REVIEW

The new genetic landscape of Alzheimer's disease: from amyloid cascade to genetically driven synaptic failure hypothesis?

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Abstract

A strong genetic predisposition (60–80% of attributable risk) is present in Alzheimer's disease (AD). In view of this major genetic component, identification of the genetic risk factors has been a major objective in the AD field with the ultimate aim to better understand the pathological processes. In this review, we present how the genetic risk factors are involved in APP metabolism, β-amyloid peptide production, degradation, aggregation and toxicity, innate immunity, and Tau toxicity. In addition, on the basis of the new genetic landscape, resulting from the recent high-throughput genomic approaches and emerging neurobiological information, we propose an over-arching model in which the focal adhesion pathway and the related cell signalling are key elements in AD pathogenesis. The core of the focal adhesion pathway links the physiological functions of amyloid precursor protein and Tau with the pathophysiological processes they are involved in. This model includes several entry points, fitting with the different origins for the disease, and supports the notion that dysregulation of synaptic plasticity is a central node in AD. Notably, our interpretation of the latest data from genome wide association studies complements other hypotheses already developed in the AD field, i.e., amyloid cascade, cellular phase or propagation hypotheses. Genetically driven synaptic failure hypothesis will need to be further tested experimentally within the general AD framework.

Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disorder and constitutes a major public health problem worldwide (with 35.6 million sufferers). AD causes memory loss and cognitive impairment, which are invariant early signs of the disease. Hippocampal atrophy due to neuronal death is one of the earliest hallmarks of AD. Preceding neuronal death, synaptic dysfunction and synapse loss have been observed in post-mortem AD brains and are correlated with cognitive decline [28]. AD is characterised by the coexistence of two main pathological lesions: (1) intraneuronal neurofibrillary tangles composed of abnormally modified Tau proteins and (2) parenchymal amyloid deposits centred around β-amyloid (Aβ) peptides. The discovery of rare mutations in *APP*, *PSEN1* and *PSEN2* causing autosomal dominant forms of the disease gave rise to the amyloid cascade hypothesis, which radically changed our understanding of AD [46]. Systematic association of pathogenic mutations with altered amyloid precursor protein (APP) metabolism and with the overproduction of longer Aβ peptides in particular—which are believed to be more neurotoxic—suggest that these peptides are at the heart of the disease process. Overproduction of these neurotoxic peptides may lead to (or accentuate) the neuron-to-neuron propagation of Tau pathology by a still unknown mechanism [20]. However, since monogenic forms represent less than 1% of all AD cases, crucial questions can be raised: (1) is the amyloid cascade hypothesis central to all forms of AD? (2) Are other pathophysiological processes involved in late-onset non-Mendelian forms of AD?

Within this context, understanding the genetics of the most common forms of AD would improve our knowledge of the underlying pathophysiological processes. Indeed, genetic risk factors account for up to 80% of attributable risk in these common forms [30]. One can thus argue that the vast majority of the AD pathophysiological pathways

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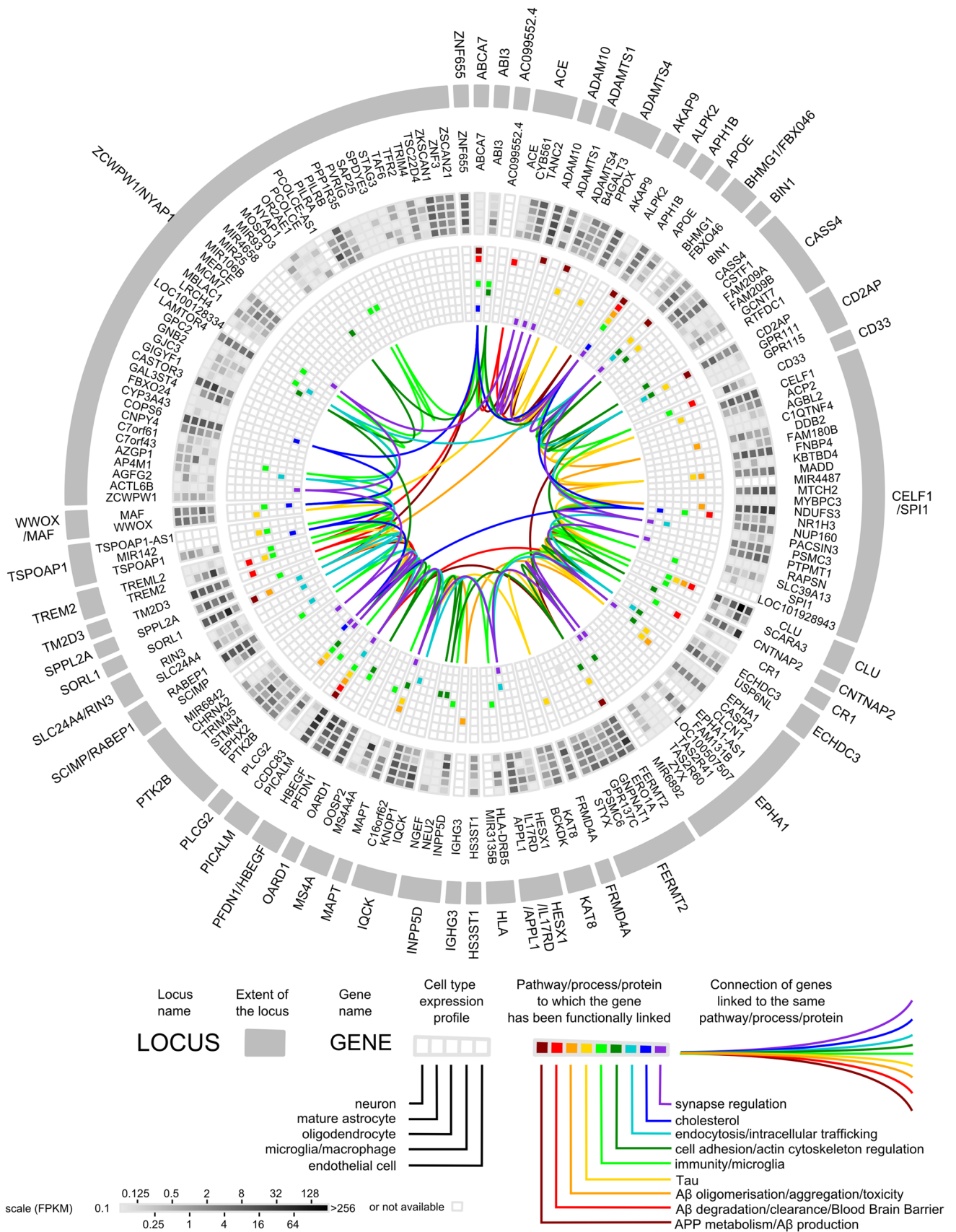
are driven by or include genetic determinants. Accordingly, describing these genetic determinants should improve our understanding of the fundamental disease processes. In this review, we present the latest advances in AD genetics and in the post-genome wide association studies (GWASs) era, and discuss how these information might change our understanding of the AD pathophysiological processes.

Genetic landscape of AD

Over a 16-year period (from 1993 to 2009), the Apolipoprotein E (*APOE*) gene was the only genetic risk factor identified for AD. The association of the *APOE* ε4 allele with AD risk has been repeatedly demonstrated, whereas the ε2 allele was associated with a protective effect [71]. *APOE* is estimated to account for 20% of the AD attributable risk, and the *APOE*-associated risk is similar to those identified for major genes in other Mendelian diseases, such as *BRCA1* in breast cancer [31]. Despite testing more than 500 candidate genes for their association with AD risk [79], we had to wait for the development of GWAS to advance the AD genetics field: since the seminal GWAS papers published in 2009 [47, 83], more than 30 loci of interest have been identified to be associated with AD risk (Suppl. Table) [50, 59, 67, 76, 84, 97, 116, 120]. Additionally, several analyses of higher complexity have been developed based on these GWAS datasets, allowing the identification of additional genes of interest (Suppl. Table) [10, 41, 67, 82].

Over the same period, next generation sequencing (NGS) has been developed and became applicable to multifactorial diseases due to remarkable cost decreases. NGS allowed the identification of rare variants in *TREM2* as major genetic risk factors for AD [39, 65]. In addition, these methodologies demonstrated that both *SORL1* and *ABCA7* genes—already detected by GWAS—carried numerous loss-of-function variants leading to strong increases in AD risk [9, 98, 128]. Finally, the Alzheimer's disease sequencing project (ADSP) recently published its first results based on whole exome sequencing analysis, encompassing more than 5000 AD cases and controls, and reported two new candidate genes, *IGHG3* and *ZNF655* (Suppl. Table) [11].

Together, these genetic analyses have pointed out more than 45 genes/loci associated with the risk of developing AD even if it is estimated that a large part of the genetic component of AD is still unknown [103]. In addition, it is essential to keep in mind that for some loci, it is difficult—if not impossible—to determine the gene responsible for the observed association, due to the presence of multiple genes in the locus and the complex linkage disequilibrium patterns involving the sentinel single-nucleotide polymorphism. Nevertheless, it is now possible to start drawing a general landscape of what the genetics is telling us. According to multiple post-genomic analyses performed in cellular and animal models, this landscape already appears to be highly complex (Fig. 1).

## The post-GWAS era and the amyloid cascade hypothesis

As previously mentioned, the identification of familial AD-linked mutations in the genes for APP, PS1, and PS2, associated with the dysregulation of Aβ peptide production has suggested that APP metabolism is at the heart of the disease process. Three main proteases (α-, β- and γ-secretases) are involved in APP processing through (1) the amyloidogenic pathway (β- and γ-secretases), which promotes Aβ production, and (2) the non-amyloidogenic pathway (α- and γ-secretases), which prevents Aβ production by cleaving APP within the Aβ sequence. In addition to secretase activity, APP trafficking by the secretory pathway is also an essential factor in APP metabolism. APP is first matured in the endoplasmic reticulum and the Golgi apparatus, and then transported to the cell surface. Alternatively, APP can end up in the lysosomal pathway and undergo proteolytic degradation [115]. Naturally, it has been rapidly proposed that GWAS-defined genes may have a role in APP metabolism, especially since gene-set enrichment analyses performed on GWAS datasets identified specific pathophysiological pathways—among others—involved in APP processing and in the regulation of endocytosis, which is central for APP metabolism (Fig. 2) [63, 76, 81].

APP metabolism and Aβ peptide production

Very recent GWASs have strengthened the importance of APP metabolism by directly pointing out two of its main actors as AD genetic risk factors: ADAM10, which carries out the main α-secretase activity in the brain, and APH1B, which is part of the γ-secretase complex [59, 76].

Based on pathway enrichment analyses, three GWAS-defined genes linked with endocytosis (*BIN1*, *CD2AP* and *PICALM*) have been proposed to modulate APP metabolism and the subsequent increase in Aβ production: the best

Fig. 2 Amyloid cascade hypothesis and genetic risk factors of AD. Autosomal dominant mutations that cause early onset familial AD (in *APP*, *PSEN1* and *PSEN2*) gave rise to the amyloid cascade hypothesis, which aims to link amyloid plaques and neurofibrillary tangles, the two classical AD hallmarks. Involvement of the genetic risk factors of late-onset AD in APP metabolism and in Aβ clearance through the blood brain barrier or microglia supports this hypothesis. Soluble forms of Aβ may be inducing neurotoxicity through modifying Tau metabolism, leading to neurofibrillary tangle formation and neuronal death. Recent GWAS-defined genes that modulate Tau toxicity may be involved in Aβ-induced neurotoxicity through mechanisms that are yet to be identified
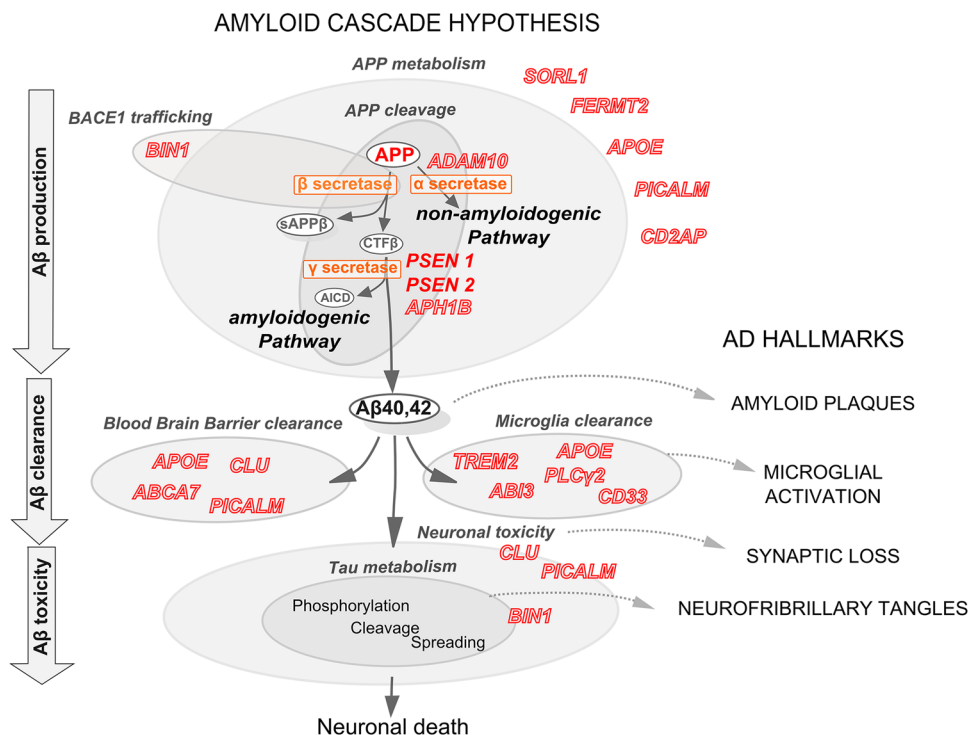
characterised function of BIN1 is its role in endocytosis, where it interacts with several proteins associated with clathrin-coated pits and endosomal sorting [99]. BIN1 depletion was associated with an increase in intracellular Aβ$_{42}$, potentially through the regulation of the β-secretase (BACE1) trafficking and accumulation in early endosomes [91, 137]. CD2AP, which is also a regulator of endosome trafficking, has been reported to control Aβ production in neurons. CD2AP depletion leads to the trapping of APP in early endosomes and the subsequent increase in Aβ [137]. However, despite these effects on Aβ production in vitro, deleting a single *BIN1* or *CD2AP* allele did not modify amyloid deposition in mouse models of AD [2, 87]. Nevertheless, it is worth noting that abnormal accumulation of insoluble BIN1 has been detected in the vicinity of amyloid plaques in different mouse models [107]. Finally, PICALM, which is also directly involved in endocytosis, has been linked to APP metabolism: PICALM underexpression decreases the levels of several APP catabolites, such as intracellular β-C-terminal fragment (β-CTF) and secreted sAPPβ, which has been attributed to its role in clathrin-mediated endocytosis [134]. Accordingly, PICALM underexpression results in reduced APP internalisation and Aβ generation [148]. As opposed to BIN1 and CD2AP, PICALM knockdown and overexpression, respectively, decreased and increased amyloid plaque loads in the hippocampi of 6-month-old APP/PS1 mice [148]. Alternatively, PICALM has been proposed to participate in the APP-CTF degradation through autophagy [135].

In addition to these three genes that are known to be directly involved in endocytosis, ABCA7 underexpression induced faster APP endocytosis, consistent with increased Aβ production in vitro and accelerated the amyloid pathology in young transgenic mice [111]. Finally, ApoE4 has been described as a potential enhancer of amyloid peptide production through stimulating APP endocytosis and metabolism, both in vitro and in vivo [48, 49].

Apart from the genes susceptible to control APP/BACE1 availability in early endosomes through the modulation of endocytosis, other GWAS-defined genes have been shown to modulate APP metabolism through affecting APP sorting from endosomes. Kindlin-2 (product of *FERMT2*) underexpression has been described to promote the recycling of full-length, mature APP from early/late endosomes into the plasma membrane. This may thus favour Aβ production by increasing the pool of full-length APP likely to be cleaved by α-, β- and γ-secretases, rather than to be degraded in lysosomes [17]. SORL1 underexpression has also been associated with an increase in Aβ production by blocking the redirection of endocytosed APP to the trans-Golgi network, which reduces APP processing in endosomes [113, 144, 152]. Alternatively, it has been suggested that SORL1 loss-of-function may decrease the degradation of intracellular Aβ by lysosomes [13].

In conclusion, post-GWAS analyses seem to place numerous GWAS-defined genes in the APP metabolism landscape, deeming its importance in late-onset AD. Remarkably, while the dysregulation of APP metabolism is believed to mainly

occur in neurons, ADAMTS4, exclusively expressed in oligodendrocytes, has been recently reported to produce strongly aggregating Aβ forms [139]. In fact, ADAMTS4 has been very recently reported as an AD genetic risk factor [59], suggesting that multiple cell types participate in Aβ production in AD.

Aβ peptide degradation/clearance

Beyond Aβ production, which is of course a major factor controlling Aβ bioavailability and potential toxicity, modulation of Aβ aggregation and/or degradation/clearance has been proposed to be essential for Aβ toxicity. The initial GWAS data rapidly led to a reappraisal of the amyloid cascade hypothesis based on Aβ accumulation and toxicity in both familial and early onset forms of AD where Aβ peptides rapidly accumulate due to their accelerated overproduction (e.g., associated with mutations in *APP*, *PSEN1* and *PSEN2*), and in late-onset forms, due to a slight, insidious Aβ clearance impairment (associated with several GWAS-defined genes) [80].

In this view, consistent evidence strongly suggest that ApoE regulates extracellular Aβ clearance in the brain [71]. In animal models, Aβ–ApoE2 and Aβ–ApoE3 complexes are cleared by the blood brain barrier (BBB) at a substantially higher rate than Aβ–ApoE4 complexes [23]. ApoE binds to a group of structurally related proteins known as the low density lipoprotein receptor (LDLR) family. LDLR overexpression dramatically enhanced Aβ clearance from the brain's extracellular fluid and reduced Aβ aggregation [72]. CLU, which is one of the most abundantly expressed apolipoproteins in the central nervous system (like ApoE) [106], participates in Aβ clearance, principally of the highly pathogenic Aβ$_{42}$ peptide, from the brain across the BBB [24]. More recently, PICALM has been described in vitro and in vivo to participate to Aβ transcytosis and clearance at the BBB through clathrin-dependent internalisation of Aβ after its binding to the LDLR-related protein-1 [157]. ABCA7 is also potentially involved in amyloid clearance at the BBB [78]. Finally, a peripheral Aβ clearance mechanism involving CR1 in human erythrocytes has been proposed to be impaired in AD cases [105].

However, beyond these potential BBB and peripheral clearance mechanisms, microglia dysfunction has also been suspected to be involved in AD through modulating Aβ aggregation/degradation [45]. Indeed, several genomic analyses suggest the involvement of microglia in AD: (1) the first reports on pathway enrichment analyses indicated the involvement of innate immunity in AD [81]; (2) as previously mentioned, these analyses highlighted the regulation of endocytosis (which is essential for phagocytosis) [64, 81]; (3) a large part of GWAS-define genes are expressed in microglia [45] (Fig. 1); and (4) a major genetic discovery

indicated that non-synonymous variants in *TREM2*, *ABI3* and *PLCγ2* were associated with AD risk [40, 65, 120]. In the brain, these three genes are almost exclusively expressed in microglia and participate in the same protein–protein interaction network [120]. In addition *SPI1* carrying a common variant associated with a decreased AD risk encodes the PU.1 transcription factor, which is a key player in microglia development [56].

Apart from ApoE [118], TREM2 is the most studied genetic risk factor in the context of the microglia-dependent pathophysiological process in AD. TREM2 has been proposed to be protective, since the AD-associated mutations (R47H, R62H) likely impair its physiological functions at two levels: (1) phagocytosis and clearance of Aβ peptides and (2) compaction of amyloid plaques and barrier formation. In AD-like transgenic mice models, TREM2 knockdown is associated with increased amyloid loads [60, 141]. TREM2-deficient microglia show reduced uptake of Aβ complex in vitro and less Aβ internalisation in vivo [150, 154]. Importantly, microglial uptake of Aβ is more efficient when TREM2 forms complexes with lipoproteins such as ApoE or CLU [132, 150] and TREM2–lipoprotein interaction is impaired by R47H and R62H mutations [3, 4]. Furthermore, microglia have been recently suggested to form a protective barrier around amyloid deposits by compacting amyloid fibrils into a potentially less toxic form [154]. This protective mechanism appears to be less efficient in AD-like models underexpressing TREM2. In addition, in the brains of humans with R47H TREM2 mutation, microglia present a markedly reduced ability to envelop amyloid deposits [154]. Again, one can suspect a protective mechanism linking ApoE and TREM2, since ApoE is also involved in the compaction of the protofibrillary Aβ into dense plaques [5, 6].

Among other GWAS-defined genes, very few have been analysed in the microglia context, and only CD33 has been described to inhibit Aβ uptake by microglia [37]. In conclusion, there is no longer any doubt that microglia participate to AD pathogenesis, potentially reinforcing the amyloid cascade hypothesis through Aβ peptide clearance and or/ compaction.

Aβ peptide toxicity

According to the amyloid cascade hypothesis, Aβ peptides are neurotoxic and supposed to lead to or accentuate neuron-to-neuron propagation of Tau pathology—leading to neuronal death—by a still unknown mechanism [20]. Beyond ApoE, which has been reported as a potential modulator of Aβ toxicity (see reviews [51, 131]), little has been done to determine whether other GWAS-defined genes are involved in Aβ toxicity. RNAi knockdown of *amph-1* and *unc-11* (orthologs of *BIN1* and *PICALM*, respectively) in transgenic *C. elegans* over-expressing Aβ$_{42}$ in body wall muscle cells

significantly delayed paralysis due to $A\beta_{42}$ toxicity [95]. However, no molecular mechanism has been proposed so far to explain these findings. CLU has also been associated with the regulation of $A\beta$ toxicity, where its knockdown leads to reduced toxicity through the involvement of Wnt-PCP-JNK pathway [70]. In conclusion, $A\beta$ toxicity needs to be explored in the view of the new genetic landscape.

Beyond Aβ peptides and the APP metabolism

Although the data described above clearly support the amyloid cascade hypothesis, it is necessary to keep in mind that the biological characterization of GWAS-defined genes was initially done by assessing their impacts on models specifically developed for this hypothesis. There is, therefore, a significant bias, potentially leading to tautological reasoning and a priori exclusion of other, potentially important pathophysiological pathways. This is especially true since most GWAS-defined genes are involved in major cell signalling pathways and have pleiotropic functions, which are poorly evaluated using in vitro and in vivo models with specific read-outs. In addition, the functions of these genes are often not fully understood, and some of these unknown functions may be essential for their involvement in AD pathophysiology. This is also true for the most recognized actors of AD pathophysiology, such as APP or Tau. For instance, our knowledge of APP's physiological functions are still very fragmented and often revolve about $A\beta$ toxicity, while ignoring the potential functions of APP other than producing $A\beta$. Furthermore, APP metabolism produces other catabolites with roles potentially as important as that of $A\beta$. Our knowledge on the role of Tau in AD is also fragmented. We are thus unable to explain how $A\beta$ peptides—despite being a part of the amyloid cascade—may participate in the neuron-to-neuron propagation of Tau pathology [20]. In conclusion, the impact of GWAS-defined genes on AD pathophysiology has so far been mostly studied in the context of the amyloid cascade hypothesis. This is clearly a limitation considering the increasing number of new genetic risk factors, which may potentially lead to the identification of not only $A\beta$ toxicity-dependent mechanisms, but also $A\beta$-independent mechanisms (potentially linked to Tau).

Post-GWAS analyses and Tau

Although GWAS-defined genes have not been extensively studied in the context of Tau pathology, it appears that several of them may interfere with Tau in AD. Among them, the largest amount of compiled evidence is on *BIN1*, which has been identified as the first AD genetic risk factor linked to Tau pathology. Loss- and gain-of-function of the *Drosophila*

ortholog of *BIN1* modified the rough eye phenotype induced by human Tau expression [18]. In addition, a functional risk variant of *BIN1* has been associated with Tau loads (but not $A\beta$ loads) in AD brains [18]. Furthermore, human BIN1 directly binds Tau and this interaction in neurons depends on the level of BIN1 expression, as well as the phosphorylation statuses of both BIN1 and Tau [85, 89, 110, 124]. Moreover, human BIN1 overexpression in a mouse model of tauopathy has been shown to increase BIN1–Tau interaction in the neuronal network and to rescue long-term memory deficits and Tau somatic inclusions induced by human Tau overexpression [110].

The *Drosophila* rough eye phenotype has also been used to perform genetic screens to systematically test GWAS-defined genes as potential modulators of Tau toxicity [25]. Beyond *BIN1*, this approach identified *p130CAS*, *Fak*, *Eph*, *Rab3-GEF*, *cindr*, *Fit1, Aret* and *Rhea* respective orthologs of *CASS4*, *PTK2B*, *EPHA1*, *MADD*, *CD2AP*, *FERMT2, CELF1* and *TLN2* [26, 42, 119]. Pyk2 (product of *PTK2B*) has been further shown to accumulate early in the somata of neurons exhibiting Tau pathology in AD patients and in a mouse model [26]. In addition, being a tyrosine kinase, Pyk2 has been shown to directly phosphorylate Tau [86]. In conclusion, a non-negligible part of GWAS-defined genes are also potentially involved in pathophysiological processes related to Tau.

Post-GWAS functional screens point towards the core of the focal adhesion pathway

Remarkably, a large part of these GWAS-defined genes interacting with Tau pathology take part in the focal adhesion complex, mainly downstream of integrins (Suppl. Table 1; Fig. 2). Pyk2 and CASS4 are members of the FAK and CAS families of proteins that interact physically and mediate cell adhesion signalling [8]. CD2AP is involved in cell–cell adhesion, regulates the actin cytoskeleton and physically interacts with p130CAS (CASS1) [61, 74]. Kindlin-2 is a focal adhesion (FA) protein involved in integrin activation [77] and is also able to directly bind filamentous actin (F-actin) to modulate its organisation [12]. TLN2 is a cytoplasmic adapter protein essential for integrin-mediated cell adhesion to the extracellular matrix [35]. Finally, without being previously described as part of the core of the FA pathway, BIN1 physically interacts with FA kinase (FAK), which presents strong homology with Pyk2 [90]. In addition, BIN1 binds to F-actin and microtubule-binding protein CLIP170 in non-neuronal cells [21] and directly remodels actin dynamics through its BAR domain [27].

Importantly, high-content screening also identified numerous FA pathway members—including Kindlin-2—as modulators of APP metabolism, highlighting the relevance of the core FA proteins to the AD process [17]. Therefore,

despite not been considered initially, systematically screening AD risk factors for their capacity to modulate Tau toxicity and APP metabolism (in *Drosophila* and in cellular models) highlighted the core of the FA pathway for its potential involvement in the molecular mechanisms of AD pathogenesis (Fig. 3).

Focal adhesion pathway, GWAS-defined genes and synapse dynamics

Among numerous biological functions, the FA pathway can modulate F-actin dynamics through regulating multiple actin-binding proteins, e.g., cortactin, profilin, drebrin or cofilin, and controls the shape of the dendritic spine [125]. The integrin-dependent FA pathway has been subsequently involved in synaptic density and activity through spine shape, stability and signalling machinery therein [54]. Since synaptic dysfunction and loss is one of the very early hallmarks of AD correlated with early cognitive decline, the high number of genetic determinants situated in a pathway

Fig. 3 Interactions between integrin, APP and receptor tyrosine kinases (RTKs) at the cell surface modulate cell adhesion. The GWAS-defined genes *FERMT2*, *Cass4*, *PTK2B* and *CD2AP*, recently identified for their roles in APP metabolism (in green) and/or Tau pathology (in red), are involved in the focal adhesion complex, which regulates several downstream cell signalling pathways as well as the actin cytoskeleton. This observation supports the concept that the focal adhesion core, together with its related downstream pathways, may be an important actor in the AD process

that is heavily involved in synapse dynamics naturally calls for the assessment of the potential roles of these genes in synapse dynamics.

To date, only a few GWAS-defined genes have been studied in the context of synapses. Nevertheless, several lines of evidence seem to emerge to support their potential involvement in synapse dynamics [69]. As previously mentioned, products of several GWAS-defined genes are already known to regulate the actin cytoskeleton, e.g., CD2AP, Kindlin-2 and BIN1. Besides regulating the F-actin network, several of these GWAS-defined genes are directly involved in synapses in the physiological context. Our preliminary data concerning Kindlin-2 indicate that this protein is localized in both pre- and post-synaptic compartments (unpublished observations). Pyk2 is also localised to synapses and decreased Pyk2 expression in mice has recently been associated with alterations in dendritic spine density and in *N*-methyl-D-aspartate receptors (NMDAR) and PSD-95 distribution in spines [33]. Consistently, Pyk2 was involved in long-term potentiation (LTP) through the regulation of Src in an activity-dependent fashion [57], and in long-term depression (LTD) [55, 109]. Finally, increased expression of BIN1 in mice has also been associated with alterations in dendritic spine density and in LTP dysregulation [22].

APP's role in synaptic function and AD-related synaptic dysfunction

A growing body of evidence also suggests a physiological role for APP in synaptic functions [96], potentially through cell adhesion. During development, APP is enriched in axonal growth cones and acts as a co-receptor for guidance cues through its interaction with the extracellular matrix [122, 123]. Accordingly, APP–integrin interaction is required for neurite outgrowth and contact guidance [123, 153]. After differentiation, APP acts as a synaptic adhesion molecule required at both presynaptic and postsynaptic membranes for correct synapse patterning [142]. Inhibition of APP shedding strongly enhances cell adhesion and synaptogenic activity [127]. The APP intracellular domain (AICD) is required for normal synaptic morphology and synaptic plasticity, suggesting the involvement of other interactors for proper synapse formation [75]. Thirty-five percent decrease in spine density has been observed in neurons derived from APP$^{-/-}$ mice, which was partially rescued by sAPP-α conditioned medium [136]. In this context, modified APP cleavage/degradation may modulate the membranous pool of APP or its metabolic products (e.g., AICD, APPs-α) and impair APP function in cell adhesion and synaptic plasticity [117]. These APP functions appear to be related to the FA pathway: integrin and APP share a number of interactors, including Fe65, a cytoplasmic adaptor protein that can simultaneously bind two NPXY motifs (carried by both integrins and APP)
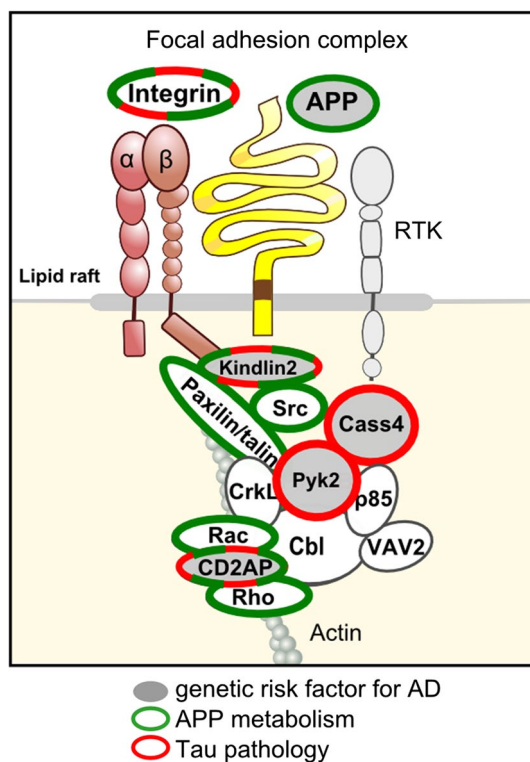
to form tripartite complexes [108]. Accordingly, APP can be recruited into a multimeric complex with β1-integrin. Altogether, these observations imply that cell surface APP modulates integrin signalling by recruiting different intracellular partners. Notably, targeting cell surface APP with antibodies induces neuronal injury through dysregulation of FAK and paxillin phosphorylation [149].

Beyond their impact on Aβ production (as described earlier), AD genetic risk factors may disrupt APP function and/or its interaction with the FA pathway. For example, Kindlin-2 expression is required for the recruitment and activation of FAK to trigger integrin signalling [100, 133], but Kindlin-2 is also a modulator of cell surface APP levels [17]. Interestingly, SORL1 has also been described to shuttle APP from early endosomes back to the Golgi apparatus and to subsequently impair its trafficking to the cell surface [1, 114]. Finally, the α-secretase ADAM10 has been functionally associated with several integrins [62, 121]. In conclusion, reports of numerous genetic risk factors involved in the core of the FA pathway point to a potential impairment of APP functions in cell adhesion and synaptic plasticity in AD, potentially independent of Aβ peptide production.

Aβ toxicity and synaptic dysfunction through FA

FAs have also been established as regulators of Aβ signalling [15]; however, the mechanistic details of the regulatory mechanisms are poorly understood, as are their potential links to the genetic component of the AD. Integrin signalling has been described to mediate Aβ-induced neurotoxicity in hippocampal neurons via FAK signalling [44]. Activation of integrin signalling by Aβ fibrils has been associated with enhanced NMDAR sensitivity [138] and inhibition of LTP [140]. In addition, aberrant activation of the FA pathway may mediate Aβ fibril-induced neuronal dystrophy [36]. Aβ fibril-induced dystrophy requires the activation of FA pathway and the formation of aberrant FAs, suggesting a mechanism of maladaptive plasticity in AD. More specifically, rapid tyrosine phosphorylation of neuronal proteins including Tau and FAK can be observed in response to Aβ exposure involving Src family kinases [143]. It has been also proposed that the scaffolding protein RanBP9, which exhibits an overall increase in AD brains, simultaneously promotes Aβ generation and FA disruption by accelerating APP and β1-integrin endocytosis [145]. RanBP9 activates/dephosphorylates cofilin, a key regulator of actin dynamics [146]. Formation of cofilin–actin rods in distal dendrites is detrimental for synapses [7, 19] and cofilin–actin rod pathology has been observed in the brains of post-mortem AD patients [101] and in animal models of AD [7]. Together, these results implicate the integrin–cofilin pathway to be critical in synaptic dysfunction in AD [36, 147]. Cumulatively, these studies strongly suggest that AD is accompanied

by an impairment of the FA pathway—potentially linked to Aβ toxicity—leading to altered synapse dynamics and eventually to synapse loss.

Tau in synaptic function and AD-related synaptic dysfunction

The potential involvement of GWAS-defined genes related to Tau toxicity in synapse dynamics and in AD synaptic pathology would be supported if Tau itself had a role in synaptic function. Interestingly, several recent studies suggest that Tau may directly regulate synaptic function and plasticity: in healthy neurons, Tau is observed in the dendritic shaft as well as in pre- and post-synaptic structures [92, 94, 156]. Post-synaptic Tau has been demonstrated to be crucial for LTD [73]. Importantly, Tau's role in regulating synapses does not appear to be redundant or functionally compensated in Tau knockout mice, suggesting a physiological role for Tau in synapses [151]. While little is known about the cellular mechanisms linking Tau with synaptic function, Tau activity, localization and function in synapses appear to be phosphorylation-dependent [58].

Whereas the physiological roles of Tau in synapses have recently been identified (and require further investigation), numerous studies have already established Tau as a mediator of AD-related synaptic deficits (for a review see [126]). Indeed, Tau has been implicated in the synaptotoxicity induced by Aβ exposure [102]. In this context, Tau is partially re-localized to the post-synaptic domain where it is thought to promote Aβ toxicity in pathological conditions by modifying NMDAR activation [53]. Aβ-induced dendritic spine loss [88] and neuronal death [130] depend on Tau phosphorylation. Aβ exposure modifies Tau's phosphorylation status and prevents it from relocalizing away from the post-synaptic domain following synaptic activation [29]. Moreover, Tau–Fyn interaction in synapses has been shown to be required to induce pathology in mice over-expressing APP, where reduced Tau levels decrease excitotoxicity and reduced Fyn levels prevent Aβ toxicity [104].

Very few data are currently available linking GWAS-defined genes with Tau pathology and with synapses. The most promising results are for Pyk2 which may be participating in the Fyn–Tau crosstalk. As mentioned earlier, we were able to detect a genetic interaction between Pyk2 and Tau [26]. Pyk2 has been reported to mediate GSK-3 activation and subsequent Tau phosphorylation [112]. In addition, Pyk2 is able to activate Fyn [16], which, in turn, modulates Pyk2 activation in mouse brains [43]. This reciprocal regulation is further supported by the observation that Aβ-induced Fyn signalling is associated with downstream Pyk2 phosphorylation [68]. Finally, Pyk2 has recently been shown to mediate Aβ-dependent synapse loss [109]. In conclusion, based on the limited amount of data currently available, we

propose that emerging evidence supports that Tau function is crucial for normal synaptic physiology and it may be dysregulated in AD potentially through interaction with genetic risk factors in an Aβ-dependent or Aβ-independent manner.

From an Aβ-centred to a synapse-centred hypothesis?

Over one decade, GWASs and high-throughput sequencing approaches have fully revolutionized our knowledge of the genetics of AD. In this new genetic landscape, as mentioned earlier, AD appears as a complex, multifactorial disease resulting from a complex crosstalk between different pathophysiological processes. Importantly, the amyloid cascade hypothesis appears to be supported by this new genetic landscape, which additionally implicates microglia to have a major role in common AD forms potentially through Aβ peptide clearance. However, these genetic data also highlight the core FA and its related downstream pathways to be potentially central to AD pathophysiology. Interestingly, this particular pathway was not predicted by in silico gene ontology enrichment analyses conducted on GWAS-based gene lists; it rather emerged on the basis of in vivo and in vitro biological evidence. Notably, several functions of GWAS-defined genes were unknown before this evidence was obtained.

When placing these new genetic and biological data into the broader context of known AD pathogenic mechanisms, several general conclusions seem to emerge, allowing us to propose an interpretation linking the main information resulting from this new genetic landscape into a global schema (Fig. 4):

1. The focus is shifted towards the synapse as the subcellular compartment where an important and early part of the pathogenesis takes place.
2. A genetic-dependent dysregulation of synapse dynamics and downstream cellular signalling through the core FA pathway may participate in AD processes, independently of Aβ toxicity.
3. The normal cellular functions of APP and Tau also appear to play central roles in synaptic plasticity, and their dysfunction may thus participate in the AD pathology, independently of the known toxic properties of their aggregated forms.
4. Synaptic dysfunction may thus simply link APP and Tau in the same subcellular compartment and APP functions may be also dependent on the FA pathway.
5. Aβ toxicity may, however, participate in several of these harmful dysfunctions, for instance through integrin over-activation. Under pathophysiological conditions, these dysfunctions might be either induced by massive Aβ peptide overproduction or accentuated by insidious Aβ accumulation through degradation/clearance failure. In monogenic forms of AD, Aβ would still be responsible for the pathogenesis, whereas in sporadic forms, Aβ would be a somewhat important accelerator of the pathological process.
6. Finally, genetic-dependent microglia dysfunction may take place in this synapse-centred model at two distinct levels: through Aβ clearance failure and/or synapse pruning. Aβ clearance failure may of course increase Aβ toxicity in the vicinity of synapses. It is also suspected that perturbations in homeostatic microglia functions at synapses may lead to early synapse loss in an Aβ-dependent or potentially independent manner [52, 93].

Within this background, dysregulation of at least one of these functions/processes (and/or of the crosstalk between them) may be sufficient to establish a vicious cycle leading to synaptic failure with multiple entry points (Fig. 5). This interpretation of the GWAS data does not exclude other hypotheses developed in the AD field:

1. Even if our interpretation implies the need to reappraise the amyloid cascade hypothesis from a linear model to an over-arching circular model, one could argue that our proposition is a reorganization of the various components of the amyloid cascade hypothesis and thus does not disqualify it. However, it is important to note that, since the model is no longer linear, Aβ peptides may be sufficient but not necessary to develop AD.
2. Similarly, the cellular phase hypothesis has recently been described to consist of "a long and complex phase consisting of feedback and feedforward responses of astrocytes, microglia and vasculature" [129]. These initially compensatory processes become subsequently irreversible and deleterious, leading to a progressive neurodegeneration. A synapse-centred hypothesis is not in contradiction with the latter since synapse homeostasis is strongly dependent on the interaction of multiple cell types in the brain. Genetic susceptibility may thus potentiate specific compensatory processes—particularly in the synapse—which become deleterious and lead to synapse loss. In addition, feedback and feedforward responses may be modified by genetic factors promoting or demoting synaptic failure. For instance, little is known about how AD genetic risk factors may modulate astrocyte functions in AD, and this aspect deserves to be studied, considering that a large part of the focal adhesion genes are also expressed in this cell type.
3. A synapse-centred hypothesis also does not preclude the spreading hypothesis [34, 66], which could be either a downstream pathological event or a potential trigger
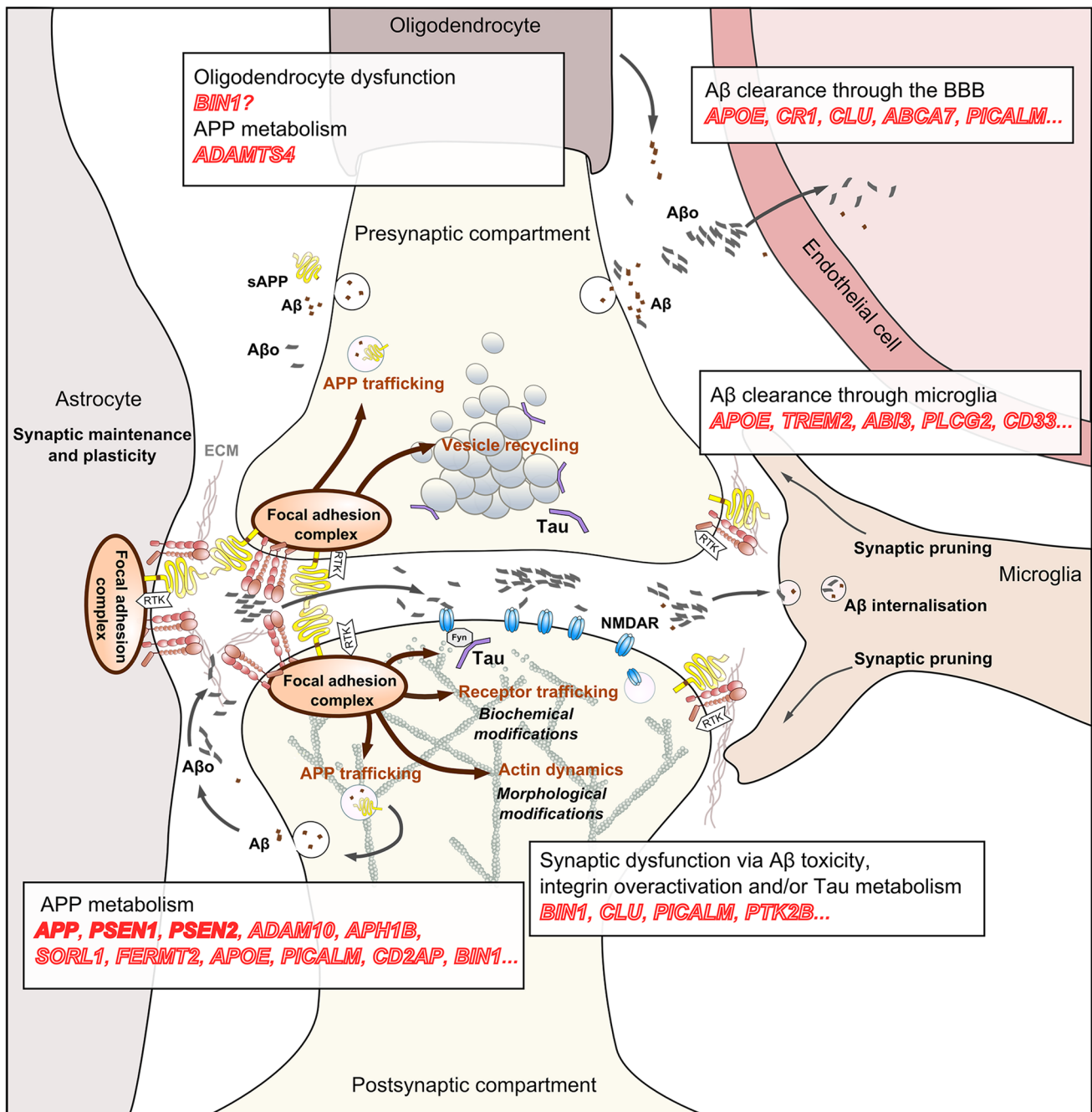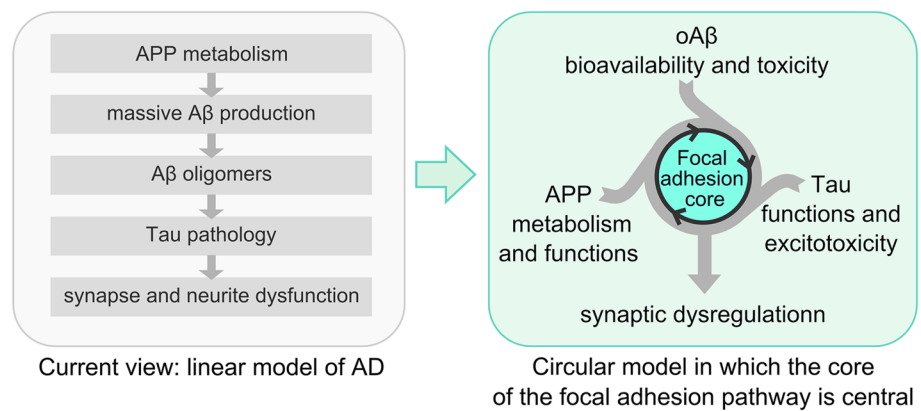
Fig. 4 Genetic risk factors and synapse dysfunction in AD pathogenesis. Regulation of the focal adhesion pathway plays central roles in synaptic plasticity (synaptic maintenance, actin cytoskeleton remodelling, vesicle, and receptor cycling). Dysfunction of downstream cellular signalling pathways involving APP and/or Tau may thus participate in synapse loss. Additionally, dysregulation of the core FA pathway could modulate APP and Tau metabolisms, leading to an exacerbation of synaptotoxicity through Aβ overproduction and Tau-modulated excitotoxicity. Finally, Aβ availability at the synapses is dependent on its clearance through the blood brain barrier and/or by microglial cells

of Tau-related excitotoxicity and synaptic failure. One can argue that spreading of an AD-specific Tau strain [32] may be involved in one of the entry points of the vicious cycle, leading to synaptic failure. Notably, BIN1 has been reported to potentially modulate the spread-

ing of Tau aggregates through their internalization via endocytosis and endosomal trafficking [14].

Fig. 5 Reappraisal of the amyloid cascade hypothesis into a circular model. In this new model, dysfunction of the FA pathway at synapses could be the basis of a vicious cycle with multiple entry points linking AD hallmarks to synapse dysregulation, synapse loss, and subsequent cognitive decline

Current view: linear model of AD

Circular model in which the core of the focal adhesion pathway is central

Conclusions

Therapeutic approaches based on the classical amyloid cascade hypothesis have mostly failed, suggesting that our understanding of AD is far from being complete. The proportion of risk attributable to genetic susceptibility factors for AD has been estimated to be between 60 and 80% [30], which is exceptionally high for a common, multifactorial aging-related disease. The identification of this genetic variability and of the genes that carry it is, therefore, decisive for characterising the key pathophysiological elements in AD and for improving our understanding of its mechanisms and targets of interest. We thus hypothesized that exhaustive knowledge of the genetic determinants of AD and integration of their potential physiological and pathological functions would help better understand AD processes. This was made possible with the development of high-throughput genomic methodologies, e.g., GWAS and sequencing, potentially leading to an exhaustive overview of the AD genetic component in the medium-term. To date, more than 45 loci/genes have been characterised, and—keeping in mind the significant bias and tautological reasoning—numerous AD genetic risk factors appeared to support the amyloid cascade hypothesis through Aβ production or clearance. However, this strong genetic component also indicates—as suggested by other AD fields, e.g., imaging, biomarkers, disease models—that this hypothesis has to be reformulated to clearly describe AD and to take these recent advances into account. We thus propose an over-arching model that could help better define and target relevant pathophysiological processes. This approach led to the proposition that synaptic failure in AD may be one of the main pathophysiological events driven by genetics, and that the core of the FA pathway is a central node of this deleterious process. This model implies a vicious cycle that integrates the main actors of AD—APP and Tau—with the genetic risk factors identified for AD. This model also suggests that treatment options would depend on both the entry point into the vicious cycle and the interplay between different pathophysiological actors. For instance, therapies targeting Aβ peptides may not be effective if this entry point is relatively unimportant for a particular patient. It thus would be necessary to develop multiple therapies targeting different entry points. Once a range of treatment options become available, an individualized model of AD pathology would be feasible, such that polytherapies and personalised medicine approaches can be developed.

References

1. Andersen OM, Reiche J, Schmidt V, Gotthardt M, Spoelgen R, Behlke J et al (2005) Neuronal sorting protein-related receptor sorLA/LR11 regulates processing of the amyloid precursor protein. Proc Natl Acad Sci USA 102:13461–13466. https://doi.org/10.1073/pnas.0503689102

2. Andrew RJ, De Rossi P, Nguyen P, Kowalski HR, Recupero AJ, Guerbette T et al (2019) Reduction of the expression of the late-onset Alzheimer's disease (AD) risk-factor *BIN1* does not affect amyloid pathology in an AD mouse model. J Biol Chem 294:4477–4487. https://doi.org/10.1074/jbc.ra118.006379

3. Atagi Y, Liu C-C, Painter MM, Chen X-F, Verbeeck C, Zheng H et al (2015) Apolipoprotein E is a ligand for triggering receptor expressed on myeloid cells 2 (TREM2). J Biol Chem 290:26043–26050. https://doi.org/10.1074/jbc.m115.679043

4. Bailey CC, Devaux LB, Farzan M (2015) The triggering receptor expressed on myeloid cells 2 binds apolipoprotein E. J Biol Chem 290:26033–26042. https://doi.org/10.1074/jbc.m115.677286

5. Bales KR, Verina T, Cummins DJ, Du Y, Dodel RC, Saura J et al (1999) Apolipoprotein E is essential for amyloid deposition in the APP(V717F) transgenic mouse model of Alzheimer's disease. Proc Natl Acad Sci USA 96:15233–15238

6. Bales KR, Verina T, Dodel RC, Du Y, Altstiel L, Bender M et al (1997) Lack of apolipoprotein E dramatically reduces amyloid beta-peptide deposition. Nat Genet 17:263–264. https://doi.org/10.1038/ng1197-263

7. Bamburg JR, Bernstein BW (2016) Actin dynamics and cofilin–actin rods in alzheimer disease. Cytoskeleton 73:477–497

8. Beck TN, Nicolas E, Kopp MC, Golemis EA (2014) Adaptors for disorders of the brain? The cancer signaling proteins NEDD9, CASS4, and PTK2B in Alzheimer's disease. Oncoscience 1:486–503. https://doi.org/10.18632/oncoscience.64

9. Bellenguez C, Charbonnier C, Grenier-Boley B, Quenez O, Le Guennec K, Nicolas G et al (2017) Contribution to Alzheimer's disease risk of rare variants in TREM2, SORL1, and ABCA7 in 1779 cases and 1273 controls. Neurobiol Aging 59:220.e1–220.e9. https://doi.org/10.1016/j.neurobiolaging.2017.07.001

10. Benitez BA, Jin SC, Guerreiro R, Graham R, Lord J, Harold D et al (2014) Missense variant in TREML2 protects against Alzheimer's disease. Neurobiol Aging 35:1510.e19–1510.e26. https://doi.org/10.1016/j.neurobiolaging.2013.12.010

11. Bis JC, Jian X, Kunkle BW, Chen Y, Hamilton-Nelson KL, Bush WS et al (2018) Whole exome sequencing study identifies novel rare and common Alzheimer's-associated variants involved in immune response and transcriptional regulation. Mol Psychiatry. https://doi.org/10.1038/s41380-018-0112-7

12. Bledzka K, Bialkowska K, Sossey-Alaoui K, Vaynberg J, Pluskota E, Qin J et al (2016) Kindlin-2 directly binds actin and regulates integrin outside-in signaling. J Cell Biol 213:97–108. https://doi.org/10.1083/jcb.201501006

13. Caglayan S, Takagi-Niidome S, Liao F, Carlo A-S, Schmidt V, Burgert T et al (2014) Lysosomal sorting of amyloid-β by the SORLA receptor is impaired by a familial Alzheimer's disease mutation. Sci Transl Med 6:223ra20. https://doi.org/10.1126/scitranslmed.3007747

14. Calafate S, Flavin W, Verstreken P, Moechars D (2016) Loss of Bin1 promotes the propagation of Tau pathology. Cell Rep 17:931–940. https://doi.org/10.1016/j.celrep.2016.09.063

15. Caltagarone J, Jing Z, Bowser R (2007) Focal adhesions regulate Abeta signaling and cell death in Alzheimer's disease. Biochim Biophys Acta 1772:438–445. https://doi.org/10.1016/j.bbadis.2006.11.007

16. Canobbio I, Cipolla L, Guidetti GF, Manganaro D, Visconte C, Kim S et al (2015) The focal adhesion kinase Pyk2 links Ca2+ signalling to Src family kinase activation and protein tyrosine phosphorylation in thrombin-stimulated platelets. Biochem J 469:199–210. https://doi.org/10.1042/bj20150048

17. Chapuis J, Flaig A, Grenier-Boley B, Eysert F, Pottiez V, Deloison G et al (2017) Genome-wide, high-content siRNA screening identifies the Alzheimer's genetic risk factor FERMT2 as a major modulator of APP metabolism. Acta Neuropathol 133:955–966. https://doi.org/10.1007/s00401-016-1652-z

18. Chapuis J, Hansmannel F, Gistelinck M, Mounier A, Van Cauwenberghe C, Kolen KV et al (2013) Increased expression of BIN1 mediates Alzheimer genetic risk by modulating Tau pathology. Mol Psychiatry 18:1225–1234. https://doi.org/10.1038/mp.2013.1

19. Cichon J, Sun C, Chen B, Jiang M, Chen XA, Sun Y et al (2012) Cofilin aggregation blocks intracellular trafficking and induces synaptic loss in hippocampal neurons. J Biol Chem 287:3919–3929. https://doi.org/10.1074/jbc.m111.301911

20. Clavaguera F, Bolmont T, Crowther RA, Abramowski D, Frank S, Probst A et al (2009) Transmission and spreading of tauopathy in transgenic mouse brain. Nat Cell Biol 11:909–913. https://doi.org/10.1038/ncb1901

21. D'Alessandro M, Hnia K, Gache V, Koch C, Gavriilidis C, Rodriguez D et al (2015) Amphiphysin 2 orchestrates nucleus positioning and shape by linking the nuclear envelope to the actin and microtubule cytoskeleton. Dev Cell 35:186–198. https://doi.org/10.1016/j.devcel.2015.09.018

22. Daudin R, Marechal D, Wang Q, Abe Y, Bourg N, Sartori M et al (2018) BIN1 genetic risk factor for Alzheimer is sufficient to induce early structural tract alterations in entorhinal cortex-dentate gyrus pathway and related hippocampal multi-scale impairments. bioRxiv. https://doi.org/10.1101/437228

23. Deane R, Sagare A, Hamm K, Parisi M, Lane S, Finn MB et al (2008) apoE isoform-specific disruption of amyloid beta peptide clearance from mouse brain. J Clin Invest 118:4002–4013. https://doi.org/10.1172/jci36663

24. DeMattos RB, Cirrito JR, Parsadanian M, May PC, O'Dell MA, Taylor JW et al (2004) ApoE and clusterin cooperatively suppress Abeta levels and deposition: evidence that ApoE regulates extracellular Abeta metabolism in vivo. Neuron 41:193–202

25. Dourlen P (2017) Identification of Tau toxicity modifiers in the Drosophila eye. Methods Mol Biol 1523:375–389

26. Dourlen P, Fernandez-Gomez FJ, Dupont C, Grenier-Boley B, Bellenguez C, Obriot H et al (2017) Functional screening of Alzheimer risk loci identifies PTK2B as an in vivo modulator and early marker of Tau pathology. Mol Psychiatry 22:874–883. https://doi.org/10.1038/mp.2016.59

27. Dräger NM, Nachman E, Winterhoff M, Brühmann S, Shah P, Katsinelos T et al (2017) Bin1 directly remodels actin dynamics through its BAR domain. EMBO Rep 18:2051–2066. https://doi.org/10.15252/embr.201744137

28. Forner S, Baglietto-Vargas D, Martini AC, Trujillo-Estrada L, LaFerla FM (2017) Synaptic impairment in Alzheimer's disease: a dysregulated symphony. Trends Neurosci 40:347–357. https://doi.org/10.1016/j.tins.2017.04.002

29. Frandemiche ML, De Seranno S, Rush T, Borel E, Elie A, Arnal I et al (2014) Activity-dependent Tau protein translocation to excitatory synapse is disrupted by exposure to amyloid-beta oligomers. J Neurosci 34:6084–6097. https://doi.org/10.1523/jneurosci.4261-13.2014

30. Gatz M, Reynolds CA, Fratiglioni L, Johansson B, Mortimer JA, Berg S et al (2006) Role of genes and environments for explaining Alzheimer disease. Arch Gen Psychiatry 63:168–174. https://doi.org/10.1001/archpsyc.63.2.168

31. Genin E, Hannequin D, Wallon D, Sleegers K, Hiltunen M, Combarros O et al (2011) APOE and Alzheimer disease: a major gene with semi-dominant inheritance. Mol Psychiatry 16:903–907. https://doi.org/10.1038/mp.2011.52

32. Gibbons GS, Banks RA, Kim B, Changolkar L, Riddle DM, Leight SN et al (2018) Detection of Alzheimer disease (AD)-specific Tau pathology in AD and non-AD tauopathies by immunohistochemistry with novel conformation-selective Tau antibodies. J Neuropathol Exp Neurol 77:216–228. https://doi.org/10.1093/jnen/nly010

33. Giralt A, Brito V, Chevy Q, Simonnet C, Otsu Y, Cifuentes-Díaz C et al (2017) Pyk2 modulates hippocampal excitatory synapses and contributes to cognitive deficits in a Huntington's disease model. Nat Commun 8:15592. https://doi.org/10.1038/ncomms15592

34. Goedert M, Spillantini MG (2017) Propagation of Tau aggregates. Mol Brain 10:18. https://doi.org/10.1186/s13041-017-0298-7

35. Gough RE, Goult BT (2018) The tale of two talins—two isoforms to fine-tune integrin signalling. FEBS Lett 592:2108–2125. https://doi.org/10.1002/1873-3468.13081

36. Grace EA, Busciglio J (2003) Aberrant activation of focal adhesion proteins mediates fibrillar amyloid beta-induced neuronal dystrophy. J Neurosci 23:493–502

37. Griciuc A, Serrano-Pozo A, Parrado AR, Lesinski AN, Asselin CN, Mullin K et al (2013) Alzheimer's disease risk gene CD33 inhibits microglial uptake of amyloid beta. Neuron 78:631–643. https://doi.org/10.1016/j.neuron.2013.04.014

38. Gu Z, Gu L, Eils R, Schlesner M, Brors B (2014) circlize Implements and enhances circular visualization in R. Bioinformatics 30:2811–2812. https://doi.org/10.1093/bioinformatics/btu393

39. Guerreiro R, Wojtas A, Bras J, Carrasquillo M, Rogaeva E, Majounie E et al (2013) TREM2 variants in Alzheimer's disease. N Engl J Med 368:117–127. https://doi.org/10.1056/nejmoa1211851

40. Guerreiro R, Wojtas A, Bras J, Carrasquillo M, Rogaeva E, Majounie E et al (2013) *TREM2* variants in Alzheimer's disease. N Engl J Med 368:117–127. https://doi.org/10.1056/nejmoa1211851

41. Gusareva ES, Carrasquillo MM, Bellenguez C, Cuyvers E, Colon S, Graff-Radford NR et al (2014) Genome-wide association interaction analysis for Alzheimer's disease. Neurobiol Aging 35:2436–2443. https://doi.org/10.1016/j.neurobiolaging.2014.05.014

42. Gusareva ES, Twizere J-C, Sleegers K, Dourlen P, Abisambra JF, Meier S et al (2018) Male-specific epistasis between WWC1 and TLN2 genes is associated with Alzheimer's disease. Neurobiol Aging 72:188.e3–188.e12. https://doi.org/10.1016/j.neurobiolaging.2018.08.001

43. Haas LT, Strittmatter SM (2016) Oligomers of amyloid prevent physiological activation of the cellular prion protein-metabotropic glutamate receptor 5 complex by glutamate in Alzheimer disease. J Biol Chem 291:17112–17121. https://doi.org/10.1074/jbc.m116.720664

44. Han H-Y, Zhang J-P, Ji S-Q, Liang Q-M, Kang H-C, Tang R-H et al (2014) αν and β1 Integrins mediate Aβ-induced neurotoxicity in hippocampal neurons via the FAK signaling pathway. PLoS One 8:e64839. https://doi.org/10.1371/journal.pone.0064839

45. Hansen DV, Hanson JE, Sheng M (2018) Microglia in Alzheimer's disease. J Cell Biol 217:459–472. https://doi.org/10.1083/jcb.201709069

46. Hardy J, Selkoe DJ (2002) The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science 297:353–356. https://doi.org/10.1126/science.1072994

47. Harold D, Abraham R, Hollingworth P, Sims R, Gerrish A, Hamshere ML et al (2009) Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer's disease. Nat Genet 41:1088–1093. https://doi.org/10.1038/ng.440

48. He X, Cooley K, Chung CHY, Dashti N, Tang J (2007) Apolipoprotein receptor 2 and X11 alpha/beta mediate apolipoprotein E-induced endocytosis of amyloid-beta precursor protein and beta-secretase, leading to amyloid-beta production. J Neurosci 27:4052–4060. https://doi.org/10.1523/jneurosci.3993-06.2007

49. Hoe H-S, Pocivavsek A, Dai H, Chakraborty G, Harris DC, Rebeck GW (2006) Effects of apoE on neuronal signaling and APP processing in rodent brain. Brain Res 1112:70–79. https://doi.org/10.1016/j.brainres.2006.07.035

50. Hollingworth P, Harold D, Sims R, Gerrish A, Lambert J-C, Carrasquillo MM et al (2011) Common variants at ABCA7, MS4A6A/MS4A4E, EPHA1, CD33 and CD2AP are associated with Alzheimer's disease. Nat Genet 43:429–435. https://doi.org/10.1038/ng.803

51. Holtzman DM, Herz J, Bu G (2012) Apolipoprotein E and apolipoprotein E receptors: normal biology and roles in Alzheimer disease. Cold Spring Harb Perspect Med 2:a006312. https://doi.org/10.1101/cshperspect.a006312

52. Hong S, Beja-Glasser VF, Nfonoyim BM, Frouin A, Li S, Ramakrishnan S et al (2016) Complement and microglia mediate early synapse loss in Alzheimer mouse models. Science 352:712–716. https://doi.org/10.1126/science.aad8373

53. Hoover BR, Reed MN, Su J, Penrod RD, Kotilinek LA, Grant MK et al (2010) Tau mislocalization to dendritic spines mediates synaptic dysfunction independently of neurodegeneration. Neuron 68:1067–1081. https://doi.org/10.1016/j.neuron.2010.11.030

54. Hotulainen P, Hoogenraad CC (2010) Actin in dendritic spines: connecting dynamics to function. J Cell Biol 189:619–629. https://doi.org/10.1083/jcb.201003008

55. Hsin H, Kim MJ, Wang C-F, Sheng M (2010) Proline-rich tyrosine kinase 2 regulates hippocampal long-term depression. J Neurosci 30:11983–11993. https://doi.org/10.1523/jneurosci.1029-10.2010

56. Huang K-L, Marcora E, Pimenova AA, Di Narzo AF, Kapoor M, Jin SC et al (2017) A common haplotype lowers PU.1 expression in myeloid cells and delays onset of Alzheimer's disease. Nat Neurosci 20:1052–1061. https://doi.org/10.1038/nn.4587

57. Huang Y, Lu W, Ali DW, Pelkey KA, Pitcher GM, Lu YM et al (2001) CAKbeta/Pyk2 kinase is a signaling link for induction of long-term potentiation in CA1 hippocampus. Neuron 29:485–496

58. Ittner LM, Ke YD, Delerue F, Bi M, Gladbach A, van Eersel J et al (2010) Dendritic function of Tau mediates amyloid-beta toxicity in Alzheimer's disease mouse models. Cell 142:387–397. https://doi.org/10.1016/j.cell.2010.06.036

59. Jansen IE, Savage JE, Watanabe K, Bryois J, Williams DM, Steinberg S et al (2019) Genome-wide meta-analysis identifies new loci and functional pathways influencing Alzheimer's disease risk. Nat Genet 51(3):404–413. https://doi.org/10.1038/s41588-018-0311-9

60. Jay TR, Hirsch AM, Broihier ML, Miller CM, Neilson LE, Ransohoff RM et al (2017) Disease progression-dependent effects of TREM2 deficiency in a mouse model of Alzheimer's disease. J Neurosci 37:637–647. https://doi.org/10.1523/jneurosci.2110-16.2016

61. Johnson RI, Seppa MJ, Cagan RL (2008) The *Drosophila* CD2AP/CIN85 orthologue Cindr regulates junctions and cytoskeleton dynamics during tissue patterning. J Cell Biol 180:1191–1204. https://doi.org/10.1083/jcb.200706108

62. Jones AV, Lambert DW, Speight PM, Whawell SA (2013) ADAM 10 is over expressed in oral squamous cell carcinoma and contributes to invasive behaviour through a functional association with αvβ6 integrin. FEBS Lett 587:3529–3534. https://doi.org/10.1016/j.febslet.2013.09.010

63. Jones L, Lambert JC, Wang LS, Choi SH, Harold D, Vedernikov A et al (2015) Convergent genetic and expression data implicate immunity in Alzheimer's disease. Alzheimer's Dement 11:658–671. https://doi.org/10.1016/j.jalz.2014.05.1757

64. Jones L, Lambert J-C, Wang L-S, Choi S-H, Harold D, Vedernikov A et al (2015) Convergent genetic and expression data implicate immunity in Alzheimer's disease. Alzheimer's Dement 11:658–671. https://doi.org/10.1016/j.jalz.2014.05.1757

65. Jonsson T, Stefansson H, Steinberg S, Jonsdottir I, Jonsson PV, Snaedal J et al (2013) Variant of TREM2 associated with the risk of Alzheimer's disease. N Engl J Med 368:107–116. https://doi.org/10.1056/nejmoa1211103

66. Jucker M, Walker LC (2011) Pathogenic protein seeding in Alzheimer disease and other neurodegenerative disorders. Ann Neurol 70:532–540. https://doi.org/10.1002/ana.22615

67. Jun G, Ibrahim-Verbaas CA, Vronskaya M, Lambert J-C, Chung J, Naj AC et al (2015) A novel Alzheimer disease locus located near the gene encoding Tau protein. Mol Psychiatry. https://doi.org/10.1038/mp.2015.23

68. Kaufman AC, Salazar SV, Haas LT, Yang J, Kostylev MA, Jeng AT et al (2015) Fyn inhibition rescues established memory and synapse loss in Alzheimer mice. Ann Neurol 77:953–971. https://doi.org/10.1002/ana.24394

69. Kilinc D (2018) The emerging role of mechanics in synapse formation and plasticity. Front Cell Neurosci 12:483. https://doi.org/10.3389/fncel.2018.00483

70. Killick R, Ribe EM, Al-Shawi R, Malik B, Hooper C, Fernandes C et al (2014) Clusterin regulates β-amyloid toxicity via Dickkopf-1-driven induction of the wnt-PCP-JNK pathway. Mol Psychiatry 19:88–98. https://doi.org/10.1038/mp.2012.163

71. Kim J, Basak JM, Holtzman DM (2009) The role of apolipoprotein E in Alzheimer's disease. Neuron 63:287–303. https://doi.org/10.1016/j.neuron.2009.06.026

72. Kim J, Castellano JM, Jiang H, Basak JM, Parsadanian M, Pham V et al (2009) Overexpression of low-density lipoprotein receptor in the brain markedly inhibits amyloid deposition and increases extracellular A beta clearance. Neuron 64:632–644. https://doi.org/10.1016/j.neuron.2009.11.013

73. Kimura T, Whitcomb DJ, Jo J, Regan P, Piers T, Heo S et al (2014) Microtubule-associated protein Tau is essential for long-term depression in the hippocampus. Philos Trans R Soc Lond B Biol Sci 369:20130144. https://doi.org/10.1098/rstb.2013.0144

74. Kirsch KH, Georgescu MM, Ishimaru S, Hanafusa H (1999) CMS: an adapter molecule involved in cytoskeletal rearrangements. Proc Natl Acad Sci USA 96:6211–6216

75. Klevanski M, Herrmann U, Weyer SW, Fol R, Cartier N, Wolfer DP et al (2015) The APP intracellular domain is required for normal synaptic morphology, synaptic plasticity, and hippocampus-dependent behavior. J Neurosci 35:16018–16033. https://doi.org/10.1523/jneurosci.2009-15.2015

76. Kunkle BW, Grenier-Boley B, Sims R, Bis JC, Damotte V, Naj AC et al (2019) Genetic meta-analysis of diagnosed Alzheimer's disease identifies new risk loci and implicates Aβ, Tau, immunity and lipid processing. Nat Genet 51:414–430. https://doi.org/10.1038/s41588-019-0358-2

77. Lai-Cheong JE, Parsons M, McGrath JA (2010) The role of kindlins in cell biology and relevance to human disease. Int J Biochem Cell Biol 42:595–603. https://doi.org/10.1016/j.biocel.2009.10.015

78. Lamartinière Y, Boucau M-C, Dehouck L, Krohn M, Pahnke J, Candela P et al (2018) ABCA7 downregulation modifies cellular cholesterol homeostasis and decreases amyloid-β peptide efflux in an in vitro model of the blood–brain barrier. J Alzheimers Dis 64:1195–1211. https://doi.org/10.3233/jad-170883

79. Lambert J-C, Amouyel P (2007) Genetic heterogeneity of Alzheimer's disease: complexity and advances. Psychoneuroendocrinology 32(Suppl 1):S62–S70. https://doi.org/10.1016/j.psyneuen.2007.05.015

80. Lambert J-C, Amouyel P (2011) Genetics of Alzheimer's disease: new evidences for an old hypothesis? Curr Opin Genet Dev 21:295–301. https://doi.org/10.1016/j.gde.2011.02.002

81. Lambert J-C, Grenier-Boley B, Chouraki V, Heath S, Zelenika D, Fievet N et al (2010) Implication of the immune system in Alzheimer's disease: evidence from genome-wide pathway analysis. J Alzheimers Dis 20:1107–1118. https://doi.org/10.3233/jad-2010-100018

82. Lambert J-C, Grenier-Boley B, Harold D, Zelenika D, Chouraki V, Kamatani Y et al (2013) Genome-wide haplotype association study identifies the FRMD4A gene as a risk locus for Alzheimer's disease. Mol Psychiatry 18:461–470. https://doi.org/10.1038/mp.2012.14

83. Lambert J-C, Heath S, Even G, Campion D, Sleegers K, Hiltunen M et al (2009) Genome-wide association study identifies variants at CLU and CR1 associated with Alzheimer's disease. Nat Genet 41:1094–1099. https://doi.org/10.1038/ng.439

84. Lambert JC, Ibrahim-Verbaas CA, Harold D, Naj AC, Sims R, Bellenguez C et al (2013) Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. Nat Genet 45:1452–1458. https://doi.org/10.1038/ng.2802

85. Lasorsa A, Malki I, Cantrelle F-X, Merzougui H, Boll E, Lambert J-C et al (2018) Structural basis of Tau interaction with BIN1 and regulation by Tau phosphorylation. Front Mol Neurosci 11:421. https://doi.org/10.3389/fnmol.2018.00421

86. Li C, Götz J (2018) Pyk2 is a novel Tau tyrosine kinase that is regulated by the tyrosine kinase fyn. J Alzheimers Dis 64:205–221. https://doi.org/10.3233/jad-180054

87. Liao F, Jiang H, Srivatsan S, Xiao Q, Lefton KB, Yamada K et al (2015) Effects of CD2-associated protein deficiency on amyloid-β in neuroblastoma cells and in an APP transgenic mouse model. Mol Neurodegener 10:12. https://doi.org/10.1186/s13024-015-0006-y

88. Mairet-Coello G, Courchet J, Pieraut S, Courchet V, Maximov A, Polleux F (2013) The CAMKK2-AMPK kinase pathway mediates the synaptotoxic effects of Aβ oligomers through Tau phosphorylation. Neuron 78:94–108. https://doi.org/10.1016/j.neuron.2013.02.003

89. Malki I, Cantrelle F-X, Sottejeau Y, Lippens G, Lambert J-C, Landrieu I (2017) Regulation of the interaction between the neuronal BIN1 isoform 1 and Tau proteins—role of the SH3 domain. FEBS J 284:3218–3229. https://doi.org/10.1111/febs.14185

90. Messina S, Onofri F, Bongiorno-Borbone L, Giovedì S, Valtorta F, Girault JA et al (2003) Specific interactions of neuronal focal adhesion kinase isoforms with Src kinases and amphiphysin. J Neurochem 84:253–265. https://doi.org/10.1046/j.1471-4159.2003.01519.x

91. Miyagawa T, Ebinuma I, Morohashi Y, Hori Y, Young Chang M, Hattori H et al (2016) BIN1 regulates BACE1 intracellular trafficking and amyloid-β production. Hum Mol Genet 25:2948–2958. https://doi.org/10.1093/hmg/ddw146

92. Mondragón-Rodríguez S, Trillaud-Doppia E, Dudilot A, Bourgeois C, Lauzon M, Leclerc N et al (2012) Interaction of endogenous tau protein with synaptic proteins is regulated by N-methyl-D-aspartate receptor-dependent Tau phosphorylation. J Biol Chem 287:32040–32053. https://doi.org/10.1074/jbc.m112.401240

93. Morris GP, Clark IA, Zinn R, Vissel B (2013) Microglia: a new frontier for synaptic plasticity, learning and memory, and neurodegenerative disease research. Neurobiol Learn Mem 105:40–53. https://doi.org/10.1016/j.nlm.2013.07.002

94. Morris M, Knudsen GM, Maeda S, Trinidad JC, Ioanoviciu A, Burlingame AL et al (2015) Tau post-translational modifications in wild-type and human amyloid precursor protein transgenic mice. Nat Neurosci 18:1183–1189. https://doi.org/10.1038/nn.4067

95. Mukherjee S, Russell JC, Carr DT, Burgess JD, Allen M, Serie DJ et al (2017) Systems biology approach to late-onset Alzheimer's disease genome-wide association study identifies novel candidate genes validated using brain expression data and Caenorhabditis elegans experiments. Alzheimer's Dement. https://doi.org/10.1016/j.jalz.2017.01.016

96. Müller UC, Deller T, Korte M (2017) Not just amyloid: physiological functions of the amyloid precursor protein family. Nat Rev Neurosci 18:281–298. https://doi.org/10.1038/nrn.2017.29

97. Naj AC, Jun G, Beecham GW, Wang L-S, Vardarajan BN, Buros J et al (2011) Common variants at MS4A4/MS4A6E, CD2AP, CD33 and EPHA1 are associated with late-onset Alzheimer's disease. Nat Genet 43:436–441. https://doi.org/10.1038/ng.801

98. Pottier C, Hannequin D, Coutant S, Rovelet-Lecrux A, Wallon D, Rousseau S et al (2012) High frequency of potentially pathogenic SORL1 mutations in autosomal dominant early-onset Alzheimer disease. Mol Psychiatry 17:875–879. https://doi.org/10.1038/mp.2012.15

99. Prokic I, Cowling BS, Laporte J (2014) Amphiphysin 2 (BIN1) in physiology and diseases. J Mol Med 92:453–463. https://doi.org/10.1007/s00109-014-1138-1

100. Qu H, Tu Y, Guan J-L, Xiao G, Wu C (2014) Kindlin-2 tyrosine phosphorylation and interaction with Src serve as a regulatable switch in the integrin outside-in signaling circuit. J Biol Chem 289:31001–31013. https://doi.org/10.1074/jbc.m114.580811

101. Rahman T, Davies DS, Tannenberg RK, Fok S, Shepherd C, Dodd PR et al (2014) Cofilin rods and aggregates concur with Tau pathology and the development of Alzheimer's disease. J Alzheimers Dis 42:1443–1460. https://doi.org/10.3233/jad-140393

102. Rapoport M, Dawson HN, Binder LI, Vitek MP, Ferreira A (2002) Tau is essential to beta-amyloid-induced neurotoxicity. Proc Natl Acad Sci USA 99:6364–6369. https://doi.org/10.1073/pnas.092136199

103. Ridge PG, Hoyt KB, Boehme K, Mukherjee S, Crane PK, Haines JL et al (2016) Assessment of the genetic variance of late-onset Alzheimer's disease. Neurobiol Aging 41:200.e13–200.e20. https://doi.org/10.1016/j.neurobiolaging.2016.02.024

104. Roberson ED, Scearce-Levie K, Palop JJ, Yan F, Cheng IH, Wu T et al (2007) Reducing endogenous Tau ameliorates amyloid beta-induced deficits in an Alzheimer's disease mouse model. Science 316:750–754. https://doi.org/10.1126/science.1141736

105. Rogers J, Li R, Mastroeni D, Grover A, Leonard B, Ahern G et al (2006) Peripheral clearance of amyloid β peptide by complement C3-dependent adherence to erythrocytes. Neurobiol Aging 27:1733–1739. https://doi.org/10.1016/j.neurobiolaging.2005.09.043

106. Roheim PS, Carey M, Forte T, Vega GL (1979) Apolipoproteins in human cerebrospinal fluid. Proc Natl Acad Sci USA 76:4646–4649

107. De Rossi P, Andrew RJ, Musial TF, Buggia-Prevot V, Xu G, Ponnusamy M et al (2018) Aberrant accrual of BIN1 near Alzheimer's disease amyloid deposits in transgenic models. Brain Pathol 5:5. https://doi.org/10.1111/bpa.12687

108. Sabo SL, Ikin AF, Buxbaum JD, Greengard P (2001) The Alzheimer amyloid precursor protein (APP) and FE65, an APP-binding protein, regulate cell movement. J Cell Biol 153:1403–1414

109. Salazar SV, Cox TO, Lee S, Brody AH, Chyung AS, Haas LT et al (2018) Alzheimer's disease risk factor Pyk2 mediates amyloid-β induced synaptic dysfunction and loss. J Neurosci 1873:18. https://doi.org/10.1523/jneurosci.1873-18.2018

110. Sartori M, Mendes T, Desai S, Lasorsa A, Herldean A, Malmanche N et al (2018) BIN1 recovers tauopathy-induced long-term memory deficits in mice and interacts with Tau through Thr348 phosphorylation. bioRxiv. https://doi.org/10.1101/462317

111. Satoh K, Abe-Dohmae S, Yokoyama S, St George-Hyslop P, Fraser PE (2015) ATP-binding cassette transporter A7 (ABCA7) loss of function alters Alzheimer amyloid processing. J Biol Chem 290:24152–24165. https://doi.org/10.1074/jbc.m115.655076

112. Sayas CL, Ariaens A, Ponsioen B, Moolenaar WH (2006) GSK-3 is activated by the tyrosine kinase Pyk2 during LPA1-mediated neurite retraction. Mol Biol Cell 17:1834–1844. https://doi.org/10.1091/mbc.e05-07-0688

113. Schmidt V, Baum K, Lao A, Rateitschak K, Schmitz Y, Teichmann A et al (2012) Quantitative modelling of amyloidogenic processing and its influence by SORLA in Alzheimer's disease. EMBO J 31:187–200. https://doi.org/10.1038/emboj.2011.352

114. Schmidt V, Subkhangulova A, Willnow TE (2017) Sorting receptor SORLA: cellular mechanisms and implications for disease. Cell Mol Life Sci 74:1475–1483. https://doi.org/10.1007/s00018-016-2410-z

115. Selkoe DJ, Yamazaki T, Citron M, Podlisny MB, Koo EH, Teplow DB et al (1996) The role of APP processing and trafficking pathways in the formation of amyloid beta-protein. Ann N Y Acad Sci 777:57–64

116. Seshadri S, Fitzpatrick AL, Ikram MA, DeStefano AL, Gudnason V, Boada M et al (2010) Genome-wide analysis of genetic loci associated with Alzheimer disease. JAMA 303:1832–1840. https://doi.org/10.1001/jama.2010.574

117. Sheng B, Song B, Zheng Z, Zhou F, Lu G, Zhao N et al (2009) Abnormal cleavage of APP impairs its functions in cell adhesion and migration. Neurosci Lett 450:327–331. https://doi.org/10.1016/j.neulet.2008.11.046

118. Shi Y, Holtzman DM (2018) Interplay between innate immunity and Alzheimer disease: APOE and TREM2 in the spotlight. Nat Rev Immunol 18:759–772. https://doi.org/10.1038/s41577-018-0051-1

119. Shulman JM, Imboywa S, Giagtzoglou N, Powers MP, Hu Y, Devenport D et al (2014) Functional screening in Drosophila identifies Alzheimer's disease susceptibility genes and implicates Tau-mediated mechanisms. Hum Mol Genet 23:870–877. https://doi.org/10.1093/hmg/ddt478

120. Sims R, van der Lee SJ, Naj AC, Bellenguez C, Badarinarayan N, Jakobsdottir J et al (2017) Rare coding variants in PLCG2, ABI3, and TREM2 implicate microglial-mediated innate immunity in Alzheimer's disease. Nat Genet 49:1373–1384. https://doi.org/10.1038/ng.3916

121. Siney EJ, Holden A, Casselden E, Bulstrode H, Thomas GJ, Willaime-Morawek S (2017) Metalloproteinases ADAM10 and ADAM17 mediate migration and differentiation in glioblastoma sphere-forming cells. Mol Neurobiol 54:3893–3905. https://doi.org/10.1007/s12035-016-0053-6

122. Soldano A, Hassan BA (2014) Beyond pathology: APP, brain development and Alzheimer's disease. Curr Opin Neurobiol 27:61–67. https://doi.org/10.1016/j.conb.2014.02.003

123. Sosa LJ, Bergman J, Estrada-Bernal A, Glorioso TJ, Kittelson JM, Pfenninger KH (2013) Amyloid precursor protein is an autonomous growth cone adhesion molecule engaged in contact guidance. PLoS One 8:e64521. https://doi.org/10.1371/journal.pone.0064521

124. Sottejeau Y, Bretteville A, Cantrelle F-X, Malmanche N, Demiaute F, Mendes T et al (2015) Tau phosphorylation regulates the interaction between BIN1's SH3 domain and Tau's proline-rich domain. Acta Neuropathol Commun 3:58. https://doi.org/10.1186/s40478-015-0237-8

125. Spence EF, Soderling SH (2015) Actin out: regulation of the synaptic cytoskeleton. J Biol Chem 290:28613–28622. https://doi.org/10.1074/jbc.R115.655118

126. Spires-Jones TL, Hyman BT (2014) The intersection of amyloid beta and Tau at synapses in Alzheimer's disease. Neuron 82:756–771. https://doi.org/10.1016/j.neuron.2014.05.004

127. Stahl R, Schilling S, Soba P, Rupp C, Hartmann T, Wagner K et al (2014) Shedding of APP limits its synaptogenic activity and cell adhesion properties. Front Cell Neurosci 8:410. https://doi.org/10.3389/fncel.2014.00410

128. Steinberg S, Stefansson H, Jonsson T, Johannsdottir H, Ingason A, Helgason H et al (2015) Loss-of-function variants in ABCA7 confer risk of Alzheimer's disease. Nat Genet. https://doi.org/10.1038/ng.3246

129. De Strooper B, Karran E (2016) The cellular phase of Alzheimer's disease. Cell 164:603–615. https://doi.org/10.1016/j.cell.2015.12.056

130. Tackenberg C, Grinschgl S, Trutzel A, Santuccione AC, Frey MC, Konietzko U et al (2013) NMDA receptor subunit composition determines beta-amyloid-induced neurodegeneration and synaptic loss. Cell Death Dis 4:e608. https://doi.org/10.1038/cddis.2013.129

131. Tai LM, Ghura S, Koster KP, Liakaite V, Maienschein-Cline M, Kanabar P et al (2015) APOE-modulated Aβ-induced neuroinflammation in Alzheimer's disease: current landscape, novel data, and future perspective. J Neurochem 133:465–488. https://doi.org/10.1111/jnc.13072

132. Terwel D, Steffensen KR, Verghese PB, Kummer MP, Gustafsson J-Å, Holtzman DM et al (2011) Critical role of astroglial apolipoprotein E and liver X receptor-α expression for microglial Aβ phagocytosis. J Neurosci 31:7049–7059. https://doi.org/10.1523/JNEUROSCI.6546-10.2011

133. Theodosiou M, Widmaier M, Böttcher RT, Rognoni E, Veelders M, Bharadwaj M et al (2016) Kindlin-2 cooperates with talin to activate integrins and induces cell spreading by directly binding paxillin. Elife 5:e10130. https://doi.org/10.7554/eLife.10130

134. Thomas RS, Henson A, Gerrish A, Jones L, Williams J, Kidd EJ (2016) Decreasing the expression of PICALM reduces endocytosis and the activity of β-secretase: implications for Alzheimer's disease. BMC Neurosci 17:50. https://doi.org/10.1186/s12868-016-0288-1

135. Tian Y, Chang JC, Fan EY, Flajolet M, Greengard P (2013) Adaptor complex AP2/PICALM, through interaction with LC3, targets Alzheimer's APP-CTF for terminal degradation via autophagy. Proc Natl Acad Sci 110:17071–17076. https://doi.org/10.1073/pnas.1315110110

136. Tyan S-H, Shih AY-J, Walsh JJ, Maruyama H, Sarsoza F, Ku L et al (2012) Amyloid precursor protein (APP) regulates synaptic structure and function. Mol Cell Neurosci 51:43–52. https://doi.org/10.1016/j.mcn.2012.07.009

137. Ubelmann F, Burrinha T, Salavessa L, Gomes R, Ferreira C, Moreno N et al (2017) Bin1 and CD2AP polarise the endocytic generation of beta-amyloid. EMBO Rep 18:102–122. https://doi.org/10.15252/embr.201642738

138. Uhász GJ, Barkóczi B, Vass G, Datki Z, Hunya A, Fülöp L et al (2010) Fibrillar Abeta (1-42) enhances NMDA receptor sensitivity via the integrin signaling pathway. J Alzheimers Dis 19:1055–1067. https://doi.org/10.3233/JAD-2009-1301

139. Walter S, Jumpertz T, Hüttenrauch M, Ogorek I, Gerber H, Storck SE et al (2018) The metalloprotease ADAMTS4 generates N-truncated Aβ4–x species and marks oligodendrocytes as a source of amyloidogenic peptides in Alzheimer's disease. Acta Neuropathol. https://doi.org/10.1007/s00401-018-1929-5

140. Wang Q, Klyubin I, Wright S, Griswold-Prenner I, Rowan MJ, Anwyl R (2008) Alpha v integrins mediate beta-amyloid induced inhibition of long-term potentiation. Neurobiol Aging 29:1485–1493. https://doi.org/10.1016/j.neurobiolaging.2007.03.018

141. Wang Y, Ulland TK, Ulrich JD, Song W, Tzaferis JA, Hole JT et al (2016) TREM2-mediated early microglial response limits diffusion and toxicity of amyloid plaques. J Exp Med 213:667–675. https://doi.org/10.1084/jem.20151948

142. Wang Z, Wang B, Yang L, Guo Q, Aithmitti N, Songyang Z et al (2009) Presynaptic and postsynaptic interaction of the amyloid precursor protein promotes peripheral and central synaptogenesis. J Neurosci 29:10788–10801. https://doi.org/10.1523/JNEUROSCI.2132-09.2009

143. Williamson R, Scales T, Clark BR, Gibb G, Reynolds CH, Kellie S et al (2002) Rapid tyrosine phosphorylation of neuronal proteins including Tau and focal adhesion kinase in response to amyloid-beta peptide exposure: involvement of Src family protein kinases. J Neurosci 22:10–20

144. Willnow TE, Andersen OM (2013) Sorting receptor SORLA—a trafficking path to avoid Alzheimer disease. J Cell Sci 126:2751–2760. https://doi.org/10.1242/jcs.125393

145. Woo JA, Jung AR, Lakshmana MK, Bedrossian A, Lim Y, Bu JH et al (2012) Pivotal role of the RanBP9-cofilin pathway in Aβ-induced apoptosis and neurodegeneration. Cell Death Differ 19:1413–1423. https://doi.org/10.1038/cdd.2012.14

146. Woo JA, Roh S-E, Lakshmana MK, Kang DE (2012) Pivotal role of RanBP9 in integrin-dependent focal adhesion signaling and assembly. FASEB J 26:1672–1681. https://doi.org/10.1096/fj.11-194423

147. Woo JA, Zhao X, Khan H, Penn C, Wang X, Joly-Amado A et al (2015) Slingshot-Cofilin activation mediates mitochondrial and synaptic dysfunction via Aβ ligation to β1-integrin conformers. Cell Death Differ 22:921–934. https://doi.org/10.1038/cdd.2015.5

148. Xiao Q, Gil S-C, Yan P, Wang Y, Han S, Gonzales E et al (2012) Role of phosphatidylinositol clathrin assembly lymphoid-myeloid leukemia (PICALM) in intracellular amyloid precursor protein (APP) processing and amyloid plaque pathogenesis. J Biol Chem 287:21279–21289. https://doi.org/10.1074/jbc.M111.338376

149. Xu Y-X, Wang H-Q, Yan J, Sun X-B, Guo J-C, Zhu C-Q (2009) Antibody binding to cell surface amyloid precursor protein induces neuronal injury by deregulating the phosphorylation of focal adhesion signaling related proteins. Neurosci Lett 465:276–281. https://doi.org/10.1016/j.neulet.2009.09.022

150. Yeh FL, Wang Y, Tom I, Gonzalez LC, Sheng M (2016) TREM2 binds to apolipoproteins, including APOE and CLU/APOJ, and thereby facilitates uptake of amyloid-beta by microglia. Neuron 91:328–340. https://doi.org/10.1016/j.neuron.2016.06.015

151. Yi JH, Brown C, Whitehead G, Piers T, Lee YS, Perez CM et al (2017) Glucocorticoids activate a synapse weakening pathway culminating in Tau phosphorylation in the hippocampus. Pharmacol Res 121:42–51. https://doi.org/10.1016/j.phrs.2017.04.015

152. Yin R-H, Yu J-T, Tan L (2015) The role of SORL1 in Alzheimer's disease. Mol Neurobiol 51:909–918. https://doi.org/10.1007/s12035-014-8742-5

153. Young-Pearse TL, Chen AC, Chang R, Marquez C, Selkoe DJ (2008) Secreted APP regulates the function of full-length APP in neurite outgrowth through interaction with integrin beta1. Neural Dev 3:15. https://doi.org/10.1186/1749-8104-3-15

154. Yuan P, Condello C, Keene CD, Wang Y, Bird TD, Paul SM et al (2016) TREM2 haplodeficiency in mice and humans impairs the microglia barrier function leading to decreased amyloid compaction and severe axonal dystrophy. Neuron 90:724–739. https://doi.org/10.1016/j.neuron.2016.05.003

155. Zhang Y, Sloan SA, Clarke LE, Caneda C, Plaza CA, Blumenthal PD et al (2016) Purification and characterization of progenitor and mature human astrocytes reveals transcriptional and functional differences with mouse. Neuron 89:37–53. https://doi.org/10.1016/j.neuron.2015.11.013

156. Zhao Y, Tseng I-C, Heyser CJ, Rockenstein E, Mante M, Adame A et al (2015) Appoptosin-mediated caspase cleavage of Tau contributes to progressive supranuclear palsy pathogenesis. Neuron 87:963–975. https://doi.org/10.1016/j.neuron.2015.08.020

157. Zhao Z, Sagare AP, Ma Q, Halliday MR, Kong P, Kisler K et al (2015) Central role for PICALM in amyloid-β blood-brain barrier transcytosis and clearance. Nat Neurosci 18:978–987. https://doi.org/10.1038/nn.4025

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