Cellular and Molecular Life Sciences (2022) 79:101
https://doi.org/10.1007/s00018-021-04090-4

REVIEW

Revisiting APP secretases: an overview on the holistic effects of retinoic acid receptor stimulation in APP processing

José J. M. Vitória[1] · Diogo Trigo[1] · Odete A. B. da Cruz e Silva[1]

Received: 17 July 2021 / Revised: 18 November 2021 / Accepted: 1 December 2021 / Published online: 28 January 2022

Abstract

Alzheimer's disease (AD) is the leading cause of dementia worldwide and is characterized by the accumulation of the β-amyloid peptide (Aβ) in the brain, along with profound alterations in phosphorylation-related events and regulatory pathways. The production of the neurotoxic Aβ peptide via amyloid precursor protein (APP) proteolysis is a crucial step in AD development. APP is highly expressed in the brain and is complexly metabolized by a series of sequential secretases, commonly denoted the α-, β-, and γ-cleavages. The toxicity of resulting fragments is a direct consequence of the first cleaving event. β-secretase (BACE1) induces amyloidogenic cleavages, while α-secretases (ADAM10 and ADAM17) result in less pathological peptides. Hence this first cleavage event is a prime therapeutic target for preventing or reverting initial biochemical events involved in AD. The subsequent cleavage by γ-secretase has a reduced impact on Aβ formation but affects the peptides' aggregating capacity. An array of therapeutic strategies are being explored, among them targeting Retinoic Acid (RA) signalling, which has long been associated with neuronal health. Additionally, several studies have described altered RA levels in AD patients, reinforcing RA Receptor (RAR) signalling as a promising therapeutic strategy. In this review we provide a holistic approach focussing on the effects of isoform-specific RAR modulation with respect to APP secretases and discuss its advantages and drawbacks in subcellular AD related events.

Keywords APP-secretases · APP · RAR stimulation · Neuroregeneration · Alzheimer's disease

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disease and the main cause of dementia in the elderly population [1], affecting around 6% of individuals over the age of 65 [2]. Although there are families with higher AD incidence (Familial AD, FAD), caused by autosomal dominant mutations in genes coding for the amyloid precursor protein (APP) and Presenilins (PSEN1 and PSEN2) [3], the main mechanisms causing AD are still, to some extent, unclear, with most cases occurring spontaneously.

Biochemically, AD is characterised by abnormal intracellular deposition of hyperphosphorylated Tau and extracellular accumulation of the amyloid beta (Aβ) peptide and the mechanisms of Aβ processing and prevention are a current topic of extensive research. The shedding of the APP ectodomain can be catalysed by two alternative proteases, α- and β-, which compete for the first APP cleavage [4], resulting in the APP secreted fragment (sAPP). The β-secretase pathway is the major contributor to the consequential Aβ production, while cleavage by α-secretase prevents its accumulation [3]. Subsequently, γ-secretase cleavage generates the p3 (α-secretase pathway) or Aβ (β-secretase pathway) peptides.

Although ubiquitously expressed in all tissues, the APP695 isoform is enriched in the brain. This is a single-pass transmembrane protein with a large extracellular N-terminus and a short cytosolic C-terminus [5]; following protein synthesis in the endoplasmic reticulum (ER)-associated polysomes, APP is *N*-glycosylated in the ER and transported to the Golgi apparatus where it undergoes *O*- and *N*-glycosylation, phosphorylation and sulphonation [6, 7].

APP is part of the type-I transmembrane mammal protein family, which includes the similarly processed APP-like protein 1 (APLP1) and 2 (APLP2). The human APP gene is located on chromosome 21 and contains 18 exons, spanning 290 kilobases [8], with three major isoforms resulting

✉ Odete A. B. da Cruz e Silva
odetecs@ua.pt

[1] Department of Medical Sciences, Neurosciences and Signalling Group, Institute of Biomedicine, University of Aveiro, 3810-193 Aveiro, Portugal

from alternative splicing as follows: APP695, APP751 and APP770 [9]. The two larger isoforms contain a 56-amino acid Kunitz Protease Inhibitor (KPI) extracellular domain and are expressed in most tissues [10], while APP695 lacks the KPI domain and is principally expressed in neurons [11]. The KPI domain is primarily a serine protease inhibitor [12] reported to play a role in APP dimerization, regulating its sub-cellular location, secretory pathway, and consequent processing of KPI-containing APP isoforms [13]. Protein and mRNA levels of KPI-containing APP isoforms are elevated in AD brains and correlate with increased Aβ deposition [14, 15]. In neurons, prolonged activation of extra-synaptic NMDA receptor can shift APP expression from APP695 to KPI-containing APP isoforms, accompanied by increased production of Aβ [16]. APP695 associates with NMDA receptors, in a manner implying regulation of intracellular trafficking [17], strengthening the theory that dysregulated splicing of APP RNA [15] and favouring APP isoforms facilitating access to the γ-secretase complex [16] contributes to AD pathogenesis.

Even though the inherent biological role of APP is of understandable interest for Alzheimer's research, its physiological function remains puzzlingly elusive. Its most validated role is in synaptic formation and repair, with APP expression being upregulated during neuronal differentiation and following neural injury [18]. Roles in cell signalling, long-term potentiation, cell adhesion, and transport, have been proposed, but are supported by, as-yet, limited research [19, 20]. Similarities in post-translational processing have warranted comparisons with the signalling role of the surface receptor protein Notch, a shared substrate of several APP secretases [21].

Literature suggests additional functions for APP as a cell surface receptor-like protein and ligand, mediating several physiological or pathological effects, either from the cell surface or via the released proteolytic fragments [7]. Moreover, APP presence is described in spermatozoa [22], marking it as a sentinel protein for male reproduction [23], suggesting a wide range of yet unravelled functions.

The importance of phosphorylation in AD is well established [24], with research correlating α-secretase phosphorylation with increased cleavage activity (and consequent amyloid protection) [25]. Moreover, APP phosphorylation is particularly significant, as its trafficking is regulated by the phosphorylation state of the cytoplasmatic domain [26]. Phosphorylation at serine 655 determines the fate of APP with to respect to Golgi or lysosomal targeting [27, 28]. But most relevant to the work here discussed is that threonine 668 (Thr668) phosphorylation by MAPK8 promotes β-cleavage, by facilitating secretase-APP interaction [29, 30] (Fig. 1). However, this theory remains unconfirmed, as the same Thr668 phosphorylation also decreases extracellular Aβ and γ-secretase activity [31].

As it is evident, proteolytic processing of the transmembrane region of APP is a crucial step in the progression of AD and, as such, has been the subject of extensive research, revealing novel secretases and cleavages, beyond the classic α-, β-, and γ-cleavages. The C-terminus is generated by sequential cleavages by the γ-secretase complex (ε-cleavage [32] followed by ζ- [33] and γ-cleavages) resulting in release of either p3 or Aβ, depending on the original cleavage (α-, β-, respectively) [34].

APP secretases

α-Secretases

α-secretase is manly localised in the plasma membrane, where it cleaves full-length APP, but can also be found in the Golgi apparatus [35–37]. APP α-cleavage occurs between Lys-16 and Leu-17 within the Aβ peptide, believed to be determined by an α-helical conformation and membrane distance from the hydrolysed bond. The action of α-secretase on APP results in a membrane-anchored carboxyterminal fragment (C83) and the extracellular release of the large soluble fragment sAPPα [38–40].

The soluble APP N-terminal fragment derived from α-cleavage, sAPPα, is proposed to be associated with neurotrophic and neuroprotective functions, further supporting the therapeutic value of increasing APP α-secretase cleavage [41]. sAPPα has been shown to be constitutively secreted from cells and stimulation of protein kinase C (PKC) by phorbol esters increases sAPPα release, demonstrating that APP cleavage by α-secretase can either be constitutive or regulated by phosphorylation, potentially suggesting the existence of different α-secretase proteases [42–44].

The anti-amyloidogenic α-secretase A Disintegrin And Metalloproteinase (ADAM) domain-containing protein 10 (ADAM10) is a relevant α-secretase with constitutive activity that directly competes for APP at the cell surface [45]. The ADAM protein family is characterised by conserved amino-acid domains, which include an N-terminal signal sequence (required for directing the proteins to the secretory pathway), a pro-domain (responsible for proper protein folding), a metalloproteinase domain, a disintegrin domain, a cysteine-rich region, an EGF-like domain (with the exception of ADAM10 and ADAM17), a transmembrane domain, and a cytoplasmic domain [46, 47].

The diversity of the ADAM protein family is increased by alternative splicing, with 21 described human isoforms. ADAMs are divided in two groups as follows: the catalytically inactive group, which includes proteases lacking a functional Zn-binding active site, acting via other mechanisms such as protein folding or protein interaction, and the catalytically active group (where ADAM10 and ADAM17

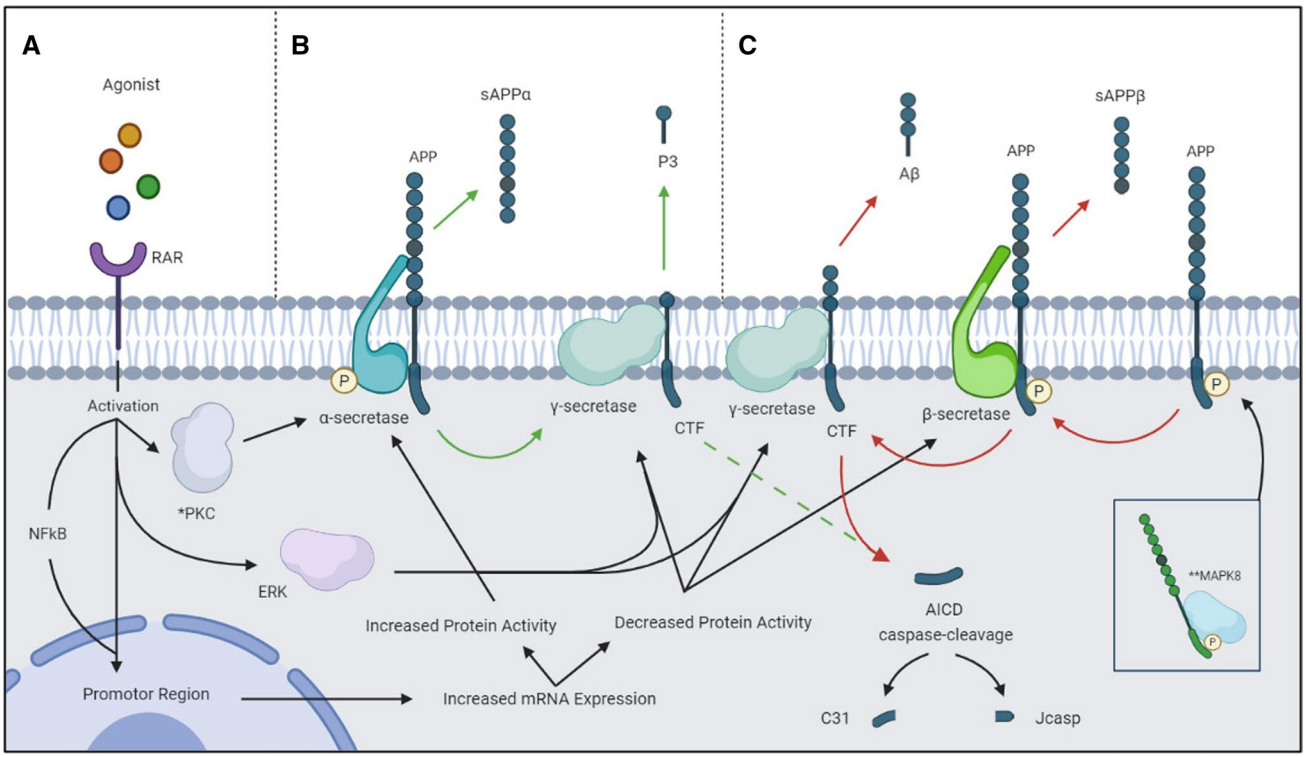

Fig. 1 Retinoid signalling and the integrated impact on APP processing and consequent fragment production. Treatment with atRA alters the gene promotor region for each of secretase. This stimulus can be either direct [120] or mediated by NFkB [87]. Activation of several kinases by the RA receptors (represented by PKC) can have a direct impact on α-secretase activation, contributing to augmented non-amyloidogenic APP processing. ERK pathway activation by RAR stimulus also results in loss of γ-secretase activity, even though its mRNA levels are increased; the same observations are described for the β-secretase BACE1. AICD resulting from β-cleavage is more transcriptionally active (represented by the solid arrow, while the dashed arrow corresponds to the less transcriptionally active). APP´s 3 main structural elements are represented accordingly: circles representing the extracellular domain; linear representing the transmembrane domain; continuous representing the intracellular domain. Red arrows correspond to the amyloidogenic pathway while green arrows correspond to the anti-amyloidogenic pathway. **A**—RAR activation. **B**—Anti-amyloid pathway. **C**—Amyloid cascade. *PKC is represented since it is the most relevant kinase activated by RAR, but other kinases are described to take part in RAR-indued activation of α-secretase. **MAPK8 is represented to phosphorylate APP in Thr668 since it is the kinase most frequently described to produce this effect, but several other kinases are shown to produce the same modification

are included), containing proteases with a Zn-binding active site [37, 46]. α-secretase cleavage was classically described as a sequence independent process, determined by an α-helical conformation and a 12–13 residue interval between the membrane cleavage site [37], but a cleavage preference for ADAM10 was eventually described [48]. Initially reported to be responsible for the proteolytic activation of the membrane precursor of TNFα [1], ADAM17, like ADAM10, was found to target a range of substrates implicated in several physiological mechanisms [49]. Notch receptors, ligands, cadherins, IL-6 receptor, EGF receptor ligands, and other type-I transmembrane proteins are also cleaved by α-secretases, resulting in the release of their respective extracellular domains [50].

Several ADAM proteases have α-secretase activity [51]: selective interference of individual ADAM10, ADAM17, and ADAM19 genes, in cell and animal models, had no noticeable impact on non-amyloid APP processing [52, 53]. ADAM10 was shown to have the most relevant α-secretase activity in neurons [45]. We have described that even though several ADAMs act on APP, only ADAM10 and ADAM17 interact directly with it, with other proteins playing a supporting role such as escorting or bridging α-secretase activators through post-transduction modifications (most commonly phosphorylation) (da Cruz e Silva et al., submitted). Additionally, the secretase ADAMTS4 (A disintegrin and metalloproteinase with thrombospondin motifs 4) was shown to interact with APP in in vitro models [54].

Retinoic Acid (RA) metabolism and signalling are essential for neuronal health, and several studies have described its impairment in AD patients, where RA precursor levels are decreased [55, 56]. Considering the promising results of promoting α-secretase expression in AD, functional studies described two potential RA responsive elements in the ADAM10 promotor region, 203 and 302 bp upstream from gene translation start site [57]. Promotor reporter assays in

neuroblastoma cells treated with all–trans RA (atRA) demonstrated significant increase in ADAM10 transcriptional activity, mRNA, and protein levels and, consequently, sAPPα secretion [58–60]. RA receptor (RAR) activation (discussed below in "modulation of retinoic acid receptors") as a means to increase α-secretase regulatory activity is well established, as is the case for ADAM10 [61]. Moreover, RA activates several kinase proteins (including PKC) [60, 62] with anti-amyloid effects, both by interacting with target promotors [63] and through direct activation of α-secretase activity via phosphorylation [64] (Fig. 1).

Even though α-secretases are complex therapeutical targets, due to their large substrate number and the range of signalling pathways in which they are involved, they are, nonetheless, prime candidates to prevent Aβ deposition. However, most studies regarding AD, Aβ formation, and APP proteolytic processing, focus on β and γ-secretases, and their influence on APP cleavage events, lacking a holistic approach encompassing α-secretases and their supporting interactors [65].

β-Secretases

BACE1 (beta-site APP cleaving enzyme 1) is the principal protein with β-secretase activity [66]. This secretase plays a central role in Aβ generation, being considered by some as the initial (and rate-limiting) stage of APP amyloid processing [67]. These observations result from repeated and well-validated experiments whereby knocking out BACE1, Aβ formation completely ceases [68–70].

BACE1 is a membrane-bound aspartyl protease, structurally similar to the pepsin family [71], containing two active site motifs in the luminal domain (amino acids 93–96 and 289–292) [72]. Each motif contains a highly conserved signature sequence of aspartic proteases, D $^{T}/_{S}$ G $^{T}/_{S}$, in which the aspartic acid residue is essential for catalytic activity. BACE1 also has four putative N-linked glycosylation sites and six luminal cysteines, which allow for the formation of up to three intramolecular disulphide bonds.

β-secretase activity is highest in the secretory pathway compartments, namely the Golgi apparatus, trans-Golgi network (TGN), secretory vesicles, and endosomes [73]. Like APP, it is highly expressed in the brain, but is nonetheless ubiquitously present in most tissues, with the pancreas being a close second. Pancreatic presence is marked by high levels of an mRNA splice variant, lacking exon 3, resulting in a different isoform with low activity, but its relevance is not yet clear [74, 75].

The therapeutical value of β-secretase has been widely investigated, with progress being made in regards to an inhibitor [76, 77], that although promising, fails to specifically inhibit the cleavage of APP alone, interfering with other BACE1 substrates. Specific inhibition proved particularly challenging, due to the fact that there are approximately 70 putative substrates cleaved by β-secretase, mostly other type I transmembrane proteins [78–80].

It is apparently contradictory that BACE1 knockout mice are viable, fertile, and lack morphological or developmental alterations [68–70]. However, these animals show subtle behavioural phenotypes, with mild memory impairment and spontaneous activity changes [81, 82], reiterating the complexity of BACE1 selective inhibition.

The phenotypes observed in animal models can be explained by the role of BACE1 in the myelination process [83] as follows: very highly expressed during post-natal stages, BACE1 acts on the NRG1 (Neuregulin-1) signalling pathway, believed to promote myelinization [84]. Consistently, all BACE1 knockout animal models present hypomyelination [83, 85]. The association between BACE1 and myelination, however, remains controversial, with as yet-limited research. BACE1 has also been described to regulate voltage-dependent sodium channels [86], although with a probably diminished impact on behavioural changes.

Like α-secretases, BACE1 activity also correlates with RA. Treatment with atRA was shown to alter both BACE1 expression and activity in a human neuroblastoma IMR-32 cell line, while its homologue BACE2 remained unaltered [60]. Interestingly, BACE1 mRNA levels are significantly increased, but have no impact in overall protein quantity [60]. In a different study, using rat primary cultures of cortical neurons, BACE1 expression levels were reduced by atRA treatment [87]. The same authors described that this alteration to BACE1 expression was mediated through NFkB (Fig. 1); disruption of NFkB led to increased transcription of BACE1 and reversed the effects of atRA treatment [87].

Although BACE2 is homologous to BACE1, its involvement in APP processing has not been fully described. BACE2 was initially considered a β-secretase [88–90], cleaving APP at the β-site [90]. Later studies showed BACE2 to cleave within the Aβ region [91], similar to α-secretase, suggesting a protective role [92–94], as BACE2 overexpression prevents production of Aβ [91, 95–98]. Given that BACE2 expression is lower in the brain [99], its impact on AD may be minor. However, its β-secretase activity has recently been reiterated, particularly when facilitated by AD-associated conformational changes in APP [100]. The corelation of BACE2 with AD pathophysiology is corroborated by its increased activity in pre-clinical AD [101]. These findings further strengthen the need for a holistic approach to AD, revealing novel pathways in which the amyloid process can be decreased/inhibited.

γ-Secretases

γ-secretase is a multiprotein complex consisting of presenilin (PSEN1 and 2), nicastrin, Aph-1, and Pen-2, with

PSEN proteases containing the two catalytic aspartates that mediate peptide bond scission [102], and cleaving APP within the transmembrane domain (TMD) [103]. The cleavage occurs by the two critical aspartyl residues within TMDs 6 and 7 of PSEN1/2 [104]. Although the specific function of each component of this complex has been subject to intense scrutiny over the last decade, consensus has not been achieved [6, 105–108].

PSEN1 and PSEN2 are involved in the processing of type-1 transmembrane proteins, including APP [6, 109]. Their closely related genes were discovered as mutated loci in a large proportion of human pedigrees with inherited early AD onset; these two genes encode components of γ-secretase complexes that cleave transmembrane proteins within lipid bilayers, including APP, the Notch receptor, E-cadherin, Nectin1, and others [110, 111].

Importantly, γ-secretase intramembrane processing of APP is not restricted to a single site; this complex is widely accepted to cleave at several sites within the TMD of their targets, and in the case of APP with three cleavage points separated by approximately three amino acids each [112–115]. Under physiological conditions, the last cleavage is variable, occurring between positions 37–43 of the Aβ peptide. This variation is highly relevant for AD pathology, directly and proportionally linked to Aβ aggregation, deposition, and toxicity [116]. These multiple cleavages are thought to be due to a stepwise cleavage mechanism, and research suggests that this may be a general characteristic of all γ-like-secretases [117–119]. The distinction between the three cleavages is of great importance to AD and may hold the key to therapeutic strategies [76], being that the longer peptides exhibit a greater tendency to aggregate.

RAR signalling might not just be restricted to α and β-secretases, but may also impact the γ-secretase complex. Its activity is largely reduced with RA treatment, leading to a threefold increase of γ-secretase substrate, C99 [120]. This is an important objection against the therapeutic effects of RA, since the cellular accumulation of C99 is toxic [121]. The same study showed that isolated inhibition of γ-cleavage reduces Aβ secretion and that RA-mediated γ-secretase inhibition requires ERK activation [120]. RA regulates various signalling pathways, including kinases, and the ERK-pathway is a negative regulator of γ-secretase [122]. A more targeted analysis of the impact of atRA treatment on PSEN1 and 2 revealed increased mRNA levels of PSEN1, but, mirroring the situation with BACE secretases, unaltered for PSEN2 [60]. In addition, although PSEN1 mRNA levels are increased, protein levels remain largely unchanged, and activity is actually decreased (Fig. 1).

Alternative APP-cleaving secretases

Besides the above-described proteases, other APP cleaving enzymes have recently been described.

Membrane-Type Matrix Metalloproteinases (MT-MMP) were shown to be involved in the regulation of APP processing, cleaving, and shedding of ectodomain fragments, generating CTFs, specifically MT1-MMP, MT3-MMP, and MT5-MMP [123, 124]. Mouse AD models suggest pro-amyloidogenic roles for MT1-MMP. [125], while the absence of MT5-MMP (MT5-MMP$^{-/-}$) increased cognitive function in a FAD mouse model, without altering α-, β- and γ-secretases' activities, but altering sAPP secretion [126]. Additionally, MT5-MMP also promotes AD pathogenesis in the same model [127]. The same study found the impact of MT5-MMP expression in APP processing to reside on its ability to affect cellular APP trafficking [127].

Consistently, inhibition of the lysosomal aspartic endoprotease cathepsin D was also beneficial in reducing Aβ load and improving memory, in a transgenic mouse model [128]. Early studies corelated cathepsin D with AD [129, 130], without affecting Aβ formation in a cathepsin D knockout model [131]. Cathepsin D gained more significance when animal studies described a specificity for the APP β-cleavage site [132], which also highlighted that selective inhibition of the lysosomal cysteine protease cathepsin B significantly decreased Aβ(40/42) production, independent of β-secretase activity.

Other proteins involved in APP processing should be mentioned, among them meprin B, which can act as a sheddase for APP [133], cleaving within the N-terminal region without toxic fragment production [134, 135]. Also noteworthy, overexpression of ADAMTS4 in cell models increased Aβ secretion, verified in in vivo AD model, where ADAMTS4$^{-/-}$ knockout resulted in decreased Aβ [136]. The study further presented oligodendrocytes as a source of amyloid peptides, shedding new light on the peptide's origin.

Except for some tenuous associations (namely with MT5-MMP), the impact of RA in alternative APP cleaving secretases remains elusive [137]. This adds another layer for the potential therapeutic exploitation, should the alterations induced by RA prove beneficial in the AD context.

Modulation of retinoic acid receptors

RA exerts a profound effect on homeostatic properties and signalling pathways [138], ranging from physiological functions to pathology [139, 140], and the nervous system is importantly regulated by this pathway. Unravelling the modulation of RAR in AD is of paramount importance, as regulation of APP cleaving secretases is a strong candidate for translational research for a therapy [141]. Most

studies on RA-induced alteration to secretase activity are based exclusively on atRA [60]. However, the influence of isoform specific RAR signalling in neuronal function and homeostasis is currently well defined [142, 143] and its overall significance in the context of AD has received recent interest, with some retinoid drugs currently undergoing clinical trials (Table 1). RAR activation as a therapeutical candidate is being explored in AD models [144, 145], as it reduces neuroinflammation and contributes to neuroregeneration [146], adding possible paths to promote neuronal health and rehabilitation [147]. The Aβ peptide inhibits RA synthesis, aggravating AD symptoms and progression [145], which correlates with the observed decreased serum levels of retinoid metabolites in AD patients [55, 56]. The potential of systemic retinoid as therapy has long been established, although not completely without side-effects [148], and its use has been approved for several conditions (Table 1). However, systemic retinoid therapy requires careful patient monitorisation, as information on long-term use and mechanism of potential adverse reactions is still lacking [149].

RA signalling is translated via two families of nuclear receptors as follows: RAR has three isoforms (α, β and γ) that can be activated by both atRA and 9-cis-RA enantiomer [150]. The retinoic X receptor (RXR) also has three isoforms and is activated by 9-cis-RA [151], playing a role in the RA-related negative feedback system, mediating antiproliferative effects [152]. RXR increases DNA binding and transcriptional function, with a direct effect on their respective response elements [102]. Both families can form heterodimers as RAR/RXR [153].

Similar to other type II nuclear receptors, each RAR isoform produces several splice variants [154–156]. Agonist binding results in detachment of corepressor proteins, activating the receptor [153]; RAR signalling is highly dependent on recruiting coactivator proteins promoting downstream gene expression [157]. RAR gene expression is itself regulated by RAR activation via promotor methylation events [158]. While RARα and RARβ have been extensively studied and explored, the isoform RARγ is less well described [159], although the physiological processes regulated by this receptor are not entirely clear [160], it appears to share some of the broad functions in embryogenesis and cell differentiation, common to other members of the RAR family [161].

RAR/RXR ligand binding and heterodimer crosstalk

Although RARs can also be activated by atRA, RXRs are only activated by the less lipophilic 9-cis [150, 162]. Previous research has demonstrated that retinoid effects are also mediated by heterodimers formed by different RAR and RXR isotypes, which can act as transcription repressors or activators [163].

RXR Arg316 is the only polar contact, where its ligands can form an ionic connection; binding shape and lipophilic contacts are the primary determinants of ligand recognition, as most RXR ligands have the classic fatty acid design [164]. New classes of agonists with a better safety profile and less lipophilic properties are being developed [165, 166].

RXR regulates lipid, carbohydrate, and amino acid metabolism [167–169]. RXR activation affects lipid metabolism by increasing the expression of ApoE (apolipoprotein E) and ABCA1 (ATP-binding cassette transporter ABCA1), which leads to an increase in ApoE lipidation mediated by ABCA1 and HDL levels in the brain [170, 171]. This is particularly relevant because APP processing, beta amyloid generation, and plaque development in vivo are all affected by changes in intracellular lipid homeostasis [172], much of which is controlled by the ApoE lipoprotein transport system [173, 174]. The convergence of the amyloid cascade theory (which posits Aβ brain deposition as the fundamental step in AD) [175] and the ApoE/lipid recycling cascade concept [176] supports lipid homeostasis changes as a common denominator for ApoE and Aβ dysfunctions in AD. Furthermore, RXR activation by bexarotene has been reported to cause Aβ phagocytosis in brain myeloid cells, linked to an increase in the expression of the phagocytic receptors [177].

Table 1 Retinoids undergoing pre-clinical or clinical trials for AD

Drug	Effect	Other conditions	Status in AD
9-cis retinoic acid	Pan agonist, RXR preference	Kaposi's sarcoma and chronic hand eczema—approved	Explored [226]
Tamibarotene (AM-80)	RARα/β agonist	Acute Promyelocytic Leukaemia—approved (Japan), under development (US, EU, China)	Explored in AD, no outcomes [227]
Isotretinoin	Possible precursor to RAR/RXR agonists [228]	Acne Vulgaris—approved	Explored [146, 229]
Acitretin	Possible RAR/RXR agonist	Psoriasis—approved	Explored [230]
Bexarotene	RXR Agonist	Cutaneous T cell lymphoma—approved	Explored in clinical trials: negative outcome [231]
Tazarotene	RAR-γ and RAR-β agonist	Psoriasis; Acne Vulgaris -approved	Considered [146, 232]

RARα

RARα is also denominated nuclear receptor subfamily 1, group B, member 1 (NR1B1) [178]; its activation by the selective agonist AM580 is protective against the decreased RA synthesis in a neuroblastoma cell line [145], inhibits Aβ generation in vitro via increased ADAM10 expression [48, 100], and directly inhibits γ-secretase cleavage of APP in cellular models [120]. Of note, not only does RARα signalling prevent Aβ synthesis, but it is also neuroprotective against Aβ [152].

RARα activation plays a central role in cell growth [180], differentiation [181], and organ formation during embryonic development [182]. RARα signalling has been linked to various pathways [183], especially in early embryonic development [184], inducing differentiation of Neuronal Progenitor Cells (NPC) into migrating fibroblasts and consequent maturation into neurons [185]. It plays a central role in regulating neural differentiation [186], via the expression of the pro-neural induction factor Neurogenin 2 [187, 188].

RARβ

RARβ is another cytoplasmic nuclear receptor [189], directed to subnuclear compartments following activation [190]. This receptor also mediates signalling in cell growth, differentiation, and embryonic events: it has been described to increase the proliferation of NPCs through the Sonic Hedgehog Pathway (Shh) [185] and to be a key player in the neurite growth through the signalling sequence for the Nerve Growth Factor (NGF) [191]. Curiously, it is theorized to limit the growth of many cell types by regulating gene expression, as it acts in embryonic development controlling numerous aspects of cell proliferation, differentiation, and inducing apoptosis of selected cell populations [182, 192–194].

A Genome-wide association study associates RARβ as a risk gene for several neurodegenerative pathologies, including Alzheimer's, Parkinson's, and Huntington's diseases [195]. Its activation in a neuropathic pain model restores mechanisms involved in cell adhesion [196], neuronal cone growth [197], gap junction [198], and pain-related pathways [199]. RARβ is central for retinoid-mediated neurite outgrowth [200], also acting in mature neurons [201] recruiting mitochondria to the neurite growth cone [147]. Moreover, RARβ neuroprotective roles additionally include the reduction of neuroinflammation and increase of neuroplasticity [202].

Activation of RAR in a neuronal setting

Modulating different RAR isoforms can induce significantly different physiological responses [203]. Targeting RAR as a potential therapeutic target for neurodegenerative diseases has been a topic of extensive research [144, 146, 204], with several studies showing a clear difference between isoform-specific stimulation [205–209]. Specific RARγ stimulus has been linked to apoptosis in a melanoma cell line and to increased cell differentiation [205]. Moreover, a study in embryonal carcinoma cells revealed that different RAR isoforms perform distinct roles in the differentiation of spiny neurons [207].

The combined modulation of RAR differs from the conjugated effects of isolated isoform stimulus [203]. Co-activation of RARα and β is described to play an important signalling role in adult neurogenesis, modulating the Fibroblast Growth Factor (FGF) and Shh signalling pathways [185], while the sequential activation of RARα and β, in vitro, results in neuronal differentiation of cultured spinal cord progenitor cells (SCPC) [210]. Although both receptors are expressed in adult neurons of the subventricular zone (SVZ) [211] their role in neurogenesis, especially co-modulation, remains somewhat elusive [185]. Interestingly, the disruption of both RAR and RXR families, independent of isoform, causes an impairment in hippocampal memory and synaptic plasticity in mice [212].

In addition to protective effects in neurodegenerative settings [202], pan-RAR activation promotes neuroplasticity and regeneration [185, 191, 213–217], and individual activation of all RAR isoforms promotes neurite outgrowth [218]. A study in a rat model of ageing found atRA to reduce neuroinflammation [219], while activation of RARβ was described to be involved in NG2-neuronal cross-communication, diminishing the formation of the glial scar [179, 188] and promoting regeneration [179] and remyelination [188], in a rodent model of spinal cord injury. RARβ activation can also revert inhibition of neurite growth via PKC-induced events [220].

ADAM10 overexpression reduced levels of brain Aβ and reversed Long-Term Potentiation (LTP) inhibition and spatial learning impairments in APP transgenic mice, providing a proof-of-concept therapeutic option for increasing α-secretase activity [221]. Furthermore, deprenyl, an AD anti-dementia medication, appears to increase APP cleavage mediated by α-secretase in AD patients [222].

Activation of nuclear receptors is a promising therapeutic approach for AD [204]. These receptors act as ligand-activated transcription factors, regulating gene expression with cell type-specific effects [223]. AD is associated with a variety of pathophysiological features beyond amyloid plaques, including inflammation, cell death and regeneration processes, altered neurotransmission, and age-related changes. RARs and retinoids are a potential therapeutic target, as they are involved in all of these [204, 223]. As such, considering the plethora of crucial pathways involved, the future possibilities of targeting RAR for

neurodegenerative disease therapy and regeneration cannot be overstated.

Towards a holistic and systems approach

A relevant approach of pivotal importance to AD is promoting APP α-secretase cleavage, which may be crucial to delaying disease onset, and understanding alterations to key proteins, induced through receptor modulation. Promoting α-cleavage of APP has long been a prime therapeutical target in AD and, as such, the holistic methodology is a relevant approach; this strategy investigates global and dynamic molecular changes, considering interactions under normal and pathological conditions, thus representing a promising approach for the study of AD and other complex pathologies [40, 224].

Applications of omics approaches is attracting growing interest due to its association with different diseases [224]. The study of protein interactions (interactomes) has shown promising results in distinguishing key chains of events and functions of important proteins, with central roles in various pathways, either physiological or associated with disease [23, 225], (da Cruz e Silva et al., submitted).

For pathologies involving many affected pathways and regulation systems, analysis and data integration from different omics technologies is crucial for a fuller understanding of the disease, supporting the development of personalized diagnostic and therapeutic tools. Several omics studies aim to determine novel pathways and networks, suggesting new pathologic mechanisms associated with disease states and cross-linked with other diseases. The limitation to the holistic approach is the challenge in distinguishing whether the alteration of molecule and marker networks are a cause or an effect of the disease. Nevertheless, it is helpful in identifying new targets or in validating previously identified ones.

Overall, the notion of APP secretases as therapeutic targets for AD grows stronger. As the three secretase classes cleave a significant pool of substrates (not restricted to APP) affecting several signalling and metabolic pathways, purposefully altering their activity is a complex procedure with possible adverse outcomes. Secretase selective inhibition establishes problems in maintaining the physiological pathways inherent to normal cell function, with the answer lying on targeted modulation of several pathways. Besides, substrate build-up can have unforeseen cytotoxic effects and thus be counterproductive for promoting homeostasis and preventing neurodegeneration.

RAR-induced secretase alterations have been, to some extent, described in a specific context, lacking a holistic approach to determine whether they are restricted to the studied protein complex, or actually have deeper effects in the AD interactome. This knowledge is of upmost importance, as it allows determining whether these alterations are compatible with homeostasis and, consequently, a potential AD therapy.

In closing, the holistic and systems approach focuses on several molecular players and not only the underlying individual disease processes, with the unique advantage of identifying signalling cascades and crosstalk between different pathways, related to a specific molecular target, involving many fronts of the disease.

Funding This work was supported by ccdrc (Grant no. CENTRO-01-0145-FEDER-000003), fundação para a ciência e a tecnologia (Grant nos. PTDC/DTP-PIC/5587/2014, UID/BIM/04501/2013, 2020.02006.CEECIND).

References

1. Marambaud P, Vintgdeux V (2012) Identification and biology of α-secretases. J Neurochem 120:34–45. https://doi.org/10.1111/j.1471-4159.2011.07477.x
2. Vincent B, Govitrapong P (2011) Activation of the apha-secretase processing of ABetaPP as a therapeutic approach in alzheimer's disease. J Alzheimer Dis 24:75–94. https://doi.org/10.3233/JAD-2011-110218
3. Epis R, Marcello E, Fabrizio Gardoni MDL (2012) Alpha, beta- and gamma-secretases in Alzheimer's disease. Front Biosci S4(42):1126–1150
4. Komano H, Seeger M, Gandyl S et al (1999) Involvement of cell surface glycosyl-phosphatidylinositol-linked aspartyl proteases in α-secretase-type cleavage and ectodomain solubilization of human Alzheimer β-amyloid precursor protein in yeast. J Biol Chem 273:31648–31651. https://doi.org/10.1074/jbc.273.48.31648
5. Sun J, Roy S (2013) The physical approximation of APP and BACE-1 - a key event in Alzheimer's disease pathogenesis. Dev Neurobiol. https://doi.org/10.1002/dneu
6. Haapasalo A, Kovacs DM (2011) The many substrates of presenilin/γ-secretase. J Alzheimer's Dis 25:3–28. https://doi.org/10.3233/JAD-2011-101065
7. 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
8. Müller UC, Zheng H (2012) Physiological functions of APP family proteins. Cold Spring Harb Perspect Med 2:1–17. https://doi.org/10.1101/cshperspect.a006288
9. Nalivaeva NN, Turner AJ (2013) The amyloid precursor protein: a biochemical enigma in brain development, function and disease. FEBS Lett 587:2046–2054. https://doi.org/10.1016/j.febslet.2013.05.010
10. Da Cruz e Silva EF, Da Cruz e Silva OAB (2003) Protein phosphorylation and APP metabolism. Neurochem Res 28:1553–1561. https://doi.org/10.1023/A:1025630627319
11. Zheng H, Koo EH (2006) The amyloid precursor protein: beyond amyloid. Mol Neurodegener 1:1–12. https://doi.org/10.1186/1750-1326-1-5
12. Beckmann A-M, Glebov K, Walter J et al (2016) The intact Kunitz domain protects the amyloid precursor protein from being processed by matriptase-2. Biol Chem 397:777–790. https://doi.org/10.1515/hsz-2015-0263

13. Ben KN, Tyteca D, Marinangeli C et al (2012) Structural features of the KPI domain control APP dimerization, trafficking, and processing. FASEB J 26:855–867. https://doi.org/10.1096/fj.11-190207
14. Menéndez-González M, Pérez-Pinera P, Martínez-Rivera M et al (2006) APP processing and the APP-KPI domain involvement in the amyloid cascade. Neurodegener Dis 2:277–283. https://doi.org/10.1159/000092315
15. Matsui T, Ingelsson M, Fukumoto H et al (2007) Expression of APP pathway mRNAs and proteins in Alzheimer's disease. Brain Res 1161:116–123. https://doi.org/10.1016/j.brainres.2007.05.050
16. Belyaev ND, Kellett KAB, Beckett C et al (2010) The transcriptionally active amyloid precursor protein (APP) intracellular domain is preferentially produced from the 695 isoform of APP in a β-secretase-dependent pathway. J Biol Chem 285:41443–41454. https://doi.org/10.1074/jbc.M110.141390
17. Cousins SL, Hoey SEA, Anne Stephenson F, Perkinton MS (2009) Amyloid precursor protein 695 associates with assembled NR2A- and NR2B-containing NMDA receptors to result in the enhancement of their cell surface delivery. J Neurochem 111:1501–1513. https://doi.org/10.1111/j.1471-4159.2009.06424.x
18. O'Brien RJ, Wong PC (2011) Amyloid precursor protein processing and alzheimer's disease. Annu Rev Neurosci 34:185–204. https://doi.org/10.1146/annurev-neuro-061010-113613
19. Lee KJ, Moussa CEH, Lee Y et al (2010) Beta amyloid-independent role of amyloid precursor protein in generation and maintenance of dendritic spines. Neuroscience 169:344–356. https://doi.org/10.1016/j.neuroscience.2010.04.078
20. Midthune B, Tyan SH, Walsh JJ et al (2012) Deletion of the amyloid precursor-like protein 2 (APLP2) does not affect hippocampal neuron morphology or function. Mol Cell Neurosci 49:448–455. https://doi.org/10.1016/j.mcn.2012.02.001
21. Groot AJ, Vooijs MA (2012) The role of adams in notch signaling. Adv Exp Med Biol 727:15–36. https://doi.org/10.1007/978-1-4614-0899-4_2
22. Fardilha M, Vieira SI, Barros A et al (2007) Differential distribution of Alzheimer's amyloid precursor protein family variants in human sperm. Ann N Y Acad Sci 1096:196–206. https://doi.org/10.1196/annals.1397.086
23. Silva JV, Yoon S, Domingues S et al (2015) Amyloid precursor protein interaction network in human testis: Sentinel proteins for male reproduction. BMC Bioinformatics 16:1–12. https://doi.org/10.1186/s12859-014-0432-9
24. Oliveira J, Costa M, De Almeida MSC et al (2017) Protein phosphorylation is a key mechanism in alzheimer's disease. J Alzheimer's Dis 58:953–978. https://doi.org/10.3233/JAD-170176
25. Xu P, Derynck R (2010) Direct activation of TACE-mediated ectodomain shedding by p38 MAP kinase regulates EGF receptor-dependent cell proliferation. Mol Cell 37:551–566. https://doi.org/10.1016/j.molcel.2010.01.034
26. da Cruz e Silva OAB, Rebelo S, Vieira SI, et al (2009) Enhanced generation of Alzheimer's amyloid-β following chronic exposure to phorbol ester correlates with differential effects on alpha and epsilon isozymes of protein kinase C. J Neurochem 108:319–330. https://doi.org/10.1111/j.1471-4159.2008.05770.x
27. Vieira SI, Rebelo S, Domingues SC et al (2009) S655 phosphorylation enhances APP secretory traffic. Mol Cell Biochem 328:145–154. https://doi.org/10.1007/s11010-009-0084-7
28. Vieira SI, Rebelo S, Esselmann H et al (2010) Retrieval of the Alzheimer's amyloid precursor protein from the endosome to the TGN is S655 phosphorylation state-dependent and retromer-mediated. Mol Neurodegener 5:1–21. https://doi.org/10.1186/1750-1326-5-40
29. Chang K-A, Kim H-S, Ha T-Y et al (2006) Phosphorylation of amyloid precursor protein (APP) at Thr668 regulates the nuclear translocation of the APP intracellular domain and induces neurodegeneration. Mol Cell Biol 26:4327–4338. https://doi.org/10.1128/mcb.02393-05
30. Lee MS, Kao SC, Lemere CA et al (2003) APP processing is regulated by cytoplasmic phosphorylation. J Cell Biol 163:83–95. https://doi.org/10.1083/jcb.200301115
31. Feyt C, Pierrot N, Tasiaux B et al (2007) Phosphorylation of APP695 at Thr668 decreases γ-cleavage and extracellular Aβ. Biochem Biophys Res Commun 357:1004–1010. https://doi.org/10.1016/j.bbrc.2007.04.036
32. Kametani F (2008) Epsilon-secretase: reduction of amyloid precursor protein epsilon-site cleavage in Alzheimer's disease. Curr Alzheimer Res 5:165–171. https://doi.org/10.2174/156720508783954776
33. Zhao G, Mao G, Tan J et al (2004) Identification of a new presenilin-dependent zeta-cleavage site within the transmembrane domain of amyloid precursor protein. J Biol Chem 279:50647–50650. https://doi.org/10.1074/jbc.C400473200
34. Zhao G, Cui MZ, Mao G et al (2005) γ-Cleavage is dependent on Z-cleavage during the proteolytic processing of amyloid precursor protein within its transmembrane domain. J Biol Chem 280:37689–37697. https://doi.org/10.1074/jbc.M507993200
35. Chow VW, Mattson MP, Wong PC, Gleichmann M (2010) An overview of APP processing enzymes and products. Neuromolecular Med 12:1–12. https://doi.org/10.1007/s12017-009-8104-z
36. De Strooper B, Annaert W (2000) Proteolytic processing and cell biological functions of the amyloid precursor protein. J Cell Sci 113(1):1857–1870
37. Sisodia SS (1992) Beta-Amiloid precursor protein cleavage a membrane-bound protease. Proc Natl Acad Sci USA 89:6075–6079
38. Anderson JP, Esch FS, Keim PS et al (1991) Exact cleavage site of Alzheimer amyloid precursor in neuronal PC-12 cells. Neurosci Lett 128:126–128. https://doi.org/10.1016/0304-3940(91)90775-O
39. Nunan J, Small DH (2000) Regulation of APP cleavage by α-, β- and γ-secretases. FEBS Lett 483:6–10. https://doi.org/10.1016/S0014-5793(00)02076-7
40. García-González L, Pilat D, Baranger K, Rivera S (2019) Emerging alternative proteinases in APP metabolism and Alzheimer's Disease pathogenesis: a focus on MT1-MMP and MT5-MMP. Front Aging Neurosci 11:1–19. https://doi.org/10.3389/fnagi.2019.00244
41. Postina R, Schroeder A, Dewachter I et al (2004) A disintegrin-metalloproteinase prevents amyloid plaque formation and hippocampal defects in an Alzheimer disease mouse model. J Clin Invest 114:598–598. https://doi.org/10.1172/jci20864e1
42. Nitsch RM, Kim C, Growdon JH (1998) Vasopressin and bradykinin regulate secretory processing of the amyloid protein precursor of Alzheimer's disease. Neurochem Res 23:807–814. https://doi.org/10.1023/A:1022423813362
43. Da Cruz e Silva OAB, Rebelo S, Vieira SI, Gandy S, Da Cruz e Silva EFPG (2009) Enhanced generation of Alzheimer's amyloid-β following chronic exposure to phorbol ester correlates with differential effects on alpha and epsilon isozymes of protein kinase C. J Neurochem 2009:319–330
44. Odete AB, Fardilha M, Henriques AG et al (2004) Signal transduction therapeutics: relevance for alzheimer's disease signal transduction therapeutics relevance for alzheimer's disease. J Alzheimer Dis 2004:1–2. https://doi.org/10.1385/JMN
45. Kuhn PH, Wang H, Dislich B et al (2010) ADAM10 is the physiologically relevant, constitutive α-secretase of the amyloid precursor protein in primary neurons. EMBO J 29:3020–3032. https://doi.org/10.1038/emboj.2010.167

46. Edwards DR, Handsley MM, Pennington CJ (2009) The ADAM metalloproteinases. Mol Aspects Med 29:258–289. https://doi.org/10.1016/j.mam.2008.08.001
47. Blobel CP (2005) ADAMs: Key components in EGFR signalling and development. Nat Rev Mol Cell Biol 6:32–43. https://doi.org/10.1038/nrm1548
48. Tucher J, Linke D, Koudelka T et al (2014) LC-MS based cleavage site profiling of the proteases ADAM10 and ADAM17 using proteome-derived peptide libraries. J Proteome Res 13:2205–2214. https://doi.org/10.1021/pr401135u
49. Zunke F, Rose-John S (2017) The shedding protease ADAM17: physiology and pathophysiology. Biochim Biophys Acta Mol Cell Res 1864:2059–2070. https://doi.org/10.1016/j.bbamcr.2017.07.001
50. Seals DF, Courtneidge SA (2003) The ADAMs family of metalloproteases: multidomain proteins with multiple functions. Genes Dev 17:7–30. https://doi.org/10.1101/gad.1039703
51. Allinson TMJ, Parkin ET, Turner AJ, Hooper NM (2003) ADAMs family members as amyloid precursor protein α-secretases. J Neurosci Res 74:342–352. https://doi.org/10.1002/jnr.10737
52. Weskamp G, Cai H, Brodie TA et al (2002) Mice lacking the metalloprotease-disintegrin MDC9 (ADAM9) have no evident major abnormalities during development or adult life. Mol Cell Biol 22:1537–1544. https://doi.org/10.1128/mcb.22.5.1537-1544.2002
53. Hartmann D, De Strooper B, Serneels L et al (2002) The disintegrin/metalloprotease ADAM 10 is essential for Notch signalling but not for α-secretase activity in fibroblasts. Hum Mol Genet 11:2615–2624. https://doi.org/10.1093/hmg/11.21.2615
54. Walter S, Jumpertz T, Hüttenrauch M et al (2019) The metalloprotease ADAMTS4 generates N-truncated Aβ4–x species and marks oligodendrocytes as a source of amyloidogenic peptides in Alzheimer's disease. Acta Neuropathol 137:239–257. https://doi.org/10.1007/s00401-018-1929-5
55. Jiménez-Jiménez FJ, Molina JA, de Bustos F et al (1999) Serum levels of beta-carotene, alpha-carotene and vitamin A in patients with Alzheimer's disease. Eur J Neurol 6:495–497. https://doi.org/10.1046/j.1468-1331.1999.640495.x
56. Zaman Z, Roche S, Fielden P et al (1992) Plasma concentrations of vitamins A and E and carotenoids in Alzheimer's disease. Age Ageing 21:91–94. https://doi.org/10.1093/ageing/21.2.91
57. Prinzen C, Müller U, Endres K et al (2005) Genomic structure and functional characterization of the human ADAM10 promoter. FASEB J Off Publ Fed Am Soc Exp Biol 19:1522–1524. https://doi.org/10.1096/fj.04-3619fje
58. Holback S, Adlerz L, Iverfeldt K (2005) Increased processing of APLP2 and APP with concomitant formation of APP intracellular domains in BDNF and retinoic acid-differentiated human neuroblastoma cells. J Neurochem 95:1059–1068. https://doi.org/10.1111/j.1471-4159.2005.03440.x
59. Endres K, Postina R, Schroeder A et al (2005) Shedding of the amyloid precursor protein-like protein APLP2 by disintegrin-metalloproteinases: Retinoic acid-induced upregulation of substrate and proteinase ADAM10 during neuronal cell differentiation. FEBS J 272:5808–5820. https://doi.org/10.1111/j.1742-4658.2005.04976.x
60. Koryakina A, Aeberhard J, Kiefer S et al (2009) Regulation of secretases by all-trans-retinoic acid. FEBS J 276:2645–2655. https://doi.org/10.1111/j.1742-4658.2009.06992.x
61. Tippmann F, Hundt J, Schneider A et al (2009) Up-regulation of the α-secretase ADAM10 by retinoic acid receptors and acitretin. FASEB J 23:1643–1654. https://doi.org/10.1096/fj.08-121392
62. Niles RM (1994) Interactions between retinoic acid and protein kinase C in induction of melanoma differentiation. Adv Exp Med Biol 354:37–57. https://doi.org/10.1007/978-1-4899-0939-8_3
63. Bruck N, Vitoux D, Ferry C et al (2009) A coordinated phosphorylation cascade initiated by p38MAPK/MSK1 directs RARα to target promoters. EMBO J 28:34–47. https://doi.org/10.1038/emboj.2008.256
64. Zhang T, Chen D, Lee TH (2020) Phosphorylation signaling in APP processing in Alzheimer's disease. Int J Mol Sci. https://doi.org/10.3390/ijms21010209
65. Macleod R, Hillert EK, Cameron RT, Baillie GS (2015) The role and therapeutic targeting of α-, β-and γ-secretase in Alzheimer's disease. Futur Sci OA. https://doi.org/10.4155/fso.15.9
66. Xu X (2009) γ-Secretase catalyzes sequential cleavages of the AβPP transmembrane domain. J Alzheimer's Dis 16:211–224. https://doi.org/10.3233/JAD-2009-0957
67. Vassar R (2004) BACE1: The β-secreiase enzyme in Alzheimer's disease. J Mol Neurosci 23:105–113. https://doi.org/10.1385/JMN:23:1-2:105
68. Roberds SL, Anderson J, Basi G et al (2001) BACE knockout mice are healthy despite lacking the primary β-secretase activity in brain: Implications for Alzheimer's disease therapeutics. Hum Mol Genet 10:1317–1324. https://doi.org/10.1093/hmg/10.12.1317
69. Luo Y, Bolon B, Damore MA et al (2003) BACE1 (β-secretase) knockout mice do not acquire compensatory gene expression changes or develop neural lesions over time. Neurobiol Dis 14:81–88. https://doi.org/10.1016/S0969-9961(03)00104-9
70. Cai H, Wang Y, McCarthy D et al (2001) BACE1 is the major β-secretase for generation of Aβ peptides by neurons. Nat Neurosci 4:233–234. https://doi.org/10.1038/85064
71. Hong L, Koelsch G, Lin X et al (2000) Structure of the protease domain of memapsin 2 (β-secretase) complexed with inhibitor. Science 290(80):150–153. https://doi.org/10.1126/science.290.5489.150
72. Dislich B, Lichtenthaler SF (2012) The membrane-bound aspartyl protease BACE1: molecular and functional properties in Alzheimer's disease and beyond. Front Physiol 3:1–16. https://doi.org/10.3389/fphys.2012.00008
73. Vassar R, Bennett BD, Babu-Khan S et al (1999) β-Secretase cleavage of Alzheimer's amyloid precursor protein by the transmembrane aspartic protease BACE. Science 286(80):735–741. https://doi.org/10.1126/science.286.5440.735
74. Aleksis R, Oleskovs F, Jaudzems K et al (2017) Structural studies of amyloid-β peptides: Unlocking the mechanism of aggregation and the associated toxicity. Biochimie 140:176–192. https://doi.org/10.1016/j.biochi.2017.07.011
75. Vassar R, Cole S (2008) The basic biology of BACE1: a key therapeutic target for alzheimers disease. Curr Genomics 8:509–530. https://doi.org/10.2174/138920207783769512
76. Schenk D, Basi GS, Pangalos MN (2012) Treatment strategies targeting amyloid β-protein. Cold Spring Harb Perspect Med 2:1–32. https://doi.org/10.1101/cshperspect.a006387
77. Citron M (2004) β-Secretase inhibition for the treatment of Alzheimer's disease—promise and challenge. Trends Pharmacol Sci 25:92–97. https://doi.org/10.1016/j.tips.2003.12.004
78. Hemming ML, Elias JE, Gygi SP, Selkoe DJ (2009) Identification of β-secretase (BACE1) substrates using quantitative proteomics. PLoS ONE. https://doi.org/10.1371/journal.pone.0008477
79. Barão S, Moechars D, Lichtenthaler SF, De Strooper B (2016) BACE1 physiological functions may limit its use as therapeutic target for alzheimer's disease. Trends Neurosci 39:158–169. https://doi.org/10.1016/j.tins.2016.01.003
80. Coimbra JRM, Marques DFF, Baptista SJ et al (2018) Highlights in BACE1 inhibitors for Alzheimer's disease treatment. Front Chem 6:1–10. https://doi.org/10.3389/fchem.2018.00178
81. Harrison SM, Harper AJ, Hawkins J et al (2003) BACE1 (β-secretase) transgenic and knockout mice: identification

of neurochemical deficits and behavioral changes. Mol Cell Neurosci 24:646–655. https://doi.org/10.1016/S1044-7431(03)00227-6
82. Dominguez D, Tournoy J, Hartmann D et al (2005) Phenotypic and biochemical analyses of BACE1- and BACE2-deficient mice. J Biol Chem 280:30797–30806. https://doi.org/10.1074/jbc.M505249200
83. Willem M, Garratt AN, Novak B et al (2006) Control of peripheral nerve myelination by the β-secretase BACE1. Science 314(80):664–666. https://doi.org/10.1126/science.1132341
84. Birchmeier C, Nave KA (2008) Neuregulin-1, a key axonal signal that drives schwann cell growth and differentiation. Glia 56:1491–1497. https://doi.org/10.1002/glia.20753
85. Hu X, Hicks CW, He W et al (2006) Bace1 modulates myelination in the central and peripheral nervous system. Nat Neurosci 9:1520–1525. https://doi.org/10.1038/nn1797
86. Kim DY, Carey BW, Wang H et al (2007) BACE1 regulates voltage-gated sodium channels and neuronal activity. Nat Cell Biol 9:755–764. https://doi.org/10.1038/ncb1602
87. Wang R, Chen S, Liu Y et al (2015) All-trans-retinoic acid reduces BACE1 expression under inflammatory conditions via modulation of nuclear factor κB (NFκB) signaling. J Biol Chem 290:22532–22542. https://doi.org/10.1074/jbc.M115.662908
88. Yan R, Bienkowski MJ, Shuck ME et al (1999) Membrane-anchored aspartyl protease with Alzheimer's disease β-secretase activity. Nature 402:533–537. https://doi.org/10.1038/990107
89. Lin X, Koelsch G, Wu S et al (2000) Human aspartic protease memapsin 2 cleaves the β-secretase site of β-amyloid precursor protein. Proc Natl Acad Sci 97:1456–1460. https://doi.org/10.1073/pnas.97.4.1456
90. Farzan M, Schnitzler CE, Vasilieva N et al (2000) BACE2, a β-secretase homolog, cleaves at the β site and within the amyloid-β region of the amyloid-β precursor protein. Proc Natl Acad Sci 97:9712–9717. https://doi.org/10.1073/pnas.160115697
91. Sun X, He G, Song W (2006) BACE2, as a novel APP θ-secretase, is not responsible for the pathogenesis of Alzheimer's disease in Down syndrome. FASEB J 20:1369–1376. https://doi.org/10.1096/fj.05-5632com
92. Basi G, Frigon N, Barbour R et al (2003) Antagonistic effects of β-site amyloid precursor protein-cleaving enzymes 1 and 2 β-amyloid peptide production in cells. J Biol Chem 278:31512–31520. https://doi.org/10.1074/jbc.M300169200
93. Farzan M, Schnitzler CE, Vasilieva N et al (2000) BACE2, a β-secretase homolog, cleaves at the β site and within the amyloid-β region of the amyloid-β precursor protein. Proc Natl Acad Sci USA 97:9712–9717. https://doi.org/10.1073/pnas.160115697
94. Fluhrer R, Capell A, Westmeyer G et al (2002) A non-amyloidogenic function of BACE-2 in the secretory pathway. J Neurochem 81:1011–1020. https://doi.org/10.1046/j.1471-4159.2002.00908.x
95. Yan R, Munzner JB, Shuck ME, Bienkowski MJ (2001) BACE2 functions as an alternative α-secretase in cells*. J Biol Chem 276:34019–34027. https://doi.org/10.1074/jbc.M105583200
96. Azkona G, Levannon D, Groner Y, Dierssen M (2010) In vivo effects of APP are not exacerbated by BACE2 co-overexpression: behavioural characterization of a double transgenic mouse model. Amino Acids 39:1571–1580. https://doi.org/10.1007/s00726-010-0662-8
97. Azkona G, Amador-Arjona A, Obradors-Tarragó C et al (2010) Characterization of a mouse model overexpressing beta-site APP-cleaving enzyme 2 reveals a new role for BACE2. Genes Brain Behav 9:160–172. https://doi.org/10.1111/j.1601-183X.2009.00538.x
98. Abdul-Hay SO, Sahara T, McBride M et al (2012) Identification of BACE2 as an avid ß-amyloid-degrading protease. Mol Neurodegener 7:46. https://doi.org/10.1186/1750-1326-7-46
99. Bennett BD, Babu-Khan S, Loeloff R et al (2000) Expression analysis of BACE2 in brain and peripheral tissues*. J Biol Chem 275:20647–20651. https://doi.org/10.1074/jbc.M002688200
100. Wang Z, Xu Q, Cai F et al (2019) BACE2, a conditional β-secretase, contributes to Alzheimer's disease pathogenesis. JCI Insight 4:1–15. https://doi.org/10.1172/jci.insight.123431
101. Holler CJ, Webb RL, Laux AL et al (2012) BACE2 expression increases in human neurodegenerative disease. Am J Pathol 180:337–350. https://doi.org/10.1016/j.ajpath.2011.09.034
102. Wolfe MS (2006) The γ-secretase complex: membrane-embedded proteolytic ensemble. Current 2006:45
103. De Strooper B, Iwatsubo T, Wolfe MS (2012) Presenilins and γ-secretase: structure, function, and role in alzheimer disease. Cold Spring Harb Perspect Med 2:a006304–a006304. https://doi.org/10.1101/cshperspect.a006304
104. Wolfe MS, Selkoe DJ, Xia W et al (1999) Two transmembrane aspartates in presenilin-1 required for presenilin endoproteolysis and [gamma]-secretase activity : Abstract : Nature. Nature 398:513–517
105. Chávez-Gutiérrez L, Tolia A, Maes E et al (2008) Glu332 in the nicastrin ectodomain is essential for γ-secretase complex maturation but not for its activity. J Biol Chem 283:20096–20105. https://doi.org/10.1074/jbc.M803040200
106. Hasegawa H, Sanjo N, Chen F et al (2004) Both the sequence and length of the C terminus of PEN-2 are critical for intermolecular interactions and function of presenilin complexes. J Biol Chem 279:46455–46463. https://doi.org/10.1074/jbc.M406289200
107. Shah S, Lee SF, Tabuchi K et al (2005) Nicastrin functions as a γ-secretase-substrate receptor. Cell 122:435–447. https://doi.org/10.1016/j.cell.2005.05.022
108. Edbauer D, Winkler E, Regula JT et al (2003) Reconstitution of γ-secretase activity. Nat Cell Biol 5:486–488. https://doi.org/10.1038/ncb960
109. Nornes S, Newman M, Wells S et al (2009) Independent and cooperative action of Psen2 with Psen1 in zebrafish embryos. Exp Cell Res 315:2791–2801. https://doi.org/10.1016/j.yexcr.2009.06.023
110. Hemming ML, Elias JE, Gygi SP, Selkoe DJ (2008) Proteomic profiling of γ-secretase substrates and mapping of substrate requirements. PLoS Biol 6:2314–2328. https://doi.org/10.1371/journal.pbio.0060257
111. Beel AJ, Sanders CR (2008) Substrate specificity of γ-secretase and other intramembrane proteases. Cell Mol Life Sci 65:1311–1334. https://doi.org/10.1007/s00018-008-7462-2
112. Takami M, Nagashima Y, Sano Y et al (2009) γ-Secretase: successive tripeptide and tetrapeptide release from the transmembrane domain of β-carboxyl terminal fragment. J Neurosci 29:13042–13052. https://doi.org/10.1523/JNEUROSCI.2362-09.2009
113. Qi-Takahara Y, Morishima-Kawashima M, Tanimura Y et al (2005) Longer forms of amyloid β protein: implications for the mechanism of intramembrane cleavage by γ-secretase. J Neurosci 25:436–445. https://doi.org/10.1523/JNEUROSCI.1575-04.2005
114. Weidemann A, Eggert S, Reinhard FBM et al (2002) A novel ε-cleavage within the transmembrane domain of the Alzheimer amyloid precursor protein demonstrates homology with notch processing. Biochemistry 41:2825–2835. https://doi.org/10.1021/bi015794o
115. Sastre M, Steiner H, Fuchs K et al (2001) Presenilin-dependent γ-secretase processing of β-amyloid precursor protein at a site corresponding to the S3 cleavage of Notch. EMBO Rep 2:835–841. https://doi.org/10.1093/embo-reports/kve180

116. Haass C, Selkoe DJ (2007) Soluble protein oligomers in neurodegeneration: Lessons from the Alzheimer's amyloid β-peptide. Nat Rev Mol Cell Biol 8:101–112. https://doi.org/10.1038/nrm2101
117. Fluhrer R, Steiner H, Haass C (2009) Intramembrane Proteolysis by signal peptide peptidases: a comparative discussion of GXGD-type aspartyl proteases. J Biol Chem 284:13975–13979. https://doi.org/10.1074/jbc.R800040200
118. Fluhrer R, Fukumori A, Martin L et al (2008) Intramembrane proteolysis of GXGD-type aspartyl proteases is slowed by a familial Alzheimer disease-like mutation. J Biol Chem 283:30121–30128. https://doi.org/10.1074/jbc.M806092200
119. Fluhrer R, Grammer G, Israel L et al (2006) A γ-secretase-like intramembrane cleavage of TNFα by the GxGD aspartyl protease SPPL2b. Nat Cell Biol 8:894–896. https://doi.org/10.1038/ncb1450
120. Kapoor A, Wang BJ, Hsu WM et al (2013) Retinoic acid-elicited RARα/RXRα signaling attenuates aβ production by directly inhibiting γ-secretase-mediated cleavage of amyloid precursor protein. ACS Chem Neurosci 4:1093–1100. https://doi.org/10.1021/cn400039s
121. Checler F, Afram E, Pardossi-Piquard R, Lauritzen I (2021) Is γ-secretase a beneficial inactivating enzyme of the toxic APP C-terminal fragment C99? J Biol Chem. https://doi.org/10.1016/j.jbc.2021.100489
122. Kampmann E, Mey J (2007) Retinoic acid enhances Erk phosphorylation in the chick retina. Neurosci Lett 426:18–22. https://doi.org/10.1016/j.neulet.2007.07.039
123. Higashi S, Miyazaki K (2003) Novel processing of β-amyloid precursor protein catalyzed by membrane type 1 matrix metalloproteinase releases a fragment lacking the inhibitor domain against gelatinase A. Biochemistry 42:6514–6526. https://doi.org/10.1021/bi020643m
124. Ahmad M, Takino T, Miyamori H et al (2006) Cleavage of amyloid-β precursor protein (APP) by membrane-type matrix metalloproteinases. J Biochem 139:517–526. https://doi.org/10.1093/jb/mvj054
125. Py NA, Bonnet AE, Bernard A et al (2014) Differential spatio-temporal regulation of MMPs in the 5xFAD mouse model of Alzheimer ' s disease: evidence for a pro-amyloidogenic role of MT1-MMP. Aging Neurosci 6:1–17. https://doi.org/10.3389/fnagi.2014.00247
126. Marchalant Y, Bonnet AE, Crouzin N, Carrete A (2016) MT5-MMP is a new pro-amyloidogenic proteinase that promotes amyloid pathology and cognitive decline in a transgenic mouse model of Alzheimer's disease. J Alzheimer Dis 2016:217–236. https://doi.org/10.1007/s00018-015-1992-1
127. Baranger K, Bonnet AE, Girard SD et al (2017) MT5-MMP promotes Alzheimer ' s pathogenesis in the frontal cortex of 5xFAD mice and APP trafficking in vitro. J Alzheimer Dis 9:1–17. https://doi.org/10.3389/fnmol.2016.00163
128. Hook VYH, Kindy M, Hook G (2008) Inhibitors of cathepsin B improve memory and reduce 𝔑 -amyloid in transgenic alzheimer disease mice expressing the wild-type, but not the swedish mutant, 𝔑 -secretase site of the amyloid precursor protein *. J Biol Chem 283:7745–7753. https://doi.org/10.1074/jbc.M708362200
129. Ladror US, Snyder SW, Wang GT et al (1994) Cleavage at the amino and carboxyl termini of Alzheimer's amyloid-beta by cathepsin D. J Biol Chem 269:18422–18428
130. Cataldo AM, Barnett JL, Berman SA et al (1995) Gene expression and cellular content of cathepsin D in Alzheimer's disease brain: evidence for early up-regulation of the endosomal-lysosomal system. Neuron 14:671–680. https://doi.org/10.1016/0896-6273(95)90324-0
131. Saftig P, Peters C, von Figura K et al (1996) Amyloidogenic processing of human amyloid precursor protein in hippocampal neurons devoid of cathepsin D. J Biol Chem 271:27241–27244. https://doi.org/10.1074/jbc.271.44.27241
132. Hook V, Schechter I, Hans-Ulrich Demuth GH (2009) Alternative pathways for production of beta-amyloid peptides of alzheimer's disease. Biol Chem 389:993–1006. https://doi.org/10.1515/BC.2008.124
133. Jefferson T, Čaušević M, auf dem Keller U et al (2011) Metalloprotease meprin beta generates nontoxic N-terminal amyloid precursor protein fragments in vivo. J Biol Chem 286:27741–27750. https://doi.org/10.1074/jbc.M111.252718
134. Scharfenberg F, Armbrust F, Marengo L et al (2019) Regulation of the alternative β-secretase meprin β by ADAM-mediated shedding. Cell Mol Life Sci 76:3193–3206. https://doi.org/10.1007/s00018-019-03179-1
135. Scharfenberg F, Helbig A, Sammel M et al (2020) Degradome of soluble ADAM10 and ADAM17 metalloproteases. Cell Mol Life Sci 77:331–350. https://doi.org/10.1007/s00018-019-03184-4
136. Walter S, Jumpertz T, Hüttenrauch M et al (2019) The metalloprotease ADAMTS4 generates N-truncated Aβ4-x species and marks oligodendrocytes as a source of amyloidogenic peptides in Alzheimer's disease. Acta Neuropathol 137:239–257. https://doi.org/10.1007/s00401-018-1929-5
137. Hayashita-Kinoh H, Kinoh H, Okada A et al (2001) Membrane-type 5 matrix metalloproteinase is expressed in differentiated neurons and regulates axonal growth. Cell Growth Differ Mol Biol J Am Assoc Cancer Res 12:573–580
138. Niederreither K, Dollé P (2008) Retinoic acid in development: towards an integrated view. Nat Rev Genet 9:541–553. https://doi.org/10.1038/nrg2340
139. Pino-Lagos K, Benson MJ, Noelle RJ (2008) Retinoic acid in the immune system. Ann N Y Acad Sci 1143:170–187. https://doi.org/10.1196/annals.1443.017
140. Krupsky M, Fine A, Berk JL, Goldstein RH (1993) The effect of retinoic acid on amino acid uptake and protein synthesis by lung fibroblasts. J Biol Chem 268:23283–23288. https://doi.org/10.1016/s0021-9258(19)49460-x
141. Lichtenthaler SF (2011) Alpha-secretase in Alzheimer's disease: Molecular identity, regulation and therapeutic potential. J Neurochem 116:10–21. https://doi.org/10.1111/j.1471-4159.2010.07081.x
142. Duong V, Rochette-Egly C (2011) The molecular physiology of nuclear retinoic acid receptors. From health to disease. Biochim Biophys Acta Mol Basis Dis 1812:1023–1031. https://doi.org/10.1016/j.bbadis.2010.10.007
143. Mark M, Ghyselinck NB, Chambon P (2006) Function of retinoid nuclear receptors: lessons from genetic and pharmacological dissections of the retinoic acid signaling pathway during mouse embryogenesis. Annu Rev Pharmacol Toxicol 46:451–480. https://doi.org/10.1146/annurev.pharmtox.46.120604.141156
144. Moutinho M, Codocedo JF, Puntambekar SS, Landreth GE (2019) Nuclear receptors as therapeutic targets for neurodegenerative diseases: lost in translation. Annu Rev Pharmacol Toxicol 59:237–261. https://doi.org/10.1146/annurev-pharmtox-010818-021807
145. Goncalves MB, Clarke E, Hobbs C et al (2013) Amyloid β inhibits retinoic acid synthesis exacerbating Alzheimer disease pathology which can be attenuated by an retinoic acid receptor α agonist. Eur J Neurosci 37:1182–1192. https://doi.org/10.1111/ejn.12142
146. Das BC, Dasgupta S, Ray SK (2019) Potential therapeutic roles of retinoids for prevention of neuroinflammation and neurodegeneration in Alzheimer's disease. Neural Regen Res 14:1880–1892. https://doi.org/10.4103/1673-5374.259604

147. Trigo D, Goncalves MB, Corcoran JPT (2019) The regulation of mitochondrial dynamics in neurite outgrowth by retinoic acid receptor β signaling. FASEB J 33:7225–7235. https://doi.org/10.1096/fj.201802097R
148. David M, Hodak E, Lowe NJ (1988) Adverse effects of retinoids. Med Toxicol Adverse Drug Exp 3:273–288. https://doi.org/10.1007/BF03259940
149. Aryal A, Upreti S (2017) A brief review on systemic retinoids. Int J Pharm Sci Res 8:3630–3639
150. Allenby G, Bocquel MT, Saunders M et al (1993) Retinoic acid receptors and retinoid X receptors: interactions with endogenous retinoic acids. Proc Natl Acad Sci U S A 90:30–34. https://doi.org/10.1073/pnas.90.1.30
151. Lohnes D, Kastner P, Dierich A et al (1993) Function of retinoic acid receptor γ in the mouse. Cell 73:643–658. https://doi.org/10.1016/0092-8674(93)90246-M
152. Bastien J, Rochette-Egly C (2004) Nuclear retinoid receptors and the transcription of retinoid-target genes. Gene 328:1–16. https://doi.org/10.1016/j.gene.2003.12.005
153. le Maire A, Teyssier C, Balaguer P et al (2019) Regulation of RXR-RAR heterodimers by RXR- and RAR-specific ligands and their combinations. Cells 8:1392. https://doi.org/10.3390/cells8111392
154. Smith SM (1994) Retinoic acid receptor isoform β2 is an early marker for alimentary tract and central nervous system positional specification in the chicken. Dev Dyn 200:14–25. https://doi.org/10.1002/aja.1002000103
155. Parrado A, Despouy G, Kraïba R et al (2001) Retinoic acid receptor α1 variants, RARα1ΔB and RARα1ΔBC, define a new class of nuclear receptor isoforms. Nucleic Acids Res 29:4901–4908
156. Nagpal S, Zelent A, Chambon P (1992) RAR-β4, a retinoic acid receptor isoform is generated from RAR-β2 by alternative splicing and usage of a CUG initiator codon. Proc Natl Acad Sci USA 89:2718–2722. https://doi.org/10.1073/pnas.89.7.2718
157. Pogenberg V, Guichoul JF, Vivat-Hannah V et al (2005) Characterization of the interaction between retinoic acid receptor/retinoid X receptor (RAR/RXR) heterodimers and transcriptional coactivators through structural and fluorescence anisotropy studies. J Biol Chem 280:1625–1633. https://doi.org/10.1074/jbc.M409302200
158. Rotondo JC, Borghi A, Selvatici R et al (2018) Association of retinoic acid receptor β gene with onset and progression of lichen sclerosus-associated vulvar squamous cell carcinoma. JAMA Dermatol 154:819–823. https://doi.org/10.1001/jamadermatol.2018.1373
159. Borthwick AD, Goncalves MB, Corcoran JPT (2020) Recent advances in the design of RAR α and RAR β agonists as orally bioavailable drugs. A review. Bioorganic Med Chem 28:115664. https://doi.org/10.1016/j.bmc.2020.115664
160. Lohnes D, Kastner P, Dierich A et al (1993) Function of retinoic acid receptor gamma in the mouse. Cell 73:643–658. https://doi.org/10.1016/0092-8674(93)90246-m
161. Di Rocco A, Uchibe K, Larmour C et al (2015) Selective retinoic acid receptor γ agonists promote repair of injured skeletal muscle in mouse. Am J Pathol 185:2495–2504. https://doi.org/10.1016/j.ajpath.2015.05.007
162. Heyman RA, Mangelsdorf DJ, Dyck JA et al (1992) 9-cis retinoic acid is a high affinity ligand for the retinoid X receptor. Cell 68:397–406. https://doi.org/10.1016/0092-8674(92)90479-v
163. le Maire A, Teyssier C, Balaguer P et al (2019) Regulation of RXR-RAR heterodimers by RXR- and RAR-specific ligands and their combinations. Cells. https://doi.org/10.3390/cells8111392
164. Proschak E, Heitel P, Kalinowsky L, Merk D (2017) Opportunities and challenges for fatty acid mimetics in drug discovery. J Med Chem 60:5235–5266. https://doi.org/10.1021/acs.jmedchem.6b01287
165. Pollinger J, Gellrich L, Schierle S et al (2019) Tuning nuclear receptor selectivity of Wy14,643 towards selective retinoid X receptor modulation. J Med Chem 62:2112–2126. https://doi.org/10.1021/acs.jmedchem.8b01848
166. Schierle S, Merk D (2019) Therapeutic modulation of retinoid X receptors–SAR and therapeutic potential of RXR ligands and recent patents. Expert Opin Ther Pat 29:605–621. https://doi.org/10.1080/13543776.2019.1643322
167. Wan YJ, An D, Cai Y et al (2000) Hepatocyte-specific mutation establishes retinoid X receptor alpha as a heterodimeric integrator of multiple physiological processes in the liver. Mol Cell Biol 20:4436–4444. https://doi.org/10.1128/MCB.20.12.4436-4444.2000
168. Wan YJ, Cai Y, Lungo W et al (2000) Peroxisome proliferator-activated receptor alpha-mediated pathways are altered in hepatocyte-specific retinoid X receptor alpha-deficient mice. J Biol Chem 275:28285–28290. https://doi.org/10.1074/jbc.M000934200
169. Wan Y-JY, Han G, Cai Y et al (2003) Hepatocyte retinoid X receptor-alpha-deficient mice have reduced food intake, increased body weight, and improved glucose tolerance. Endocrinology 144:605–611. https://doi.org/10.1210/en.2002-221003
170. Cramer PE, Cirrito JR, Wesson DW et al (2012) ApoE-directed therapeutics rapidly clear β-amyloid and reverse deficits in AD mouse models. Science 335:1503–1506. https://doi.org/10.1126/science.1217697
171. Jiang Q, Lee CYD, Mandrekar S et al (2008) ApoE promotes the proteolytic degradation of Abeta. Neuron 58:681–693. https://doi.org/10.1016/j.neuron.2008.04.010
172. Poirier J (2000) Apolipoprotein E and Alzheimer's disease. A role in amyloid catabolism. Ann N Y Acad Sci 924:81–90. https://doi.org/10.1111/j.1749-6632.2000.tb05564.x
173. Poirier J (1996) Apolipoprotein E in the brain and its role in alzheimer's disease. J Psychiatry Neurosci 21(2):128
174. Chang T-Y, Yamauchi Y, Hasan MT, Chang C (2017) Cellular cholesterol homeostasis and Alzheimer's disease. J Lipid Res 58:2239–2254. https://doi.org/10.1194/jlr.R075630
175. Hardy JA, Higgins GA (1992) Alzheimer's disease: the amyloid cascade hypothesis. Science 256:184–185. https://doi.org/10.1126/science.1566067
176. Poirier J (1994) Apolipoprotein E in animal models of CNS injury and in alzheimer's disease. Trends Neurosci 17:525–530. https://doi.org/10.1016/0166-2236(94)90156-2
177. Yamanaka M, Ishikawa T, Griep A et al (2012) PPARγ/RXRα-induced and CD36-mediated microglial amyloid-β phagocytosis results in cognitive improvement in amyloid precursor protein/presenilin 1 mice. J Neurosci 32:17321–17331. https://doi.org/10.1523/JNEUROSCI.1569-12.2012
178. Giguere V, Ong ES, Segui P, Evans RM (1987) Identification of a receptor for the morphogen retinoic acid. Nature 330:624–629. https://doi.org/10.1038/330624a0
179. Goncalves MB, Malmqvist T, Clarke E et al (2015) Neuronal RARβ signaling modulates PTEN activity directly in neurons and via exosome transfer in astrocytes to prevent glial scar formation and induce spinal cord regeneration. J Neurosci 35:15731–15745. https://doi.org/10.1523/JNEUROSCI.1339-15.2015
180. Wang X, Dasari S, Nowakowski GS et al (2017) Retinoic acid receptor alpha drives cell cycle progression and is associated with increased sensitivity to retinoids in T-cell lymphoma. Oncotarget 8:26245–26255. https://doi.org/10.18632/oncotarget.15441
181. Corcoran J, Shroot B, Pizzey J, Maden M (2000) The role of retinoic acid receptors in neurite outgrowth from different populations of embryonic mouse dorsal root ganglia. J Cell Sci 113(1):2567–2574

182. Mark M, Ghyselinck NB, Chambon P (2009) Function of retinoic acid receptors during embryonic development. Nucl Recept Signal. https://doi.org/10.1621/nrs.07002
183. Das BC, Thapa P, Karki R et al (2014) Retinoic acid signaling pathways in development and diseases. Bioorg Med Chem 22:673–683. https://doi.org/10.1016/j.bmc.2013.11.025
184. Duester G (2008) Retinoic acid synthesis and signaling during early organogenesis. Cell 134:921–931. https://doi.org/10.1016/j.cell.2008.09.002
185. Goncalves MBCV, Agudo M, Connor S et al (2009) Sequential RARβ and α signalling in vivo can induce adult forebrain neural progenitor cells to differentiate into neurons through Shh and FGF signalling pathways. Dev Biol 326:305–313. https://doi.org/10.1016/j.ydbio.2008.11.018
186. Al TZ, Gaouar S, Piskunov A et al (2014) Phosphorylation of the retinoic acid receptor RARγ2 is crucial for the neuronal differentiation of mouse embryonic stem cells. J Cell Sci 127:2095–2105. https://doi.org/10.1242/jcs.145979
187. Kam RKT, Deng Y, Chen Y, Zhao H (2012) Retinoic acid synthesis and functions in early embryonic development. Cell Biosci 2:11. https://doi.org/10.1186/2045-3701-2-11
188. Goncalves MB, Wu Y, Clarke E et al (2019) Regulation of myelination by exosome associated retinoic acid release from NG2-positive cells. J Neurosci 39:3013–3027. https://doi.org/10.1523/JNEUROSCI.2922-18.2019
189. Olivares AM, Moreno-Ramos OA, Haider NB (2015) Role of nuclear receptors in central nervous system development and associated diseases. J Exp Neurosci 92:93–121. https://doi.org/10.4137/JEN.S25480
190. Mattei MG, de Thé H, Mattei JF et al (1988) Assignment of the human hap retinoic acid receptor RAR beta gene to the p24 band of chromosome 3. Hum Genet 80:189–190. https://doi.org/10.1007/BF00702867
191. Corcoran J, Maden M (1999) Nerve growth factor acts via retinoic acid synthesis to stimulate neurite outgrowth. Nat Neurosci 2:307–308. https://doi.org/10.1038/7214
192. Noy N (2010) Between death and survival: retinoic acid in regulation of apoptosis. Annu Rev Nutr 30:201–217. https://doi.org/10.1146/annurev.nutr.28.061807.155509
193. Dollé P (2009) Developmental expression of retinoic acid receptors (RARs). Nucl Recept Signal 7:e006. https://doi.org/10.1621/nrs.07006
194. Gudas LJ (1994) Retinoids and vertebrate development. J Biol Chem 269:15399–15402
195. Niewiadomska-cimicka A, Krzy A, Ye T (2016) Genome-wide analysis of RAR β transcriptional targets in mouse striatum links retinoic acid signaling with Huntington's disease and other neurodegenerative disorders. Mol Neurobiol. https://doi.org/10.1007/s12035-016-0010-4
196. Patil SB, Brock JH, Colman DR, Huntley GW (2011) Neuropathic pain- and glial derived neurotrophic factor-associated regulation of cadherins in spinal circuits of the dorsal horn. Pain 152:924–935. https://doi.org/10.1016/j.pain.2011.01.017
197. Hur EM, Saijilafu ZFQ (2012) Growing the growth cone: remodeling the cytoskeleton to promote axon regeneration. Trends Neurosci 35:164–174. https://doi.org/10.1016/j.tins.2011.11.002
198. Wu A, Green CR, Rupenthal ID, Moalem-Taylor G (2012) Role of gap junctions in chronic pain. J Neurosci Res 90:337–345. https://doi.org/10.1002/jnr.22764
199. Maria B, Mendoza- A, Corcoran PT et al (2019) RAR b agonist drug (C286) demonstrates efficacy in a pre-clinical neuropathic pain model. ISCIENCE 20:554–566. https://doi.org/10.1016/j.isci.2019.09.020
200. Rataj-baniowska M, Niewiadomska-cimicka A, Paschaki X et al (2015) Retinoic acid receptor B controls development of striatonigral projection neurons through FGF-dependent and Meis1-dependent mechanisms. J Neurosci 35:14467–14475. https://doi.org/10.1523/JNEUROSCI.1278-15.2015
201. Wuarin L, Sidell N, Biology C et al (1990) Retinoids increase perinatal spinal cord neuronal survival and astroglial differentiation. Int J Develop Neurosci 8:317–326. https://doi.org/10.1016/0736-5748(90)90038
202. Clark JN, Whiting A, Mccaffery P (2020) Retinoic acid receptor targeted drugs in neurodegenerative disease. Expert Opin Drug Metab Toxicol. https://doi.org/10.1080/17425255.2020.1811232
203. Bourguet W, Gronemeyer H (2011) Retinoic acid receptor modulators: a perspective on recent advances and promises. Expert Opin Therapautic Patients 21:55–63
204. Shudo K, Fukasawa H, Nakagomi M, Yamagata N (2009) Towards retinoid therapy for alzheimers disease. Curr Alzheimer Res 6:302–311. https://doi.org/10.2174/156720509788486581
205. Spanjaard RA, Ikeda M, Lee PJ et al (1997) Specific activation of retinoic acid receptors (RARS) and retinoid X receptors reveals a unique role for RARϒ in induction of differentiation and apoptosis of S91 melanoma cells. J Biol Chem 272:18990–18999. https://doi.org/10.1074/jbc.272.30.18990
206. Hill DS, Ragsdale CW, Brockes JP (1993) Isoform-specific immunological detection of newt retinoic acid receptor y in normal and regenerating limbs. Development 117:937–945. https://doi.org/10.1242/dev.117.3.937
207. Podleśny-Drabiniok A, Sobska J, De Lera AR et al (2017) Distinct retinoic acid receptor (RAR) isotypes control differentiation of embryonal carcinoma cells to dopaminergic or striatopallidal medium spiny neurons. Sci Rep 7:1–14. https://doi.org/10.1038/s41598-017-13826-x
208. Kona SL, Shrestha A, Yi X et al (2017) RARβ2-dependent signaling represses neuronal differentiation in mouse ES cells. Differentiation 98:55–61. https://doi.org/10.1016/j.diff.2017.11.002
209. Goldfarb S, Fainstein N, Ganz T et al (2021) Electric neurostimulation regulates microglial activation via retinoic acid receptor α signaling. Brain Behav Immun. https://doi.org/10.1016/j.bbi.2021.05.007
210. Goncalves MBCV, Boyle J, Webber DJ et al (2005) Timing of the retinoid-signalling pathway determines the expression of neuronal markers in neural progenitor cells. Dev Biol 278:60–70. https://doi.org/10.1016/j.ydbio.2004.10.015
211. Haskell GT, LaMantia AS (2005) Retinoic acid signaling identifies a distinct precursor population in the developing and adult forebrain. J Neurosci 25:7636–7647. https://doi.org/10.1523/JNEUROSCI.0485-05.2005
212. Nomoto M, Takeda Y, Uchida S et al (2012) Dysfunction of the RAR/RXR signaling pathway in the forebrain impairs hippocampal memory and synaptic plasticity. Mol Brain 5:1–15. https://doi.org/10.1186/1756-6606-5-8
213. Maden M (2002) Retinoid signalling in the development of the central nervous system. Nat Rev Neurosci 3:843–853. https://doi.org/10.1038/nrn963
214. Maden M (2007) Retinoic acid in the development, regeneration and maintenance of the nervous system. Nat Rev Neurosci 8:755–765. https://doi.org/10.1038/nrn2212
215. Jarvis CI, Goncalves MB, Clarke E et al (2010) Retinoic acid receptor-α signalling antagonizes both intracellular and extracellular amyloid-β production and prevents neuronal cell death caused by amyloid-β. Eur J Neurosci 32:1246–1255. https://doi.org/10.1111/j.1460-9568.2010.07426.x
216. Mey J, McCaffery P (2004) Retinoic acid signaling in the nervous system of adult vertebrates. Neuroscientist 10:409–421. https://doi.org/10.1177/1073858404263520

217. Maden M (2000) The role of retinoic acid in embryonic and post-embryonic development. Proc Nutr Soc 59:65–73. https://doi.org/10.1017/S0029665100000082
218. Corcoran J, Shroot B, Pizzey J, Maden M (2000) The role of retinoic acid receptors in neurite outgrowth from different populations of embryonic mouse dorsal root ganglia. J Cell Sci 113:2567–2574. https://doi.org/10.1242/jcs.113.14.2567
219. Behairi N, Belkhelfa M, Rafa H et al (2016) All-trans retinoic acid (ATRA) prevents lipopolysaccharide-induced neuroinflammation, amyloidogenesis and memory impairment in aged rats. J Neuroimmunol 300:21–29. https://doi.org/10.1016/j.jneuroim.2016.10.004
220. Agudo M, Yip P, Davies M et al (2010) A retinoic acid receptor β agonist (CD2019) overcomes inhibition of axonal outgrowth via phosphoinositide 3-kinase signalling in the injured adult spinal cord. Neurobiol Dis 37:147–155. https://doi.org/10.1016/j.nbd.2009.09.018
221. Postina R, Schroeder A, Dewachter I et al (2004) A disintegrin-metalloproteinase prevents amyloid plaque formation and hippocampal defects in an Alzheimer disease mouse model. J Clin Invest 113:1456–1464. https://doi.org/10.1172/JCI20864
222. Yang H-Q, Ba M-W, Ren R-J et al (2007) Mitogen activated protein kinase and protein kinase C activation mediate promotion of sAPPα secretion by deprenyl. Neurochem Int 50:74–82. https://doi.org/10.1016/j.neuint.2006.07.016
223. Moutinho M, Landreth GE (2017) Therapeutic potential of nuclear receptor agonists in Alzheimer's disease. J Lipid Res 58:1937–1949. https://doi.org/10.1194/jlr.R075556
224. Sancesario GM, Bernardini S (2018) Alzheimer ' s disease in the omics era. Clin Biochem. https://doi.org/10.1016/j.clinbiochem.2018.06.011
225. Martins F, Marafona AM, Pereira CD et al (2018) Identification and characterization of the BRI2 interactome in the brain. Sci Rep 8:1–17. https://doi.org/10.1038/s41598-018-21453-3
226. Zhao H, Li S, Li Z et al (2020) Intranasal delivery of 9-cis retinoic acid reduces beta-amyloid deposition via inhibiting astrocyte-mediated inflammation. Aging (Albany NY) 12:5469–5478. https://doi.org/10.18632/aging.102970
227. Fukasawa H, Nakagomi M, Yamagata N et al (2012) Tamibarotene: a candidate retinoid drug for Alzheimer's disease. Biol Pharm Bull 35:1206–1212. https://doi.org/10.1248/bpb.b12-00314
228. Layton A (2009) The use of isotretinoin in acne. Dermatoendocrinol 1:162–169. https://doi.org/10.4161/derm.1.3.9364
229. Ormerod AD, Thind CK, Rice SA et al (2012) Influence of isotretinoin on hippocampal-based learning in human subjects. Psychopharmacology 221:667–674. https://doi.org/10.1007/s00213-011-2611-y
230. Dos Santos GM, Stoye NM, Rose-John S et al (2019) The Synthetic Retinoid Acitretin Increases IL-6 in the Central Nervous System of Alzheimer Disease Model Mice and Human Patients. Front Aging Neurosci 11:182. https://doi.org/10.3389/fnagi.2019.00182
231. Cummings JL, Zhong K, Kinney JW et al (2016) Double-blind, placebo-controlled, proof-of-concept trial of bexarotene Xin moderate Alzheimer's disease. Alzheimer's Res Ther 8:1–9. https://doi.org/10.1186/s13195-016-0173-2
232. Wilhelmus MMM, de Jager M, Rozemuller AJM et al (2012) Transglutaminase 1 and its regulator tazarotene-induced gene 3 localize to neuronal tau inclusions in tauopathies. J Pathol 226:132–142. https://doi.org/10.1002/path.2984