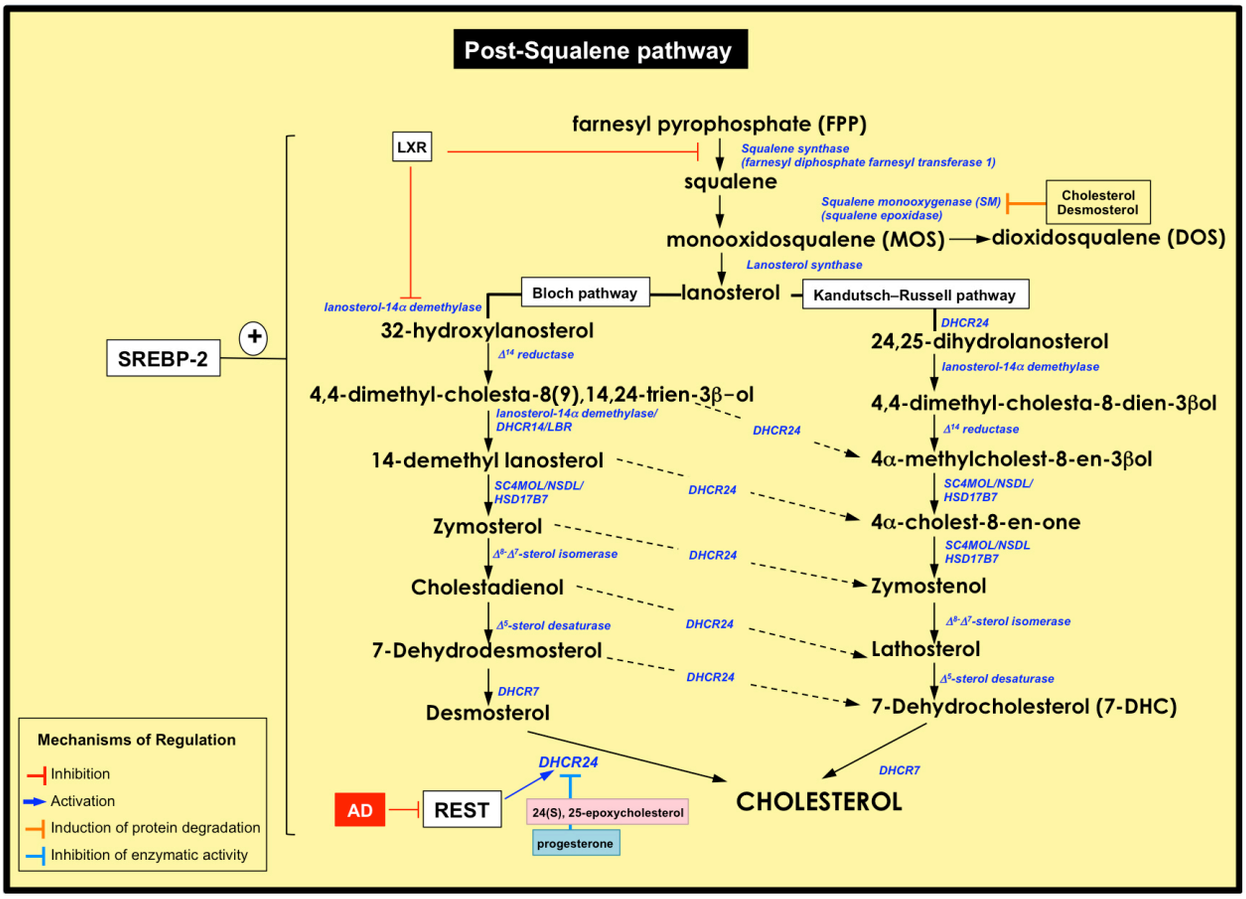


Figure 4. The post-squalene pathway. The final product of the post squalene pathway is cholesterol. Most enzymes of the post-squalene pathway are targets of SREBP-2. Other posttrancriptional regulatory mechanisms also exist.

the first sterol intermediate in cholesterol synthesis. Lanosterol is metabolized to cholesterol by 19 enzymatic steps. In the brain, as in the liver, there are two major pathways for the conversion of lanosterol to cholesterol. The Kandutsch–Russell pathway includes lathosterol and 7-dehydrocholesterol (7-DHC) as intermediates; while the Bloch pathway, uses desmosterol as an intermediate (reviewed in [172]. Post lanosterol precursors are present in all cells that synthesize cholesterol, although they might represent a minor sterol component due to their rapid conversion to downstream metabolites, or to their release from cells [173, 174]. A special scenario is present in embryonic mouse astrocytes, which, freshly dissociated from the striatum or after being cultured for several days, contain desmosterol as a major membrane sterol, accounting for roughly 50% of total sterols [175]. In young rodents, brain cholesterol is mainly synthesized via the desmosterol pathway, while the Kandutsch–Russell pathway is predominant in older rodents [176, 177]. Desmosterol transiently accumulates up to 30% of total sterols in the mammalian brain during development and in the perinatal period indicating the activity of the Bloch pathway [178-183]. In humans the Bloch-pathway plays a minor role in the formation of CNS cholesterol during aging [22]. Neurons and glia seem to use different pathways downstream of lanosterol. Neurons contain precursors for the Kandutsch-Russel pathway (*e.g.*, 7-DHC) whereas astrocytes contain precursors for the Bloch pathway (e.g.,

desmosterol) [25]. Disturbances in either of these two pathways may result in replacement of cholesterol with its precursors in the brain, which causes serious disorders of the nervous system [184, 185]. Serum lathosterol is considered an indicator of whole body cholesterol synthesis in humans [22, 186, 187]. Lanosterol and desmosterol together with lathosterol are regarded as tissue markers of local cholesterol synthesis [22].

7-DHC and desmosterol are the immediate cholesterol precursors of the Kandutsch-Russel and the Bloch pathways respectively. 7-DHC is converted to cholesterol by 7-DHC reductase (DHCR7). Mutations in the DHCR7 gene cause the human genetic disease Smith-Lemli-Opitz syndrome, characterized by a wide spectrum of developmental anomalies that may result from decreased cholesterol, increased 7-DHC, or a combination of both [184, 188, 189]. Desmosterol is reduced to cholesterol by the enzyme DHCR24, also known as seladin-1 [190]. DHCR24 catalyzes the 24,25-reduction reactions in the cholesterol biosynthesis pathway and may act on most intermediates of the Bloch pathway [23, 114, 191, 192]. Disruption of the DHCR24 gene results in accumulation of desmosterol and is characterized by multiple congenital anomalies in humans and mice [190, 193, 194]. Desmosterol is an abundant structural membrane component in astrocytes [175]. In the brain, high desmosterol levels are present during development [181, 182]. During aging, hippocampal levels of desmosterol decrease significantly in the rat [176]. Desmosterol is a natural ligand of LXR [195].

From the two reductases that participate in the later steps of cholesterol synthesis production, DHCR24 is important in AD and therefore is discussed here in more detail. DHCR24 is encoded by a single gene (Dhcr24) on chromosome 1, an evolutionarily conserved gene with homologies to a family of flavin adenine dinucleotide-dependent oxidoreductases [196]. DHCR24 is detected in many tissues, including brain, adrenal glands, pituitary, thyroid gland, ovary, testis, and prostate [197-199]. Dhcr24 was initially identified as a gene down-regulated in affected brain regions in AD [196] and consequently its product has also been called Seladin-1 from **Sel**ective **A**lzheimer's **d**isease **in**dicator 1. However, current evidence indicates that DHCR24 has functions that go beyond those expected from its enzymatic activity in the mevalonate pathway. The roles of DHCR24 in oxidative stress, hepatitis C virus infection, cardiovascular disease, prostate cancer and other conditions have been recently discussed in detail [200]. The role of DHCR24 in AD is discussed in Section 3.3.3.

3.3.1. Shunt in the post-squalene pathway

Conversion of MOS to DOS establishes an alternate pathway leading to the production of (24S, 25)-epoxycholesterol (25-EC) [201] (Figure 2). This shunt in the mevalonate pathway functions in parallel to the conversion of lanosterol to cholesterol [202]. 25-EC is the only oxysterol that does not derive from cholesterol. It is present in rodent brain [203], where it is proportionally more important than 24-HC during development and the perinatal period, but not in the adult [204]. Production of 25-EC represents a cellular defense mechanism against accumulation of cholesterol that derives from the mevalonate pathway (as opposed to exogenously-derived cholesterol) [202]. 25-EC is responsible of the fine-tuning of cholesterol synthesis, and without it, acute cholesterol synthesis is exaggerated [205]. 25-EC is synthesized in both human neurons and astrocytes, and the proportion synthesized by astrocytes is an order of magnitude higher

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than that of neurons [206]. Astrocytes but not neurons secrete 25-EC and neurons internalize this oxysterol. Interestingly, 25-EC reduced the expression of SREBP-2 target genes and increased expression of LXR target genes in both astrocytes and neurons [205-208]. 25-EC may represent an additional regulatory signal between astrocytes and neurons in cholesterol homeostasis [206]. 25-EC is an important negative regulator of the mevalonate pathway (Section 3.2.1).

3.3.2. Regulation of enzymes of post-squalene pathway

All the enzymes of the post-squalene pathway are transcriptionally activated by SREBP-2 [67, 132, 209]. In addition, LXRα represses transcription of squalene synthase and lanosterol-14α demethylase directly [102].

Posttranslationally, cholesterol and desmosterol but none of the oxysterols enhance SM degradation [210]. MARCH6, also known as Teb4, functions as a selective ubiquitin ligase for SM ubiquitination and consequent proteasomal degradation [146, 211]. Cholesterol-induced degradation of SM is a novel feedback mechanism regulating the mevalonate pathway to prevent cholesterol accumulation without affecting isoprenoid supply.

DHCR24 is regulated by diverse mechanisms at the transcriptional and posttranslational levels. Several studies have identified the Dhcr24 gene as a target of SREBPs [67, 212-214]. In brains of statin-treated mice, there is activation of SREBP-2 and significant up-regulation of DHCR24 in cortex and hippocampus [215]. SREBP-2 binds to two (SREs) present within the Dhcr24 promoter, inducing a novel mode of transcriptional regulation for SREBP-2, characterized by homotypic cooperativity [77]. This type of regulation may warrant that a threshold of active SREBP-2 is reached before committing to the energetically expensive process of cholesterol synthesis [77, 200]. A novel mechanism of DHCR24 transcriptional activation by the transcription factor RE1-silencing transcription factor (REST), which is normally a repressor, has been recently reported [183]. Although this may be a secondary mechanism of DHCR24, the reduced levels of REST present in the brain during development may explain, at least in part, the reduced activity of DHCR24 and the consequent elevation of desmosterol [183]. Interestingly LXR has also been implicated in the regulation of DHCR24 as data from a whole genome screen for LXR binding sites showed that the Dhcr24 gene contained a functional LXR response element [216]. LXR regulation of DHCR24 seems to be tissue specific. LXR did not influence DHCR24 expression in some studies [77], and at least in studies using mice deficient in LXRβ, this regulation does not seem to take place in brain [216]. DHCR24 displays epigenetic regulation by methylation and histone acetylation due to the presence of GC rich regions within the DHCR24 promoter [217]. At the post-translational level DHCR24 activity is inhibited by certain oxysterols (25EC) [218] and by progesterone possibly by direct enzyme inhibition [182]. In addition, a novel mode of DHCR24 inhibition through phosphorylation has been demonstrated, which may allow a rapid inhibition of cholesterol synthesis [219].

3.3.3. Post-squalene pathway in AD

From the enzymes involved in the post-squalene section of the mevalonate pathway, DHCR24 is the most important in AD. A study comparing gene expression by using mRNA differential

display identified the down-regulation of DHCR24 in large pyramidal neurons in vulnerable regions in AD but not in healthy brains [196]. This finding was confirmed by others [220], although this may not apply to all AD patients [221]. The down-regulation in DHCR24 transcription was associated with hyperphosphorylated tau but not with β-amyloid deposition [220]. Single nucleotide polymorphisms of DHCR24 have been associated with AD risk [222]. However, these associations have not been confirmed, and other polymorphisms of DHCR24 only associated with AD in men but not in women [223]. Based on the evidence that DHCR24 expression is higher in neural stem cells than in differentiated neurons [224] it was hypothesized that reduced DHCR24 expression might be due to the existence of an impaired neuronal stem cell compartment [225]. Alternatively, transcriptional regulation of DHCR24 may be altered in AD. Indeed, recent studies indicated that the transcription factor REST, identified as a DHCR24 transcriptional activator [183] is lost in mild cognitive impairment and AD [226]. In addition, we have demonstrated that Aβ causes a significant decrease of SREBP-2 activation in neurons [106]; and we found reduced SREBP-2 activation in brain cortex of the AD mouse model CRND8 [107]. These observations suggest that, as the disease progresses reduced DHCR24 levels would not be unique, and that other enzymes of the mevalonate pathway would also be affected in brain cells that accumulate Aβ. However, taking in consideration the cooperative transcriptional mechanism of regulation exerted by SREBP-2 on DHCR24 [77], it is expected that DHCR24 would be particularly sensitive to reduced SREBP-2 activation. A general reduction of the mevalonate pathway could also explain why the levels of desmosterol are decreased in AD brains [227], contrary to what would be predicted if only DHCR24 were down-regulated. If these mechanisms exist in vivo in the brain, then the decrease of DHCR24 would be a consequence, rather than a cause of AD. Contrary to the findings in humans, the levels of desmosterol were elevated in the APPSLxPS1mut mouse model of AD, which also showed a significant decrease in DHCR24 in those brain areas [161]. DHCR24 has neuroprotective effects against Aβ toxicity, ER stress and oxidative stress-induced apoptosis, inhibiting caspase 3 activity and directly scavenging reactive oxygen species [196, 228, 229]. Many other studies have reported the antioxidant properties of DHCR24 in a variety of tissues and in the context of different diseases (reviewed in [200]). Importantly, DHCR24 mediates the protective effects of estrogens in cultured human neuroblasts since estrogen and selective estrogen receptor modulators (SERMs) stimulate the expression of DHCR24 in human neuroblast long-term cell cultures [230, 231]. The neuroprotective action of DHCR24 against Aβ may be due to its ability to maintain plasma membrane cholesterol at levels that prevent the rise of intracellular calcium and the production of ROS and lipoperoxidation that contributes to Aβ toxicity [232-234]. The relevance of these mechanisms in vivo in the brain requires confirmation, especially because there is ample evidence suggesting that high plasma membrane cholesterol may be detrimental in Aβ-induced toxicity (reviewed in [11]). The reduction of cholesterol in cell membranes due to DHCR24 may impair lipid raft functions and favor Aβ accumulation by a combination of inefficient Aβ degradation (due to low plasmin activity) and increased APP amyloidogenic cleavage [235]. Thus, all these mechanisms suggest the existence of vicious feedback cycles involving Aβ and DHCR24.

The post-squalene pathway results in production of cholesterol. There is little consensus about total brain cholesterol alterations in patients with AD [236-238]. Using different methods for

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measuring cholesterol (discussed in [237]), some studies found no change in cholesterol content in any portion of the brain [239, 240] or the hippocampus [241] in AD brains, while other studies reported changes in cholesterol levels in specific brain areas, particularly in regions with extensive Aβ deposits and neurofibrillary tangles (NFTs). Xiong and collaborators found an increase in cholesterol in the cortex of AD brains [104], Heverin et al. described a significant increase of cholesterol concentration in the basal ganglia but not in other brain areas in a small group of AD brains [242] and Cutler at al. reported accumulation of free cholesterol in the middle frontal gyrus and frontal cortex but not the unaffected cerebellum in AD brains from individuals expressing apoE4 [243]. It was also indicated that, as the severity of the disease progressed, there was an increase in membrane- and amyloid plaque-associated cholesterol [243-245]. Cholesterol levels were lower in the temporal gyrus of autopsied brains of AD patients compared to control subjects [246].

Analysis of post squalene cholesterol precursors also provided conflicting results. Lathosterol was reported to be elevated in the basal ganglia and the pons in AD but the ratio of lathosterol to cholesterol, used as a marker for cholesterol synthesis, was not significantly different between controls and AD patients suggesting that cholesterol synthesis is normal [242]. More recently a model for cholesterol homeostasis deregulation was proposed based on the measurement of post-squalene cholesterol precursors, cholesterol and oxysterol in brains of individuals with no-cognitive impairment, MCI and AD [247]. In 'compensated' MCI and initial AD there would be a heme oxygenase-1-mediated stimulation of cholesterol synthesis and cholesterol efflux in the astroglial compartment to allow cholesterol delivery for neuronal repair. As the disease progresses, massive uptake of cholesterol derived from widespread neuronal degeneration would overwhelm glial efflux pathways resulting in increased brain cholesterol levels and feed-back suppression of de novo cholesterol synthesis. This model could explain the findings in CSF. In CSF, cholesterol levels were significantly lower in AD patients as compared to controls [248, 249], and absolute levels of lanosterol, lathosterol and desmosterol and ratios of cholesterol precursors/cholesterol were also significantly reduced strongly indicating that *de novo* cholesterol synthesis within the CNS of AD patients might be impaired [248]. In the latter study, only the ratio of desmosterol/cholesterol was not significantly different in AD patients as compared to controls, but the increased CSF ratios of desmosterol/lathosterol suggests that the activity of the Kandutsch–Russell pathway might be reduced more than the Bloch pathway. The authors proposed that reduced expression of DHCR24 also contributes to decreased levels of cholesterol in AD patients and may explain the high levels of desmosterol found in AD in some studies [220, 250]. However, in other cases brain levels of desmosterol were reduced in AD [227]. This last finding agrees with the possibility that mevalonate pathway enzymes other than DHCR24 may also be down-regulated in AD, perhaps by a mechanism that involves SREBP-2 inhibititon. A further indication that cholesterol synthesis might be inhibited in AD is the finding that neurosteroids, which result from cholesterol metabolism, are reduced in AD temporal cortex as compared to control subjects [251]. It is important to highlight that changes in levels of cholesterol intermediates in brains of mouse AD models do not parallel changes in human patients. In the APP transgenic mice carrying the Swedish mutation (APP23), no differences in the levels of lathosterol, desmosterol or cholesterol and were found when compared with wild-type

animals [177]. These differences must be considered when using animal models to study the mevalonate pathway.

It is possible that a change in the distribution of cholesterol inside brain cells rather than a change in total cholesterol content may influence AD pathology [252]. We have shown that Aβ induces cholesterol sequestration within the neuronal endosomal/lysosomal system, and impairs intracellular trafficking [106]. Our findings provide an explanation to the cellular cholesterol overload reported in brains of AD patients [253]. They also agree with previous work that showed cholesterol sequestration specifically in Aβ-immunopositive neurons [104, 254, 255], and with studies in transgenic mouse models of AD where cholesterol sequestration in the brain was preceded by Aβ accumulation and/or coincided with areas of Aβ accumulation [244, 256, 257]. These studies underscored the relevance of cholesterol sequestration in AD. This is important because a causal relationship between cellular cholesterol sequestration and cell death has been found in Niemann-Pick Type C (NPC) pathology [258]. NPC is a disorder characterized by impairment of intracellular cholesterol trafficking and cholesterol sequestration in the endosomal compartment [259]. Accumulation of cholesterol within the endosomal-lysosomal system in NPC not only triggers degeneration of neurons in selected brain regions but also leads to abnormal processing of APP and Aβ generation as observed in AD pathology. The similarities between AD and NPC include the presence of immunologically similar tau-positive NFTs [254, 260], the influence of ε4 isoform of apoE in promoting disease pathology [261], and endosomal abnormalities associated with the accumulation of cleaved APP derivatives and/or Aβ peptides in vulnerable neurons [262, 263]. Importantly, strategies previously used to reduce cholesterol sequestration in NPC and strategies that reduce cholesterol levels by increasing cholesterol metabolism improved pathological symptoms in mouse models of AD [264, 265].

Preclinical and clinical studies have indicated the critical role of cholesterol in AD. This topic has been reviewed extensively and thoroughly in the past years [11, 12, 18, 236, 238, 266-268], thus it is not discussed in this chapter. The best-studied role of cholesterol is in the production of Aβ from amyloid precursor protein (APP). Overall, the evidence indicates that increase in cellular cholesterol causes an increase in Aβ production, although some studies showed the opposite [11, 12, 269]. Cholesterol regulates Aβ uptake and toxicity, but the evidence on whether cholesterol reduces or favors Aβ toxicity is controversial [11, 12]. Brain cholesterol is important in synapse development and maintenance [27, 270, 271]. Synaptic dysfunction is one of the earliest significant events in AD and synapse loss is the strongest anatomical correlate of the degree of clinical impairment [272, 273]. Significant decrease in dendritic spine density is present in the hippocampus of patients with AD and in transgenic mouse models of AD [274-278]. Alterations in cholesterol levels, even locally at synapses, may play a role in synapse dysfunction in AD [279].

3.4. Non-sterol isoprenoids pathway

The branch of the mevalonate pathway that leads to the production of non-sterol isoprenoids is depicted in Figure 5. The enzymes involved in these steps have been extensively reviewed [59]. The importance of this pathway is emphasized by the number of diseases

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that are associated with its dysfunction, including AD, Parkinson's disease, cancer, and tuberculosis [129, 280-282].

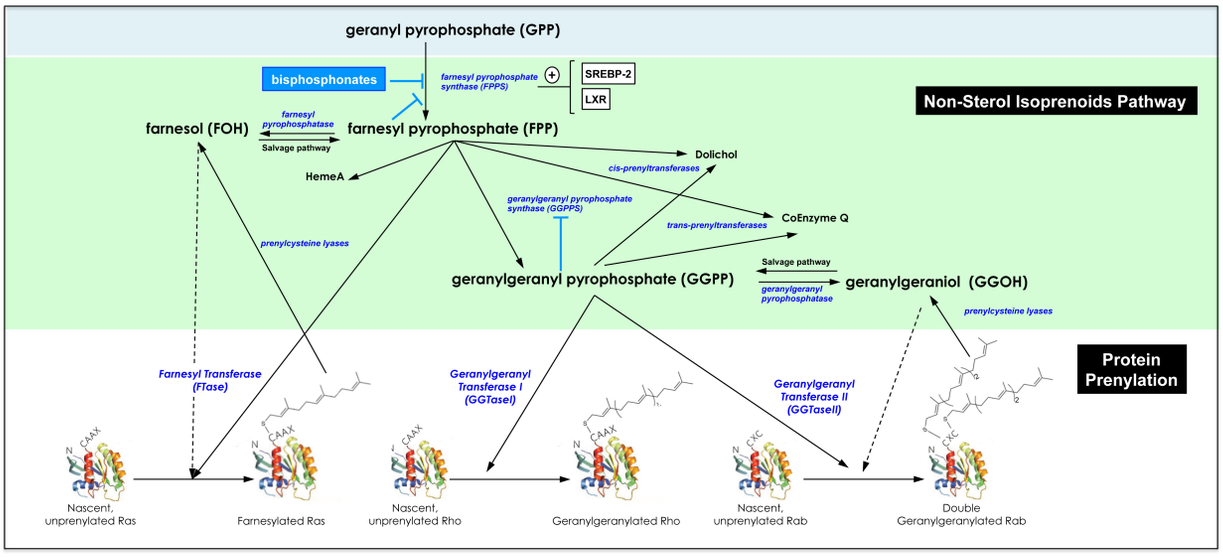


Figure 5. The non-sterol isoprenoid pathway.

FPP is the common substrate for synthesis of several end products and for the lipid modification of proteins. The enzymes responsible for synthesis of FPP and its non-sterol derivatives are prenyl-transferases that catalyze consecutive condensations of IPPs with primer substrates to form linear backbones for all isoprenoid compounds [130]. The enzyme GGPPS catalyzes the conversion of FPP into GGPP [283]. The main role of FPP and GGPP is in the posttranslational isoprenylation (*i.e.* farnesylation and geranylgeranylation) of proteins (Section 3.4.1.). Two different GGPPS activities have been described: a membrane-associated protein that produces GGPP for dolichol biosynthesis and a cytosolic protein that produces GGPP for protein prenylation [284]. In mouse brain cytosol, FPPS and GGPPS activities were higher than those in the corresponding fractions from the liver, perhaps reflecting a higher demand for protein prenylation in the brain [284]. FPPS and GGPPS activities were differentially distributed across various subregions of the brain. FPPS activity was present in all brain regions as expected by the several products that derive from FPP [285]. GGPPS activity was ~100 fold lower than FPPS activity, which agrees with the more limited use of GGPP, mostly for protein prenylation and as a precursor of a limited number of metabolites. GGPPS activity was lowest in the cerebellum [285].There have not been any reported cases of FPPS or GGPPS deficiency in humans [128]. FPPS is the target of nitrogen-containing bisphosphonate (N-BP) inhibitors, drugs used extensively to treat bone diseases [286]. A few bisphosphonate selective inhibitors for GGPPS have been reported but a clinically proven inhibitor of GGPPS has not yet been identified, limiting the validation of this enzyme as a therapeutic target [287].

Cis-prenyltransferases enzymes use FPP and GGPP for synthesis of dolichols [288, 289]. Dolichol phosphate is a lipid carrier embedded in the ER membrane, essential for the synthesis of N-glycans, GPI-anchors and protein C- and O-mannosylation [290, 291]. Dolichol is present,

as a family with different chain lengths, in the hippocampus and spinal cord in a relatively low concentration compared to other areas of the brain [285]. Dolichol increases in brain and in peripheral organs during aging [292] and is associated with increased HMGCR activity [293]. The use of dolichol level as a marker for aging has been proposed [294].

Trans-prenyltransferases convert FPP to GGPP and further polyprenyl-PP in the synthesis of Coenzyme Q (CoQ), also known as ubiquinone. In humans, the main ubiquinone is ubiquinone 10, or CoQ10, with 10 isoprene units. Ubiquinone performs major functions as an electron carrier in the electron transfers of the respiratory chain, and as an antioxidant component in cell membranes and as a key component in the maintenance of the redox homeostasis of the cell [295-298]. The CNS has a very limited ability to incorporate ubiquinone from the diet and relies mainly on synthesis "in situ" [299].

FPP and GGPP can be converted to their correspondent alcohols farnesol (FOH) and geranylgeranyol (GGOH) by farnesyl and geranylgeranyl pyrophosphatases [300, 301]. Salvage pathways for the conversion of FOH and GGOH back to their pyrophosphate counterpart seem to exist in mammalian cells [302]. FOH and GGOH can also be formed by degradation of isoprenylated proteins in reactions catalyzed by prenylcysteine lyases, enzymes highly expressed in the brain [303]. FOH and GGOH may down-regulate HMGCR (Section 3.2.1 and Figure 3) (reviewed in [128]). The role of FOH and GGOH in protein prenylation is unclear. Some studies showed that mammalian cells utilize exogenously supplied FOH and GGOH for protein isoprenylation and, when mevalonate biosynthesis is blocked by statins, free FOH and GGOH can restore the pools of FPP and GGPP, although FOH may not be converted to GGPP [302, 304, 305]. The use of FOH and/or GGOH for protein prenylation might occur preferentially under conditions of reduced FPP and GGPP production from mevalonate [306]. Contrary to the existence of a salvage pathway that uses FOH and GGOH for protein prenylation, it was demonstrated that overexpressing phosphatases that convert FPP and GGPP to FOH and GGOH in mammalian cells, decreases rather than increases protein isoprenylation (as evaluated by a decreased of Rho protein level in cell membranes) and results in defects in cell growth and cytoskeletal organization that are associated with dysregulation of Rho family GTPases [301]. Moreover, work in cancer cells proposed that GGOH would reduce protein prenylation by down-regulating HMGCR leading to a shortage of FPP and GGPP [307]. Whether any of these mechanisms take place in the brain is uncertain. FOH is present at physiologically relevant concentrations in the brain of rodents and humans, where it may act in the regulation of brain Ca^{2+} homeostasis and neurotransmitter release by inhibiting N-type Ca^{2+} channels [308]. FOH has been shown to modulate the activity of the farnesoid X receptor (FXR), a member of the nuclear hormone receptor superfamily [309].

3.4.1. Non-sterol isoprenoids and protein prenylation

FPP and GGPP are substrates for protein farnesylation and geranylgeranylation (collectively called isoprenylation). In the human genome, there are approximately 300 hypothetical prenylated proteins [310]. Among them heterotrimeric G protein subunits, nuclear lamins and small GTPases have been confirmed to be prenylated [311]. Small GTPases represent the largest group of prenylated proteins. All small GTPases are able to specifically bind GDP and GTP,

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being inactive when bound to GDP (cytosolic location) and active when bound to GTP (membrane location). They also have an intrinsic GTPase activity to hydrolyze bound GTP to GDP and phosphate (Pi) [312]. FPP and GGPP are covalently attached via thioester linkage to C-terminal cysteine residues in the context of a prenylation motif. Farnesylation is catalyzed by farnesyl protein transferase (FTase), whereas GGTase-I and geranylgeranyl transferase type II (GGTase II) or RabGGTase catalyze the addition of GGPP to specific subsets of proteins [313-315] (Figure 5). FTase and GGTase I are responsible for posttranslational lipidation of proteins with C- terminal "CAAX" motifs, where C is cysteine, A is often an aliphatic amino acid, and X at the C-terminus determines the specificity of protein prenylation. When X is a methionine or serine, as in Ras proteins, then the protein is farnesylated by FTase. However, when X is a leucine residue, as in Rho proteins (e.g. Rac1, Cdc42, RhoA), or a phenylalanine residue, then the protein is geranylgeranylated by GGTase I [316, 317]. GGTase II catalyzes prenylation of Rab proteins, which contain at their C-termini either one or, more frequently, two cysteine residues, both of which are modified by geranylgeranyl groups [318, 319]. Protein prenyltransferase inhibitors, namely FTase inhibitors (FTIs) and GGTase inhibitors (GGTIs) have been developed and evaluated as anticancer agents.

The covalent attachment of the lipophilic isoprenyl group(s) enables prenylated proteins to anchor to cell membranes, which is an essential requirement for biological function [311]. The localization of small GTPases in distinct subcellular sites defines which signaling pathways they activate, thus defining their participation in disease. As an example, some singly prenylated Rabs are mistargeted and dysfunctional [320]. Inhibiting the membrane localization of small GTPases is a therapeutic strategy in cancer [321]. In addition, isoprenoid moieties are essential in the protein-protein interaction functions of prenylated proteins since they work as molecular handles that bind to hydrophobic grooves on the surface of soluble protein factors; these factors remove the prenylated protein from membranes in a regulated manner [322]. There is evidence that unprenylated versions of some proteins may also have physiological functional effects [323, 324] or may interfere with the activity of the isoprenylated proteins during disease [325, 326]. The requirement of prenylation for membrane association has also been recently challenged [327]. Prenylated proteins may undergo other posttranslational modifications such as palmitoylation, miristoylation and/or carboxymethylation [328].

The interest in understanding the regulation of isoprenoid production and protein prenylation in the brain has increased considerably in the past few years due to the importance of protein prenylation in several cellular processes such as cell growth, cytoskeletal organization and remodeling, and vesicle trafficking; and to the fact that some of the beneficial effects of statins in neurodegenerative diseases have been attributed to changes of protein prenylation [129, 329-334]. Non-sterol isoprenoids and protein prenyltransferases have emerged as attractive therapeutic targets for several diseases [321, 329] but we still need a deeper understanding of their roles in the brain in order to determine their value for treating neurodegeneration in general, and AD in particular.

Until recently, protein prenylation was considered to function constitutively. However, there is evidence that signaling cascades activated by druggable surface receptors affect prenylation of specific small GTPases by posttranslational modifications (e.g. phosphorylation) of unpre-

nylated versions of the protein [326], or by regulating protein prenyltransferases directly [335]. Prenyltransferases are expressed in the brain, which contains the highest activity of GGTase I [336]. GGTase I plays important roles in synapse formation, where it is activated through acetylcholine receptor clustering at the postsynaptic membrane [335]. The effects of GGTase I at the synapse were suggested to be due to geranylgeranylation of Rho GTPases, although prenylation was not directly examined. Neuronal depolarization and BDNF activated GGTase I and this activity was required for dendritic arborization in hippocampal neurons and Purkinje cells [337-339].

There is a growing body of evidence indicating that inhibition of protein prenyltransferases and inhibition of the mevalonate pathway to an extent that reduces the levels of FPP and GGPP, alter many mechanisms critical for normal brain function. When analyzing studies in which statins are used it is important to consider that different statins differ in terms of their potency, stability and ability to cross the BBB [329, 331, 340]. Studies on the effect of statins or protein prenyl transferase inhibitors on neurite (dendrites or axons) extension and branching provided conflicting results depending on the type of neurons, the class of statin used and the duration of the treatments. Some studies showed that statins or inhibitors of protein prenyltransferases enhanced neurite outgrowth, number, length and/or branching [341-344] while we and others, discovered inhibition of neurite outgrowth, extension or branching [345-347]. Statins decreased neurite initiation but increased neurite branching in neuroblastoma cells [348]. The field of AD research will benefit from a deeper understanding of the roles of non-sterol isoprenoids and protein prenylation in axon regrowth.

Under certain experimental conditions statins affect survival of neurons and neuron-like cells, acting through the decrease of non-sterol isoprenoids and protein prenylation. Lovastatin but not pravastatin induced apoptosis of rat brain neuroblasts and caused a significant reduction of the membrane pool of Ras and RhoA proteins, suggesting an impairment of protein prenylation as the result of reduced isoprenoid production [349]. Similarly, we found no effect of pravastatin on survival of sympathetic and cortical neurons at concentrations that significantly reduced cholesterol synthesis [106, 347, 350]. Under these conditions, however, pravastatin did not affect protein prenylation [106]. Statins induced stellation, followed by apoptosis in cerebellar astrocytes and cell death of cerebellar neurons [351]. These latter effects were independent of reduced cholesterol synthesis but were prevented by GGPP. A very interesting discovery from the work of Marz and colleagues [351] was that neuronal cell death was significantly reduced in astrocyte/neuron co-cultures treated with statins. The authors speculated that astroglia cells might provide neuroprotective signals, perhaps GGPP, against the damaging effects that result from downregulation the mevalonate pathway. This idea of communication between glia and neurons through intermediates of the mevalonate pathway is further discussed in Section 4.

Non-sterol isoprenoids and protein prenylation may play a role in inflammatory events in the brain since statins were able to activate microglia in cultured rat hippocampal slices [352], and inhibitors of protein prenyltransferases and statins caused a reduction of apoE secretion by cultured microglia and organotypic hippocampal cultures [353]. Contradictory evidence was reported on the role of non-sterol isoprenoids and protein prenylation in long-term potentia-

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tion (LTP), an experimental model to study the synaptic basis of learning and memory [354]. While inhibitors of FTase and GGTase I had no effects on LTP in one study [355], FPP depletion and farnesylation inhibition were implicated in the enhancement of the LTP magnitude in hippocampal slices [356].

In the majority of the studies the conclusion that the effects of statins were due to the reduction of non-sterol isoprenoids and protein prenylation resulted from experiments in which FPP, GGPP or their correspondent alcohols, but not cholesterol were able to prevent the particular effect [343, 345, 346, 348, 352, 353, 357]. It will be important however, to confirm that protein prenylation is impaired upon statin treatment, especially when the duration of the treatment is short such as in the studies by Mans et al. [356]. Different prenylated proteins have half-lives that vary between 4hs and 24hs and will be differentially affected. The time required for depletion of the non-sterol isoprenoids pools may also be tissue-or cell-specific. Only a few studies examined the effect of statins on protein prenylation directly and found decreased prenylation of specific proteins under specific experimental conditions [341, 346].

The Rho family of GTPases has received a lot of attention as the mediators of the effects that result from reduction of non-sterol isoprenoids and/or inhibition of protein prenyl transferases [335, 337, 338, 341, 346, 352, 358]. This family represents a major branch of the Ras superfamily, and like Ras and Rabs, Rho proteins (e.g., RhoA, Rac1, Cdc42) function as GTP/GDP switches and alternate between an active GTP-bound state and an inactive GDP-bound state. Members of the Rho family are farnersylated and/or geranylgeranylated through the action of GGTase I [359]. Rho GTPases are pivotal in the integration of extracellular and intracellular signals. They are key regulators of the actin cytoskeleton which plays essential roles in orchestrating the development and remodeling of spines and synapses [360, 361]. Precise spatio-temporal regulation of Rho GTPase activity is critical for their function. Aberrant Rho GTPase signaling due to mutations or other causes can cause spine and synapse defects resulting in abnormal neuronal connectivity and deficient cognitive functioning in humans [360, 361]. Recent findings indicate that Rho GTPases are key components of neuronal cell degeneration pathways [362]. A number of studies examined the localization of Rho proteins to the membranes as an indication of their prenylation status. A caveat of this approach is that some prenylated Rho proteins interact with the guanidine dissociation inhibitor RhoGDI, which keep prenylated Rho proteins in the cytosol in an inactive state [363]. RhoGDI expression is affected during disease [363]. A decreased in RhoA or Rac association with membranes has been observed upon treatment with statins or protein prenyltransferase inhibitors [337, 338, 341, 346, 352]. A decrease in GTP-bound forms of Rho family proteins was also detected upon statin or protein prenyltransferase inhibitor treatments [338, 343] Moreover, RhoA was identified as a modulator of statins effects by using an unbiased genome-wide filter approach that examine more than 10,000 genes to identify gene expression changes that correlated with altered expression of HMGCR [364].

Non-sterol isoprenoids and protein prenylation not only determine the targeting of prenylated proteins to membranes, but also regulate the expression of a subset of prenylated proteins in a protein-specific manner [365, 366]. Depletion of mevalonate or treatment with protein prenyltransferase inhibitors resulted in up-regulation of Ras, Rac1, RhoB, Rab5 and Rab7 [365, 367-369]. The increase occurs at the levels of mRNA and protein in most cases, and both

unprenylated and isoprenylated forms of the proteins accumulate [365]. Reduction of non-sterol isoprenoids decreases protein degradation, including that of already isoprenylated proteins, which suggests the existence of regulatory mechanisms to sustain levels of isoprenylated proteins under conditions that would otherwise limit protein isoprenylation [370]. FPP or GGPP prevented protein up-regulation [367, 370] by transcriptional and posttranscriptional mechanisms still unidentified but independent of protein prenylation [370]. In the case of Rab proteins it has been proposed that the membrane pool of Rabs, which decreases upon depletion of GGPP, may serve as an intracellular signal for Rab expression regulation [369].

3.4.2. Regulation of enzymes of non-sterol isoprenoids pathway

FPPS is transcriptionally regulated by SREBP-2 [66, 371] and LXR [372]. A LXR response element sequence exists in the FPPS promoter overlapping with the SREBP-2 response element [372]. LXR activation of FPPS occurs under high cholesterol levels, thus SREBP-2 processing is inhibited. In this way LXR could drive the expression of FPPS in order to maintain isoprenoid supply exclusively [372]. FPPS is post-translationally regulated by a product-feedback competitive inhibition as FPP (product) competes with GPP (substrate) for the active site [373, 374].

GGPPS does not seem to be transcriptionally regulated by SREBP-2 [66, 284, 375, 376]. GGPPS activity is inhibited by GGPP [373]. The crystal structure of human GGPPS demonstrated GGPP binding to a pocket/cavity away from the chain elongation site (active site) of GGPPS, suggesting a product-feedback allosteric inhibition [377, 378]. Mammalian GGPPS can catalyze the formation of FPP as well as GGPP [379].

3.4.3. Coordination of the post-squalene and non-sterol isoprenoids branches of the mevalonate pathway

Since cells have two alternative sources of cholesterol namely intracellular synthesis and uptake but only the intracellular synthesis provides non-sterol isoprenoids, the mevalonate pathway has to maintain the minimum requirement of isoprenoids at all times irrespective of cholesterol levels. Analysis of the affinity of the enzymes in the different branches of the pathway uncovers the mechanisms that mediate such regulation. The affinity of GGPPS for FPP (K_m value of 0.6 μM) [284] is much higher than the affinity of squalene synthase for FPP (Km value of ~15 μM) [380]. Moreover, both coenzyme Q and dolichol synthesis are saturated at a much lower concentration of isoprene intermediates than the concentration required to saturate cholesterol synthesis [381, 382]. Thus, under limited concentrations of mevalonate and FPP, the non-sterol isoprenoid branch will be favored. Furthermore, inhibition of the mevalonate production by statins will reduce FPP supply for the production of cholesterol first. Because of the very high affinity of protein farnesyl transferase for FPP (Km below 0.1 μM) [383], farnesylation is preserved under many statin treatments [297, 384] and would be favored over geranylgeranylation.

3.4.4. Non-sterol isoprenoid pathway in AD

Up-regulation of 6 out of 10 genes of isoprenoid metabolism was found in autopsied hippocampus of patients with incipient AD [105], which may represent an attempt to compensate the posttranslational inhibition of the mevalonate pathway during disease.

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Dolichol is decreased in all areas of the AD brain, especially those regions affected by the disease, and dolichol-P increases in brain regions that showed morphological changes [239, 385]. In the frontal cortex and in the hippocampus the concentration of dolichol decreased by as much as 45%. The increase in dolichol-P may reflect an increased rate of glycosylation in AD brain, which may be related to the formation of amyloid plaques. Changes in dolichol and dolichol-P in AD are opposite to those present during normal aging. The amount of dolichol in different regions of the human brain, but especially in the hippocampus, increases several folds with age in humans [239, 292, 386] and rats [387, 388]. An upper limit for dolichol accumulation in tissues seems to exist since after 70 years of age there is no further increase in dolichol concentration in human brains [239]. Dolichol is present in the brain as a family with 17-21 isoprene units. This pattern of dolichol lengths is unchanged during aging; however, there are regional differences [239, 386]. Levels of dolichyl-P are already high at the time of birth and only show a moderate increase, although it varies between different brain regions [292, 386].

With respect to ubiquinone, there is a significant elevation in most regions of AD brain [239], which may reflect a futile attempt to protect the brain from oxidative stress [385]. Interestingly, the pattern of ubiquinone is also reversed in AD when compared with normal aging. Brain ubiquinone is unchanged up to the age of 55 but decreases significantly in older age groups in areas where it concentrates in human brains, mainly the nucleus caudatus, gray matter, and hippocampus [239, 386]. This decrease may indicate a reduced anti-oxidative capacity in the aging brain. Thus, when considering dolichol, dolichol-P and ubiquinone, AD cannot be regarded as a result of premature aging.

3.4.5. FPP, GGPP and protein prenylation in AD

There is limited information with respect to levels and regulation of FPP and GGPP in normal and AD brains. Recent studies showed that GGPP, FPP, and the mRNA of their respective synthases, FPPS and GGPPS, were elevated in brains of 13 male patients with AD [169], in brains of aged mice [129, 287] and in neuroblastoma SH-SY5Y cells expressing APP695 [389]. The significance of this elevation is still unknown because protein prenylation was not examined in these studies, and elevation of isoprenoids does not warrant an increase in protein prenylation. Indeed, even when GGPP levels were elevated in the aging mouse brain, the pools of Rac1, RhoA and Cdc42, associated to membranes were decreased, while Rab proteins had a mixed behavior [287]. The reduction of the subunit β of GGTase I in the aging brain may be responsible for the decreased prenylation.

The roles of non-sterol isoprenoids and protein prenylation in AD have been identified mainly by using statins and inhibitors of protein prenyltransferases. FPP, GGPP and prenylated proteins are involved in diverse processes important in AD pathology including APP metabolism, LTP and synaptic plasticity, Aβ toxicity, and oxidative stress.

The effects of statin-induced non-sterol isoprenoids depletion or inhibition of protein prenyltransferases on APP/Aβ metabolism are complex. In some cases treatment with statins or a FTase inhibitor stimulated the shedding of APP and the production of sAPPα in neuroblastoma cells overexpressing APPswe [390], while in other cases statins reduced the release of

Aβ from cells but increased the intracellular accumulation of APP and Aβ, in a process prevented by GGPP [391, 392]. The proteins affected by shortage of non-sterol isoprenoids, and responsible for the regulation APP/Aβ metabolism have been identified or proposed. The increase in APP shedding was mediated by RHO proteins [390]. Rho was also suggested to be responsible for the reduction of brain Aβ levels in the AD CRND8 mouse treated with statins, although there was no direct evidence that isoprenylation was affected [393]. The accumulation of APP and Aβ within neurons that received statins was due to decreased delivery of Rab proteins to cell membranes [392]. It is known that Rabs participate in intracellular APP trafficking and processing [394]. A study of mice treated with statins has shown significant reduction of brain levels of Aβ and the C-terminal fragments (CTFs) due to enhanced trafficking of APP-CTFs to the lysosomes for degradation [395]. The authors suggested that the process may involve a decrease in isoprenoids, and would be mediated by Rabs. However, Rab prenylation was not measured in this study and the conclusion of the involvement of isoprenoids resulted from experiments in cultured neurons in which mevalonate prevented the changes in trafficking. Unless the concentration of mevalonate is titrated to recover specifically the non-sterol isoprenoid pathway, mevalonate would also affect cholesterol levels. The regulation of APP cleavage and Aβ production by non-sterol isoprenoids and protein prenylation also involved APP secretases, although it is unclear if the decrease or the increase in isoprenoids and protein prenylation favors amyloidogenic processing of APP. Inhibition of farnesylation reduced the association of the β-secretase enzyme BACE1 with APP (although BACE itself is not farnesylated) and resulted in a dose-dependent decrease in Aβ release and production within the cell [396]. Moreover, statins caused inhibition of β-secretase dimerization into its more active form, which may be a mechanism of the reduction in Aβ production [397]. Statins also significantly decreased the association of the γ-secretase complex with lipid rafts and GGOH prevented this [398]. Contrary to this notion, in a separate study statins induced an increase of BACE levels in neurons, which was linked to the increase in Aβ production [391]. GGOH, GGPP and FPP increased Aβ production by targeting γ-secretase [399-401] but there is no consensus if this effect is dependent [401] or independent [400] of protein prenylation.

Aβ production is not significantly altered in sporadic forms of AD, which represent approximately 95% of cases [402-404]. Instead, defects in Aβ removal may be key in the development of sporadic AD [405, 406]. Statins and an FTase inhibitor promoted degradation of extracellular Aβ by microglia by stimulating the secretion of IDE (insulin degrading enzyme), an enzyme that degrades Aβ in the brain [407]. The secretion of IDE from peripheral organs into the circulation was also increased in mice treated with statins [407]. Moreover FTase but not GGTase I haplodeficiency in the APPPS1 mice increased steady-state levels of IDE [408]. The mechanisms by which farnesylation may regulate IDE secretion, are still unclear.

We have discovered that in neurons challenged with oligomeric $A\beta_{42}$, and in the cortex of the AD mouse CRND8, prenylation of Rabs and Ras proteins were reduced [106]. Since the deficit in protein prenylation induced by Aβ was prevented by GGPP we concluded that protein prenylation inhibition was due to a shortage of GGPP. More importantly GGPP was able to prevent Aβ-induced neuronal death.

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Non-sterol isoprenoids have been associated with the regulation of neuroinflammation in AD. The role of inflammation in the AD brain is well known. The pro-inflammatory response mediated mainly by microglial may exacerbate and drive the pathogenic processes leading to neuronal loss. Microglia activation may occur as a response to Aβ accumulation in the brain. Statins inhibited the production of IL-1β by monocytes after stimulation with Aβ, in a process that is independent of cholesterol but prevented by GGPP [409]. The effect was mimicked by a GGTase I inhibitor and by inactivation of Rho proteins. Statins also induced cholesterol-independent inhibition of ROS production after stimulation with Aβ [409]. Statin treatment of microglia resulted in perturbation of the cytoskeleton and morphological changes due to alteration in Rho family function [410].

During the course of AD, tau is hyper-phosphorylated, detaches from the microtubules, and aggregates in the somatodendritic compartment in NFTs [411, 412]. There is very limited information about the existence of any relationship between tau pathology and isoprenoids and/or protein prenylation. Statins caused changes in tau phosphorylation that were characteristic of those observed in preclinical stages of AD [413]. These changes were mimicked by GGTase I inhibitors and compensated by GGPP suggesting that decreased prenylation of a Rho family member may be involved. The dose of statins seems to be critical in the effects on tau. In a cellular model of tauopathy, and in primary neurons, low-to-moderate doses of statins, reduced total and phosphorylated tau levels but high doses activated caspase 3 and increased levels of caspase-cleaved tau, which may facilitate tau Aβ toxicity/apoptosis [414]. A decrease in membrane localization of several small GTPases occurred concomitantly with tau reduction and GGPP reversed statin-induced decreases in tau levels. The authors focused their attention on RhoA, speculating that the statin-induced decrease in phosphorylated tau was caused by glycogen synthase kinase 3β (GSK3β) inactivation through RhoA [414].

Some recent work in genetically modified mice supported the concept that non-sterol isoprenoids and protein prenylation may have a detrimental role in AD and suggested that inhibition of protein prenylation could be a potential strategy for effectively treating AD. The increase of isoprenoids and protein prenylation has been suggested (although not tested) to contribute to tau pathology in a transgenic APP/PS1 mouse that constitutively overexpresses (P)SREBP-2 [415]. In a different mouse model the expression of protein prenyltransferases was genetically modified in order to reduce protein prenylation independent of non-sterol isoprenoids. Heterozygous deletion of FTase reduced Aβ deposition and neuroinflammation and rescued spatial learning and memory function in APPPS1 mice. Heterozygous deletion of GGTase I reduced the levels of Aβ and neuroinflammation but had no impact on learning and memory [408]. These studies in vivo are exciting but will benefit from direct measurement of brain levels of isoprenoids or protein prenylation. Based on the complex regulation of isoprenoid production, it will be important to determine if brain isoprenoid levels change in these mice since the existence of negative-feedback regulatory mechanisms downstream SREBP-2, argue that increased levels of active SREBP-2 does not warrant an increase in non-sterol isoprenoids.

A few prenylated proteins have been linked to AD. The contributions of Rho GTPases to AD are of particular interest. Rho-family GTPases are key proteins that integrate extracellular and intracellular signals. They are important regulators of the actin cytoskeleton that play essential

roles in orchestrating the development and remodeling of spines and synapses [360, 361]. Precise spatio-temporal regulation of Rho GTPase activity is critical for their function. Aberrant Rho GTPase signaling due to mutations or other causes can cause spine and synapse defects resulting in abnormal neuronal connectivity and deficient cognitive functioning in humans [360, 361]. Deregulation of RhoGTPases may contribute to dendritic spine loss during AD and might be a key pathogenic event contributing to synaptic deficits in AD (reviewed in [362, 416]). RhoA protein was lower in the AD brain hippocampus, reflecting the loss of the membrane bound, presumably active, GTPase [417]. Rab proteins regulate intracellular membrane trafficking, motility and fusion [418]. In the nervous system Rabs participate in important processes such as axonal endocytosis, retrograde transport of growth signals, synaptic function, and polarized neurite growth [419]. Rab5 and Rab7 protein levels were upregulated within basal forebrain, frontal cortex, and hippocampus but not in the less vulnerable cerebellum and striatum in MCI and AD [420, 421]. Importantly, this upregulation correlated with cognitive decline and neuropathological criteria for AD. The increase of Rab7 and Rab5 in AD brains has been interpreted as overactivation of the endosomal pathway. In addition increased levels of Rab7 have been found in cerebrospinal fluid (CSF) from AD patients and may represent a novel AD CSF biomarker [422]. Evidence from our laboratory demonstrated increased levels of Rab7 in Aβ-treated neurons and in the cortex of CRND8 mice [107]. Rab-6 was increased in AD brain, and correlated with ER stress [423]. The increased level of Rab6 in AD was unable to protect against ER stress, suggesting that Rab6 is non-functional. Based on our discoveries, we anticipate that Rab6 prenylation may be decreased. Since the number of proteins that are prenylated is high and considering that a reduction of non-sterol isoprenoids or the inhibition of protein prenyltransferases will affect several prenylated proteins, the challenge in the next years will be to identify which prenylated proteins are affected in AD.

4. Conclusions

The analysis of the mevalonate pathway in AD reveals dysregulation. The abnormalities not only affect cholesterol but also non-sterol isoprenoids. There is a reciprocal regulation between Aβ and cholesterol at the subcellular level [11]. The evidence discussed here suggest that similar reciprocity may exist between Aβ and non-sterol isoprenoids such that isoprenylation determines the levels of intracellular Aβ [391, 392] and Aβ inhibits the mevalonate pathway causing reduction of non-sterol isoprenoid levels and protein prenylation [106]. The dysregulation of the mevalonate pathway in AD may affect neurons and glia in different ways. Our findings suggest that inhibition of the mevalonate pathway will take place specifically in cells that accumulate Aβ, most likely neurons. Depending on the size of the cell population that contains intracellular Aβ, this might or might not impact the overall content of cholesterol and isoprenoids in the brain. The decreased synthesis of cholesterol in neurons may be compensated by synthesis in astrocytes [21]. In addition, an interesting model has been proposed in which SREBPs in astrocytes would be involved in synthesis of fatty acids and perhaps other lipids for neuronal supply [424]. According to this model, glia SREBPs may work as control points of neuronal function, providing neurons with appropriate lipids when neurons cannot

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make their own. The shuttle of non-sterol isoprenoids and 25-EC from astrocytes to neurons has been suggested [206, 351]. These possible homeostatic mechanisms should be taken in consideration when brain levels of lipids are analyzed. The increase of non-sterol isoprenoids in AD brains, if confirmed in a larger cohort, may represent an astrocytic attempt to compensate for the decrease in SREBP-dependent metabolic pathways in neurons. Compensatory attempt mechanisms in brain cholesterol homeostasis in AD have been described before. The amount of CYP46, the enzyme that converts cholesterol into 24-HC decreases in neuronal cells in AD brains, but this decrease is at least in part compensated for by an induction of the enzyme in glial cells [425]. In conclusion, our knowledge on the impairment of the mevalonate pathway in AD is still very limited. The extremely complex regulation of this pathway represents a challenge for the complete understanding of the defects present during AD. Defects at the cellular level are important but ultimately we need to comprehend how the interaction neuron-glia regulates the mevalonate pathway in the brain.

5. Abreviations

24-HC: 24(S)-hydroxycholesterol; **25-HC**: 24(S),25-epoxycholesterol; **7-DHC**: 7-dehydrocholesterol; **ABC**: adenosine triphosphate-binding cassette transporter; **ACAT**: acyl coA-cholesterol acyltransferase; **AD**: Alzheimer's disease; **AMPK**: adenosine monophosphate-activated protein kinase; **apoE4**: apolipoprotein E ε4; **Aβ**: amyloid-beta peptide; **BACE-1**: beta-site APP cleaving enzyme 1; **BBB**: blood-brain-barrier; **CNS**: central nervous system; **CoA**: coenzyme A; **CSF**: cerebrospinal fluid; **CYP46A1**: 24-hydroxylase; **DHCR24**: 24-dehydrocholesterol reductase; **DMPP**: dimethylallyl pyrophosphate; **DOS**: dioxidosqualene; **FOH**: farnesol; **FPP**: farnesyl pyrophosphate; **FPPS**: FPP synthase; **FTase**: farnesyl protein transferase; **GDP**: guanosine diphosphate; **GGOH**: geranylgeraniol; **GGPP**: geranylgeranyl pyrophosphate; **GGPPS**: GGPP synthase; **GGTase-I**: geranylgeranyl transferase type I; **GPP**: geranyl pyrophosphate; **HMG**: 3-hydroxy-3-methylglutaryl-CoA; **IDE**: insulin degrading enzyme; **Insig**: insulin-induced gene; **IPP**: isopentenylpyrophosphate; **LTP**: long-term potentiation; **LXR**: liver-X-receptor; **MCI**: mild cognitive impairment; **MK**: mevalonate kinase; **MOS**: monooxidosqualene; **NFT**: neurofibrillary tangle; **NPC**: Niemann-Pick type C; **REST**: RE1-silencing transcription factor; **SCAP**: SREBP-cleavage activating protein; **SR**EBP: sterol-regulatory element binding protein; TRP: transient receptor potential

Author details

Amany Mohamed[1,2], Kevan Smith[1,2] and Elena Posse de Chaves[1,2*]

*Address all correspondence to: elena.chaves@ualberta.ca

1 Department of Pharmacology, University of Alberta, Edmonton, AB, Canada

2 Neuroscience and Mental Health Institute, University of Alberta, Edmonton, AB, Canada

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