Fleshing out the amyloid cascade hypothesis: the molecular biology of Alzheimer's disease

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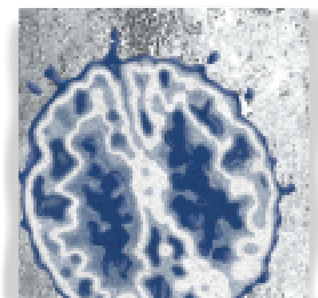

Alzheimer's disease (AD) is a disorder of two pathologies—plaques and tangles. The former have as a key constituent amyloid protein and the latter the microtubule-associated protein tau. Genetics has demonstrated that changes in either protein are sufficient to cause dementia. The amyloid cascade hypothesis proposes that plaque-related changes precede tangle-related changes and positions amyloid as central to the degeneration of AD. All the evidence suggests this is correct, including evidence that presenilins alter the processing of the amyloid precursor protein and evidence that disrupting the normal properties of tau underlies the related frontotemporal dementias. The amyloid cascade hypothesis has provided the basis for nearly a decade of intensive basic science—the skeleton of that hypothesis can now be fleshed out, and confidence is growing that this will result in useful disease-modifying therapies in the future.

Keywords: *amyloid; tau; Alzheimer's disease; tauopathy; GSK-3; APP; presenilin; Notch*

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Basic research into Alzheimer's disease (AD) more than two decades ago demonstrated early and profound loss of cholinergic neurons, a finding that led to the first therapeutic advance with the development and licensing of the first specific treatments: the acetylcholinesterase inhibitors. Whatever the therapeutic efficiency of these compounds, their impact in the field of dementia care cannot be overestimated. However, today's basic research has the power to go beyond the cholinergic hypothesis, and there is every hope that the current process of fleshing out the bones of the amyloid cascade hypothesis will yield effective disease-modifying treatments.

The amyloid cascade hypothesis

In 1992, soon after the discovery of mutations in the amyloid precursor protein gene, John Hardy proposed the amyloid cascade hypothesis, which in its most basic form states that amyloid is at the center of the pathophysiology, that amyloid deposits in AD result from a multitude of genetic or environmental insults and are at the origin of the neurodegeneration that leads to dementia.[1] Although many new questions have arisen—for instance, is the pathogenic amyloid intracellular and soluble or extracellular and fibrillar?—the hypothesis not only stands, but has been confirmed with each new advance of recent years. Furthermore, important aspects of basic research are omitted from the cascade, or at least cannot at present be easily fitted into the cascade, including the role of inflammation and the putative pathogenic events resulting from risk factors such as prior affective disorder or hypertension. Nevertheless, most of the molecular and cellular biology of AD can be discussed in the context of this important framework.

Selected abbreviations and acronyms

AD	*Alzheimer's disease*
apo E	*apolipoprotein E*
APP	*amyloid precursor protein*
BACE	*beta-site APP-cleaving enzyme*
DRAP	*Down's region aspartic protease*
FTDP-17	*frontotemporal dementia and parkinsonism linked to chromosome 17*
GSK-3	*glycogen synthase kinase-3*
NFT	*neurofibrillary tangle*
PHF	*paired helical filaments*
PKC	*protein kinase C*
PP2A	*type 2A protein phosphatase*
PS-1, -2	*presenilin-1 and -2*
PSP	*progressive supranuclear palsy*
TPK1	*tau protein kinase 1*

APP and the formation of plaques

The core component of plaques is a 4-kd peptide known as Aβ.[2,3] In plaques, the peptide forms fibrils in a beta-pleated sheet configuration, thus assuming the properties of amyloid characterized by its unique birefringence with Congo red staining. Aβ is derived from amyloid precursor protein (APP), the gene for which is on chromosome 21. The discovery that mutations in the APP gene cause a rare form of autosomal dominant AD confirmed the process of Aβ formation from APP as central to the etiopathogenesis of AD.[4-8] APP is a ubiquitous and large single-pass membrane-spanning protein, the function of which is not clear, although there are suggestions that it may have a role in cell-to-cell contact signaling or neurite outgrowth.[9,10] When derived from APP, Aβ is a peptide of between 40 and 43 amino acids that has a tendency to aggregate in vitro. This tendency is enhanced in the longer forms of the peptide, suggesting that these slightly larger peptides are more pathogenic (and that inhibiting fibril formation may therefore be therapeutic).[11-13] Although the process in vivo is not understood, it is assumed that Aβ peptide is formed intracellularly and then aggregates either within the cell or after release into the extracellular space. However, some early work did find intracellular fibrils in cells expressing the c-terminal fragment of APP, and increasing attention is being paid to the possibility of intracellular Aβ toxicity.[14-16]

These deposits of Aβ form diffuse plaques visible on immunohistochemistry in affected regions of the brain. Technically, as these diffuse plaques consist only of fibrillized extracellular peptide that is not in a beta-pleated sheet configuration and hence not birefringent, they cannot properly be said to be amyloid. Careful studies of Down's syndrome brains suggest a sequential series of steps whereby diffuse plaques form the neuritic or classic plaque containing true amyloid, which in time evolves to form the burnt-out plaque where only the amyloid deposit remains.[17]

Understanding the process whereby Aβ is generated from APP is of the utmost importance and is the most obvious target for therapy. APP is metabolized through two opposing pathways involving three proteases.[18] The first, often called the nonamyloidogenic pathway, results in cleavage of APP within the Aβ sequence moiety by the putative α-secretase. It is thought that α-secretase cleavage occurs at the extracellular membrane, but it is clear that it results in the secretion of the large extracellular portion of APP known as sAPPα. The function of this secreted peptide is not fully understood, but α-secretase cleavage certainly prevents the formation of Aβ as the cleavage site is within this part of the protein. Although the enzyme itself has not yet been identified, the regulation of the activity of α-secretase has been extensively examined. Phorbol ester activation of protein kinase C (PKC) increases sAPPα secretion into the medium of transfected cells, and in neurons very considerably so.[19-23] Interestingly, the same observation was made when acetylcholine receptors linked through second messengers to PKC were stimulated. Stimulation of other PKC-linked receptors also stimulates sAPPα release, whereas stimulation of muscarinic receptors linked to cyclic adenosine monophosphate does not.[24] These findings are intriguing and may have therapeutic significance, especially as a similarly beneficial effect of muscarinic stimulation is seen in a process thought to underlie the formation of tangles.

In contrast to nonamyloidogenic processing of APP, the production of Aβ necessitates two protease activities. The previously named enzyme β-secretase was recently identified and renamed BACE (for beta-site APP-cleaving enzyme).[25] Interestingly, a very similar protease was found near the region on chromosome 21 critical for Down's syndrome (Down's region aspartic protease [DRAP], or BACE2). These proteases cleave APP

within the extracellular domain, probably in the endosomal-lysosomal pathway following reinternalization of extracellular membrane–bound APP that escapes α-secretase cleavage.[26] Action of the putative protease γ-secretase at a second site releases free Aβ of between 40 and 42 amino acids, depending on the exact site of cleavage. The γ-secretase site is unusual in that it is buried within the lipid bilayer.

Mutations in APP and the formation of Aβ

Activity of all three secretases can be found in normal brain. Aβ and APPs can be detected from normal cells, and, in humans, Aβ is detectable by enzyme-linked immunosorbent assay (ELISA) in cerebrospinal fluid (CSF) as well as in serum. These, then, are not pathological processes per se, but rather they suggest that disease results from a tendency towards the amyloidogenic combination of secretases resulting, over a lifetime, in increased Aβ formation and increased plaque formation. What then are the known influences on these, essentially normal, processes? The first influence on APP metabolism to be discovered was the mutations in APP. Autosomal dominant AD in a few rare families results from mutations that cluster adjacent to the regions of α-, β-, or γ-secretase cleavage. The first set of mutations to be discovered were those clustering at, or adjacent to, the γ-secretase cleavage site (APP717). Expression of these mutated APP cDNAs in cells confirmed that the mutation does indeed alter APP metabolism, as relatively more of the longer forms of Aβ were generated in mutation-carrying cells.[27,28] Mutations at the c-terminal end of the Aβ sequence within APP also alter APP metabolism, presumably by interfering with BACE. These mutations, the double Swedish mutation (APP670/671), also alter APP metabolism in cultured cells, and the amount of Aβ in serum or CSF of patients carrying either the mutations near the γ- or the β-secretase site is increased.[29,30] Two very interesting mutations occur within the Aβ region close to the α-secretase site. One, at APP693, is associated with a rare disorder, hereditary cerebral hemorrhage with amyloidosis, Dutch type, and the other, at APP692, with presenile dementia and cerebral hemorrhage due to cerebral amyloid angiopathy—a clearly related, but not identical, disorder. In the APP692 disorder, but not in APP693 disease, there was not only angiopathy but large plaques and neurofibrillary tangles.[31] In cells, the effect of the APP692 mutation is to increase both Aβ40 and Aβ42 secretion, whereas APP693 does not. Thus there is, in the APP mutations, convincing evidence in favor of the amyloid cascade hypothesis—mutations associated with AD increase either all Aβ or the longer and more fibrillogenic forms of Aβ, whereas mutations associated with other disease do not.

Presenilins and APP metabolism

Mutations in two very closely homologous genes—presenilin-1 and -2 (PS-1 and -2)—also cause early-onset autosomal dominant AD.[32,33] The proteins encoded by these genes are multipass membrane–associated proteins that are certainly present in endoplasmic reticulum and possibly in nuclear envelope and plasma membrane as well.[34-37] The normal biology of the presenilins is under extensive examination, and transgenic animals have already provided some insight into this. Overexpression of APP with the disease causing mutations results in plaque-like deposits of amyloid in mice, and this process is accelerated in mice overexpressing mutated PS-1.[38,39] Knockouts of PS-1, however, are embryonically lethal. Studies from neurons from these animals, among other data, strongly suggest that the presenilins function as γ-secretase or as regulators of γ-secretase, as these neurons produce low levels of Aβ, resulting from low levels of γ-secretase activity.[40,41] Whether the Alzheimer-related mutations increase γ-secretase activity or have some other gain-of-function activity is not entirely clear, but from the transgenic animals, studies in transfected cells, and studies in fibroblasts from families carrying these mutations, it is clear that the PS-1 mutations somehow increase the production, especially of the longer forms of the amyloid peptides, offering more evidence that the amyloid cascade hypothesis is correct to position APP processing as a central event in pathogenesis.[42]

Neurofibrillary tangles and the tau question

If there has been any real controversy associated with the amyloid cascade hypothesis, this has been with the question of tau and neurofibrillary tangles (NFTs). These neuronal inclusion bodies are a defining feature of AD and are also found in other degenerative disorders such as dementia pugilistica and certain frontotemporal

dementias. The number of NFTs correlates extremely well with dementia severity, in contrast to plaques where some analyses of total amyloid load correlate with dementia, but other neuropathological studies show no such correlation.[43-45] Furthermore, NFTs show an anatomical localization in those regions where function is lost, occurring first in the transentorhinal region and spreading to hippocampal regions and then to cortex, but never occurring in cerebellum.[46,47] Plaques, on the other hand, show no such consistent progression, and while they do occur in some quantity in the hippocampus where function is lost, they also occur in cerebellum, where no such loss is noted in dementia.[48] Finally, NFTs are intraneuronal lesions, the neurons containing NFTs show loss of vital intracellular organization with the loss of normal neuronal cytoskeleton, and there is convincing neuropathological evidence that the presence of NFTs heralds the death of that neuron. All this circumstantial evidence points very firmly in the direction of NFTs being essential pathological components of the cascade resulting in dementia. Nonetheless, there was some dissension from this view—perhaps NFTs were a nonessential by-product of neurodegeneration, an epiphenomenon.

Under the electron microscope, NFTs can be seen to consist principally of paired helical filaments together with a smaller proportion of straight filaments. These filaments are composed of the microtubule-associated protein tau, present in a highly phosphorylated state, and are abnormal, being found only in dementia. In the normal state, tau is expressed to a significant extent only in neurons where it is present in axons. Here it acts to stabilize microtubules, which are an essential component of the cellular cytoskeleton and in neurons assume a straight track parallel to axons. Microtubules are essential for fast axonal transport, the process whereby vesicles and other organelles such as mitochondria are transported from the cell body to distal parts of the neuron including synapses. The consequences of loss of fast axonal transport from the neuron or destruction of microtubules are not fully understood, but would be expected to result in loss of function of the neuron if not loss of viability. Tau, therefore, has an important role in regulating the stability and function of neurons. In vitro, tau binds to tubulin (the building block of the microtubule itself) and promotes the formation of tubulin polymers and the extension of these polymers into microtubules. Six different isoforms of tau are generated from a single gene in the central nervous system, and there is some evidence that these isoforms have different abilities to promote microtubule assembly in vitro. There is developmental regulation of the expression of these isoforms, as in the fetal forms, which bind microtubules that are in excess relatively weakly, with a change to stronger binding isoforms on maturation. However, such regulation is a relatively slow process and real-time regulation of the properties of tau is almost certainly altered by the phosphorylation state of tau.

Tau phosphorylation—regulation of microtubule stability and role in Alzheimer's disease

Tau is a highly phosphorylated protein, and its ability to bind microtubules is regulated by this phosphorylation—the more phosphates, the less tau promotes microtubule assembly.[49] There is some controversy as to whether it is the amount of phosphorylation that is important or whether there are specific sites in tau that are critical in tau-tubulin interactions.[50] In the fetus, tau is very highly phosphorylated, and even in normal adult human brain examined in biopsy samples the amount of phosphorylation is relatively high.[51,52] It is likely that acute regulation by a combination of kinases and phosphatases of tau phosphorylation controls the properties of neurons, which in turn alters the rate of transport within the neuron and, perhaps, other, structural, properties of tau. Even though tau is phosphorylated in normal adult neurons, and more so in normal fetal neurons, in the PHF-tau aggregates of AD, tau is even more phosphorylated. The amount of phosphorylation is higher in total terms, and there may be specific sites of tau that are phosphorylated only in AD. Functional studies of tau from human brain reflect this phosphorylation, with tau from fetal brain being less able to promote microtubule association in vitro than normal brain, and tau from AD brain being even less able to stabilize microtubule formation than fetal tau.[49] It is not yet clear whether tau phosphorylation and the functional deficiencies seen in tau from AD brain precedes or follows aggregation. However, careful pathological studies suggest that phosphorylated epitopes of tau appear in neurons together with the appearance of tau in the cell bodies of affected neurons (tau normally being seen only in axons) before the presence of aggregates of tau in NFTs.[46,53] It is at least a viable hypothesis that an alteration in the phosphorylation state of tau results in a failure to bind microtubules, a consequent

accumulation in cell bodies, and eventual loss of microtubules and aggregation of tau into NFTs.

This hypothesis led to an intensive search for the kinases and phosphatases that might regulate tau. Of the phosphatases, type 2A protein phosphatase (PP2A) would appear to be the most viable candidate. In vitro, PP2A readily phosphorylates tau, it is found associated with microtubules, and, in cells, inhibition of PP2A results in an increase in the phosphorylation state of tau.[54-56] A parallel investigation of the kinases responsible for tau phosphorylation has proved more controversial. Many kinases act on the common serine and threonine sites phosphorylated in paired helical filaments (PHF)–tau. However, in cells, we demonstrated that it is only glycogen synthase kinase–3 (GSK-3) that is able to phosphorylate tau readily at epitopes also phosphorylated in AD.[57,58] Simultaneously, Ishiguro and colleagues purified a kinase from brain that readily phosphorylated tau, which they named tau protein kinase 1 (TPK1).[59] On purification, TPK1 was found to be GSK-3, and, although other kinases certainly do phosphorylate tau and may even be necessary to prime tau for subsequent phosphorylation, it does appear now that GSK-3 is the predominant kinase at these sites in brain.[60] Functional studies have added weight to the growing evidence for a role of GSK-3 in the phosphorylation of tau in vivo as GSK-3 activity alters the properties of tau, reducing its ability to bind and promote microtubule assembly in vitro and, in cells, reduces the ability of tau to alter the morphology and stability of microtubules.[61]

Regulation of the phosphorylation of tau

Interesting findings have emerged from studies of GSK-3 regulation, which might begin to tie together the two strands of AD basic science—the amyloid strand and the tau strand. Most enticingly, Aβ is neurotoxic to neurons in culture and matured and fibrillized Aβ peptides increase tau phosphorylation.[62,63] Inhibiting GSK-3 activity protects neurons, suggesting that GSK-3 might be an intermediary step between amyloid and tau phosphorylation.[64,65] One approach to inhibition of GSK-3 that has been used in these studies is lithium. Lithium results in developmental abnormalities in experimental models that mimic a signal transduction cascade known as Wingless (wnt in mammals). Wingless or wnt signaling results in GSK-3 inhibition, and this led Klein and Melton to hypothesize and then demonstrate that lithium mimics Wingless signal by inhibiting GSK-3.[66] In nonneuronal cells, in neurons, and in animals, lithium has now been shown to reduce tau phosphorylation as would be expected if GSK-3 is a predominant tau-kinase.[67-72] This inhibition of GSK-3 alters the properties of tau in neurons and in living nonneuronal cells, and does so within the therapeutic range of lithium. This body of work does raise the interesting question as to whether GSK-3 is the target of lithium in the therapy of affective disorders, especially as another agent used in bipolar disorder, sodium valproate, also inhibits GSK-3.[73]

Attention has recently turned to a pathway that interacts with Wingless signaling—the Notch pathway. Notch is a transmembrane protein essential for neurogenesis, but also present, and presumably therefore active, in adult brain.[74-76] Activation of Notch involves cleavage within the membrane domain, very reminiscent of the γ-secretase cleavage of APP.[77] A role for presenilins in Notch activity was first suggested by homology as the equivalent of presenilins in *Caenorhabditis elegans,* SEL12, is associated with LIN12, the *C elegans* equivalent of Notch. Human presenilins are able to compensate for loss of SEL12, but mutated human presenilins lose this ability.[78,79] In a number of different mammalian model experiments, the presenilin protein has now been shown to activate Notch.[79-84] The evidence that presenilins are involved in Notch signaling is now compelling, and this is intriguing, as Notch signaling and Wingless signaling interact.[85-87] In the Wingless signal cascade, inhibition of GSK-3 results in accumulation of a protein called β-catenin, and, to add to the complexity of this area, presenilins bind to catenins and affect β-catenin signaling.[88-92] Much needs to be done to untangle this complicated set of observations, not all of which are consistent. However, it does appear to be the case that Wingless and Notch signaling interact, and that, in doing so, GSK-3 activity is regulated, and that the presenilins are involved—certainly with Notch signaling, and possibly with Wingless signaling.

In addition to Wingless/wnt signaling, GSK-3 is inhibited by insulin signaling through protein kinase B (PKB) and PI3-kinase. As predicted, insulin not only reduces tau phosphorylation in neurons, but also increases tau-microtubule interactions.[93] Just as GSK-3 might be the missing link between amyloid and tau, so too might GSK-3 be the missing link between an important finding from epidemiology and etiopathogenesis. Diabetes has now been shown to be a significant risk factor for AD.[94]

This finding is not explained simply by the confounding factor of increasing vascular risk in people with diabetes, and the finding that insulin resistance also increases risk of AD suggests that the pathogenic factor might be a failing of insulin signaling.[95,96] If insulin signaling is deficient in some way, then might GSK-3 escape normal regulation? If this were so, then the predicted result would be increased tau phosphorylation and increased neuronal vulnerability.

Tau and the tauopathies

All doubt about the role of tau in dementia was finally laid to rest, however, when mutations in tau were shown to be the cause of some familial dementias.[97-99] Mutations in tau, both missense coding mutations and intronic, were found in some families with frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17). These families have a clinical appearance of a frontal lobe dementia, very similar in presentation to Pick's disease, but with some parkinsonism. On neuropathology, many have tau inclusion bodies in either glia or neurons or both.[100] A new classification of certain dementia disorders has now arisen, including Pick's disorder, progressive supranuclear palsy (PSP), and the frontotemporal dementias, which have variable amounts of tau pathology, in some cases caused by tau mutations—these disorders being now known as the tauopathies.[101,102] Ironically, it took the tauopathies to confirm the amyloid cascade hypothesis—mutations in APP give rise to both plaques and tangles, while mutations in tau give rise to tangles only. This is exactly the design of a genetic experiment to investigate sequential biochemical steps in a model organism. It follows, without any doubt at all, that the direction of effect is from amyloid through tau to dementia, and that tau is an essential part of the cascade. It does not follow that there are not other mechanisms whereby dementia can occur, and it might be that in some instances a remote event might give rise independently to both plaque and tangle pathology, although Occam's razor argues against this.

The effect of the intronic tau mutations appears to be to alter the proportion of isoforms with 3- and 4- microtubule binding domains expressed in brain. The mutations cluster at the splice site for these alternative isoforms and disrupt splicing.[103-105] This is very much in line with the biochemistry from pathological samples in these cases, which suggests that in frontotemporal dementia there is a disruption in the normal equal expression of 3- and 4- repeat isoforms. Both in vitro and in vivo studies of the exonic missense mutations suggest that these disrupt microtubule binding.[106-108] In our own studies, we showed that the mutations reduce the ability of tau to promote microtubule extension in cells in exactly the same manner as phosphorylation.[109] Other in vitro studies have suggested that the mutations in tau increase its propensity to self-aggregation.[110]

A molecular model of Alzheimer's disease

The amyloid cascade hypothesis can now be elaborated in some detail. Normally, APP is processed via both amyloidogenic and nonamyloidogenic routes. A number of events perturb the balance to a greater or lesser extent. Mutations in APP profoundly bias metabolism toward the amyloidogenic route, and head injury increases amyloidogenesis perhaps by simply increasing the total levels of APP expression. Somehow, amyloid production increases tau phosphorylation. Perhaps the most likely hypothesis at the present time is that amyloid peptide increases GSK-3 activity, although whether this is through intra- or extracellular amyloid is uncertain. GSK-3 activity increases tau phosphorylation, which then fails to bind microtubules, resulting in loss of microtubule stability and accumulation of tau in the cell body, which predisposes to tau aggregation. Mutations in tau also cause increased aggregation and reduced binding to microtubules in a manner analogous to phosphorylation. Mutations in presenilins certainly cause increased amyloid production from APP and might also have other effects including through Notch and/or Wingless signaling that might impact upon tau phosphorylation.

What else is known about AD that impacts upon the cascade? Most obviously omitted from this scheme is apolipoprotein E (apo E), the only confirmed genetic association with late-onset AD.[111,112] Studies of the biology of apo E have proved very difficult to conduct, with disparate results partly accounted for by technical differences in the preparation of apo E protein. Apo E has been shown to interact with amyloid peptide, but some studies show greater interaction with apo E2 and others with apo E4.[113-115] Depending upon the true result in vivo, apo E binding might enhance amyloid fibrillization and hence plaque formation, or enhance amyloid clearance and hence plaque destruction. Alternatively, apo E might affect tau phosphorylation. Tau binds apo E in an iso-

form-dependent manner, and it was hypothesized that such binding would alter the phosphorylation state of tau.[116-118] We have confirmed this is in fact the case (unpublished observations), although whether this occurs in vivo is uncertain. Indeed it is not even known if tau and apo E would meet in vivo. Some studies suggest extracellular apo E is internalized into the cytoplasm compartment.[119,120] At least one study suggests it is not.[121] In neurons, apo E appears to be in the cytoplasm, but this might result from expression of apo E in a form that is not immediately secreted.[122-124] Other cellular approaches do suggest tau alters microtubules and affects neuronal growth, both compatible with, but not proving, an effect of apo E on tau.[120,125-127] It might be that apo E has no effect on either tau or amyloid, affecting instead local cholesterol transport, neuronal viability, and resilience to damage. At present, apo E can be slotted into the cascade in too many places to be sure which is the most likely.

Epidemiology has identified a few nonaging, nongenetic factors that do fit in with the hypothesis. Head injury, for example, might influence AD by increasing amyloid production. Diabetes or insulin-resistance syndrome might affect AD by reducing inhibition of GSK-3 and increasing tau pathology. It will be interesting over the forthcoming years to see how other factors, and the genetic factors in particular, which will be identified following the systematic genome scans, enhance our understanding of the cascade. For now, however, it is clear that substantial parts of the cascade of events leading to neuronal death and dementia are understood, and, most importantly, the race is now on to convert these targets for therapies into compounds that might delay, prevent, or possibly even reverse this devastating disease. ❑

Reforzando la hipótesis de la cascada del amiloide: la biología molecular de la Enfermedad de Alzheimer

La Enfermedad de Alzheimer (EA) es un trastorno de dos patologías: placas y ovillos. Las primeras están constituidas por proteínas de amiloide y los segundos por microtúbulos asociados a la proteína tau. La genética ha demostrado que los cambios en cualquiera de las proteínas son suficientes para causar demencia. La hipótesis de la cascada de amiloide propone que los cambios relacionados con las placas preceden a los cambios asociados con los ovillos y las posiciones del amiliode como elementos centrales en la degeneración de la EA. Todas las evidencias actuales sugieren que esta hipótesis es correcta; hay evidencias que señalan que las presenilinas alteran el procesamiento de la proteína precursora de amiloide y otras que demuestran que los trastornos en las propiedades normales de la proteína tau subyacen a las demencias frontotemporales. La hipótesis de la cascada de amiloide ha proporcionado las bases, por casi una década, de numerosos trabajos en ciencias básicas (el esqueleto de esta hipótesis ahora puede ser reforzado y existe gran confianza en que esto se traducirá en terapias útiles que modificarán la enfermedad en el futuro).

Développement de l'hypothèse de la cascade amyloïde : biologie moléculaire de la maladie d'Alzheimer

La maladie d'Alzheimer (MA) est un trouble résultant de deux pathologies : les plaques séniles et la dégénérescence neurofibrillaire. La première a comme constituant clé la protéine amyloïde et la seconde la protéine tau liée aux microtubules. La recherche en génétique a démontré que des modifications d'une des deux protéines sont suffisantes pour provoquer une démence. Selon l'hypothèse de la cascade amyloïde, les modifications liées à la plaque précèderaient celles liées à la dégénérescence neurofibrillaire, conférant ainsi au peptide amyloïde une place centrale dans le processus dégénératif de la MA. Cette hypothèse semble actuellement étayée par l'ensemble des études, tant celles montrant que les présénilines altèrent le processus du peptide précurseur de l'amyloïde que celles indiquant que l'altération des propriétés normales de la protéine tau est à l'origine du développement des démences frontotemporales. L'hypothèse de la cascade amyloïde a servi de moteur à presque une décennie de recherche intensive dans le domaine des sciences fondamentales. Il reste désormais à concrétiser cette hypothèse avec l'espoir grandissant de voir se développer dans l'avenir des traitements de fond pour cette maladie.

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