Deciphering the mechanism underlying late-onset Alzheimer disease

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Abstract | Despite tremendous investments in understanding the complex molecular mechanisms underlying Alzheimer disease (AD), recent clinical trials have failed to show efficacy. A potential problem underlying these failures is the assumption that the molecular mechanism mediating the genetically determined form of the disease is identical to the one resulting in late-onset AD. Here, we integrate experimental evidence outside the 'spotlight' of the genetic drivers of amyloid-β (Aβ) generation published during the past two decades, and present a mechanistic explanation for the pathophysiological changes that characterize late-onset AD. We propose that chronic inflammatory conditions cause dysregulation of mechanisms to clear misfolded or damaged neuronal proteins that accumulate with age, and concomitantly lead to tau-associated impairments of axonal integrity and transport. Such changes have several neuropathological consequences: focal accumulation of mitochondria, resulting in metabolic impairments; induction of axonal swelling and leakage, followed by destabilization of synaptic contacts; deposition of amyloid precursor protein in swollen neurites, and generation of aggregation-prone peptides; further tau hyperphosphorylation, ultimately resulting in neurofibrillary tangle formation and neuronal death. The proposed sequence of events provides a link between Aβ and tau-related neuropathology, and underscores the concept that degenerating neurites represent a cause rather than a consequence of Aβ accumulation in late-onset AD.

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Introduction

Alzheimer disease (AD) is the most common type of age-related dementia, affecting approximately 24 million people worldwide, with the number of patients doubling every 20 years as a consequence of the ageing population.[1] This pandemic scenario will have not only a profound health and emotional influence on affected individuals and their families, but will also place a substantial economic burden on society.

The disease is characterized by progressive loss of cognitive abilities, severe neurodegeneration, and prominent neuroinflammation.[2] Neuropathological hallmarks include proteinous aggregates in the form of senile plaques, which are enriched in amyloid-β (Aβ) peptides, and neurofibrillary tangles (NFTs), consisting of hyperphosphorylated tau.[3] Dominant genetic effects of mutations in amyloid precursor protein (*APP*), presenilin-1 (*PS1*) or *PS2* are responsible for the early-onset or familial form of AD. These mutations have been shown to profoundly alter APP metabolism, favouring the production of aggregation-prone Aβ species, and such findings formed the basis of the 'amyloid cascade hypothesis' of AD pathogenesis.[4] This broadly accepted hypothesis states that the generation of neurotoxic Aβ peptides by β-secretase and γ-secretase constitute the cause of AD pathophysiology, with all other disease hallmarks developing as a consequence of this event.

Competing interests
The authors declare no competing interests.

Although the amyloid cascade hypothesis is likely to hold true for the familial form of the disease, increasing evidence suggests that the mechanisms underlying late-onset AD—the sporadic disease form that accounts for the vast majority of AD cases—could be different.[5] For example, in addition to the ε4 allele of the apolipoprotein E gene (*APOE*)[6]—a well-known risk factor for AD—recent genome-wide association studies identified significant correlations between polymorphisms in genes of the innate immune system and incidence of late-onset AD.[7,8] By contrast, no such correlation was found between polymorphisms in genes encoding APP or γ-secretase and incidence of late-onset AD.[9] Together with the observation that inflammatory mediators are abundantly present in affected brain areas[10,11] and plasma of patients with AD,[12] these newly identified risk factors imply that alterations in innate immunity might have a key role in the disease aetiology, rather than being a passive reaction to Aβ-related neuropathology.

In this article, we integrate experimental data focused on neuroinflammation with several other neuropathological aspects of the disease that have so far been considered to be secondary to Aβ-mediated neurotoxicity, and propose a sequence of neuropathological events that could lead to development of late-onset AD. This model unites many of the previously proposed mechanisms underlying AD into a comprehensive view of how the neuropathology could evolve over decades. We first present the results that have provided the rationale

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Key points

- Despite tremendous investments in basic and clinical research, no cure or preventive treatment for Alzheimer disease (AD) exists
- A re-evaluation of the current view of the mechanisms underlying late-onset AD pathology is a prerequisite for future translational approaches
- Inflammatory processes are strongly correlated with AD onset and progression in humans, and could have a pivotal role in disease aetiology
- Chronic inflammation coupled with neuronal ageing induces cellular stress and concomitant impairments in basic neuronal functions
- Inflammation-induced hyperphosphorylation and missorting of tau might represent one of the earliest neuropathological changes in late-onset AD
- Molecular changes underlying late-onset AD involve impairments in cytoskeleton stability and axonal transport, which could trigger axonal degeneration and formation of senile plaques and neurofibrillary tangles, resulting in neuronal death

for this hypothesis, which are then complemented by broader literature and experimental evidence from animal and human studies.

Inflammation hypothesis of AD

Rationale

A large body of evidence has implicated inflammatory mediators and the innate immune system of the brain in the aetiology of AD, as discussed below. The precise role of inflammatory processes in the disease pathophysiology has, however, been controversial, ranging from a possible disease cause, to a by-product of the disease, or even a beneficial response.[13]

Our previous findings in mice showed that systemic administration of the viral mimic polyriboinosinic–polyribocytidilic acid (PolyI:C) during late gestation triggered the expression of several inflammatory cytokines in the foetal brain,[14] evoked a reduction in adult neurogenesis in the offspring that was accompanied by working memory impairments,[14,15] and led to accelerated deposition of aggregated proteins in the brains of the aged offspring.[16] More recently, we demonstrated that upon second immune stimulation with PolyI:C in adulthood, prenatally challenged animals developed an AD-like phenotype.[17] The ageing-associated progression of disease in these mice was in striking similarity to that described in patients with AD.[2] In addition, systemic immune challenge in adult transgenic AD mice led to a strong aggravation of the AD-like pathology,[17] in agreement with the observation that both acute and chronic inflammation are associated with an increase in cognitive decline in patients with AD.[18] Alterations in critical inflammatory mediators might, therefore, represent a process associated with the onset and progression of the disease in humans, as already suggested by Sheng *et al.* in 1996.[19]

The model

In wild-type mice, ageing is associated with increased deposition of proteins in the brain parenchyma, and this phenomenon is highly conserved among various species.[16,20] Using 3D immunoelectron microscopy in aged wild-type mice we found that, surprisingly, these extracellular depositions originated from intracellular spheroid-like varicosities[20] and were immunoreactive for N-terminal and Aβ-containing APP fragments.[21] Some of these structures had a budding-like morphology and contained organelles, but many were detached from neurons and/or were being engulfed by microglia and astrocytes (Figure 1, step 1).[20,21] This phenomenon could, therefore, conceivably reflect a conserved neuroprotective strategy of postmitotic neurons to overcome age-related accumulation of misfolded, damaged or aberrantly cleaved proteins.[20] In line with this suggestion, a prenatal immune challenge with its chronic elevation of proinflammatory cytokines[17] accelerated the formation of these axonal buddings, and induced the accumulation of mitochondria and other organelles within these varicosities (Figure 1, step 2).[20] A strikingly similar budding phenomenon has also been observed in aged rhesus monkeys,[22] which serve as a primate model of late-onset AD.[23]

Chronic inflammation and cellular stress to neurons during ageing—owing to infection, disease, or age-related changes—induce hyperphosphorylation and missorting of tau,[17] which in turn is expected to destabilize the microtubule–actin networks and impair axonal transport.[24] Such changes might cause the protein extrusion mechanism to decline or fail completely, thereby inducing focal axonal swellings and concomitant accumulation of mitochondria and other organelles (Figure 1, step 3).[25,26] Disturbed energy metabolism in the axon could induce further tau phosphorylation,[27] an additional neuropathological event that probably facilitates the formation of paired helical filaments (PHFs; precursor elements of neurofibrillary tangles), as seen in double-immune-challenged mice.[17] This outcome would lead to further impairments in axonal transport, complete transport blockade, and ultimately axonal leakage (Figure 1, step 4; Figure 2a).[28] Loss of synaptic contacts and decline in cognitive performance constitute additional structural and functional consequences of axonal transport impairments (Figure 1, step 4).[17,29] A chronic inflammatory state also increases APP levels,[17] which may be followed by accumulation of this protein in swollen axons (Figure 1, steps 2–4; Figure 2b).[28]

In parallel with its effect on neurons, chronic systemic inflammation induces a prominent activation, or 'priming', of microglial cells and extensive astrogliosis (Figure 1, step 3).[17] Recruitment of microglia towards degenerative and/or leaking axons and axonal varicosities could, therefore, lead to over-activation of microglia and production of local inflammatory 'hot spots' that would also be expected to negatively affect nearby neurons (Figure 1, step 5). Support for this scenario is provided by our findings in double-immune-challenged mice in which individual accumulations of APP seem to involve groups of several adjacent neurites, which are surrounded by activated microglia.[17] Finally, these APP accumulations might represent a seed for other aggregation-prone peptides (Figure 1, step 5), as demonstrated in immune-challenged transgenic AD mice.[17]

On the basis of recent observations in the brains of patients with AD,[28] we propose that axonal leakage and release of intracellular contents—especially from dense autophagolysosomal vesicles[30,31] (Figure 2c–e)—including

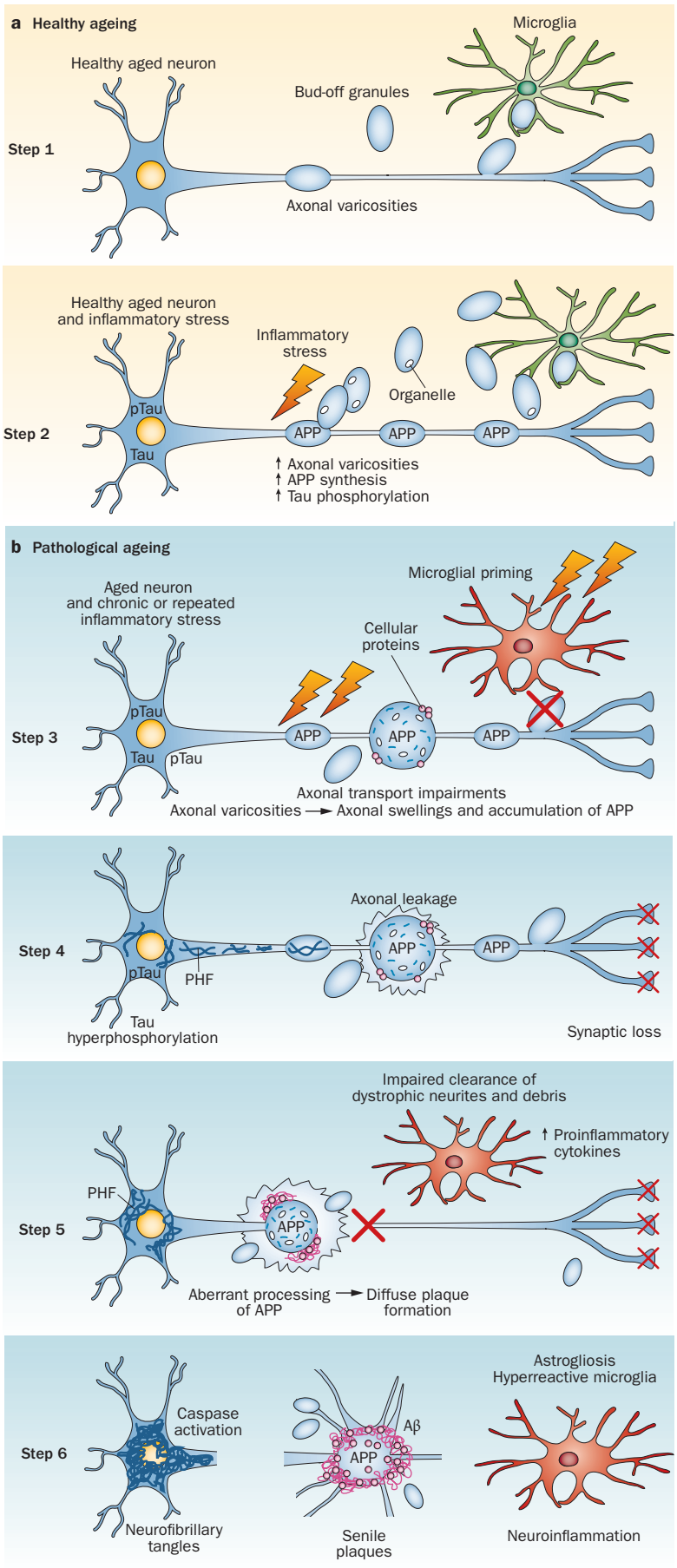

Figure 1 | The inflammation hypothesis of late-onset Alzheimer disease. **a** | During healthy ageing, a conserved protein extrusion mechanism compensates for ageing-dependent failures in protein clearance and degradation (step 1). Cellular stress to ageing neurons accelerates formation of varicosities and their extrusion into the extracellular matrix, where they are phagocytosed by surrounding glia (step 2). If aged neurons experience chronic inflammation, tau becomes hyperphosphorylated and is missorted to somatodendritic compartments, which impairs axonal transport (steps 2 and 3). **b** | Consequently, stress-induced APP accumulates in axonal compartments and in larger swellings (step 3). Chronic inflammation also 'primes' microglia to subsequent immune challenges (step 3). Blockade of axonal transport leads to synaptic destabilization or loss, and is accompanied by formation of PHFs in neurites and membrane leakage at axonal swellings (step 4). Axonal leakage exposes cellular proteins to lysosomal proteinases, promoting formation of neurotoxic peptides. Hyperreactive microglia cannot properly remove dystrophic neurites, and create a toxic proinflammatory environment that affects surrounding neurons. Senile amyloid-β plaques begin to form (step 5). In response to neuritic degeneration, caspase activation triggers formation of neurofibrillary tangles (step 6). Imbalances in excitatory–inhibitory neurotransmission and the neurotoxic proinflammatory environment initiate pathology in interconnected brain areas. Abbreviations: APP, amyloid precursor protein; PHF, paired helical filament.

accumulated APP[28] (Figure 2b,f) into the extracellular matrix (Figure 2a,b) leads to substantial local production of aggregation-prone protein fragments. This scenario is in agreement with the abundant presence of APP cleavage enzymes, such as cathepsin-D[31] (Figure 2e), and the enrichment of various truncated Aβ fragments[32] and diverse non-Aβ fragments of APP[33,34] in senile plaques. In addition, electron microscopy of human senile plaques revealed, in accordance with this proposal, an abundance of mitochondria and other organelles, as well as degenerated neurites, in the plaque core.[33,35] Finally, the proinflammatory environment and concomitant loss of axons might lead to formation of NFTs and neuronal cell death (Figure 1, step 6). This suggestion is in agreement with the observation that formation of NFT-like structures in AD transgenic mice—importantly, in the absence of mutant human tau—was accompanied by aggravated Aβ deposition, prominent neuroinflammation and considerable shrinkage of cortical areas.[36] Loss of synaptic contacts combined with persistent inflammation-induced cellular stress probably contributes to initiation of the pathophysiology in interconnected brain areas and the spread of the pathology across brain networks.

In the following sections, we summarize additional experimental data from the existing literature that support each of the proposed steps of the model.

Inflammation—a key player

Support for a key role for systemic inflammation in the aetiology of AD was first provided by a meta-analysis of 17 epidemiological studies, which indicated that non-steroidal anti-inflammatory drugs might decrease the

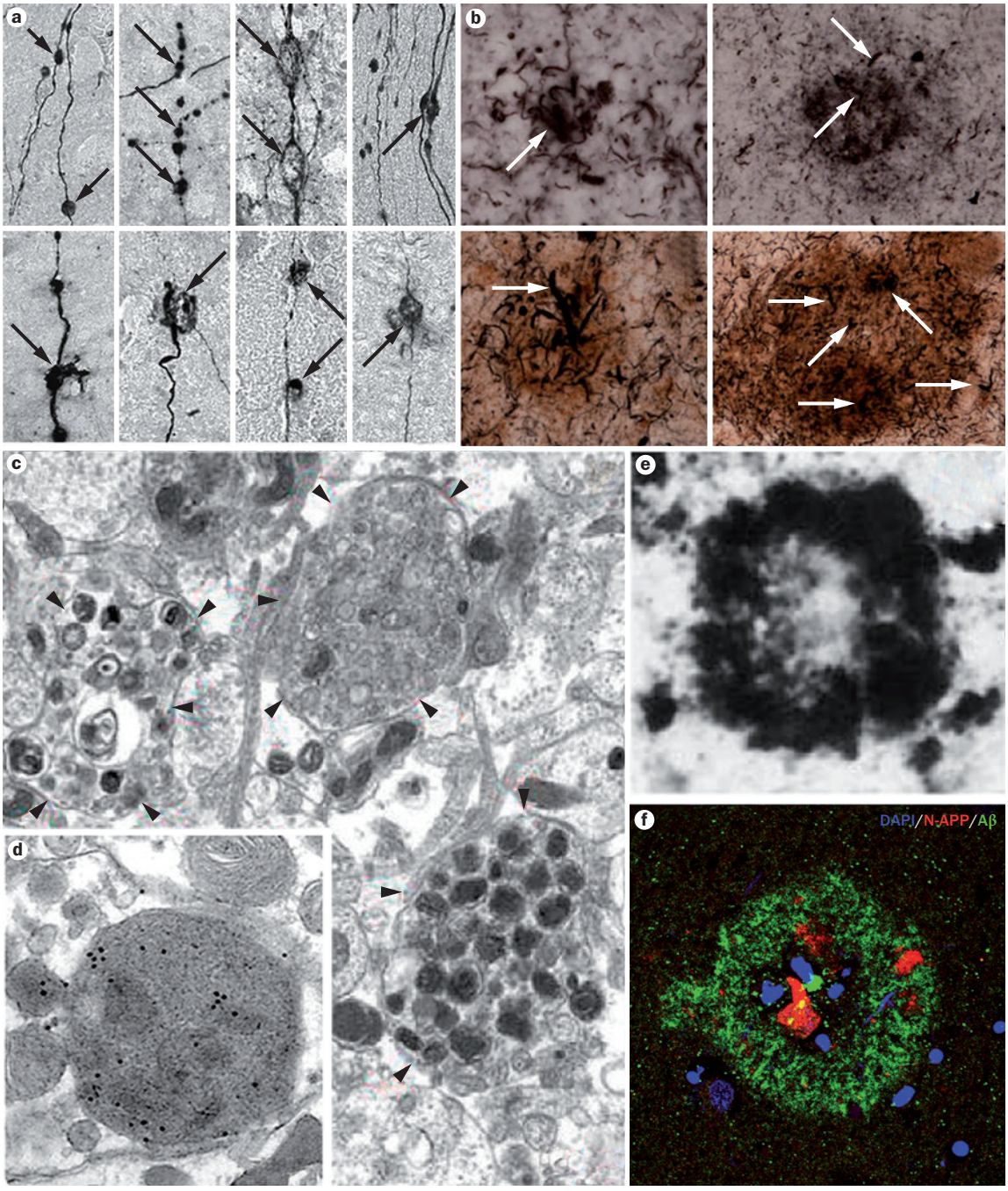

Figure 2 | Axonal swellings and leakage as a trigger of senile plaque formation in patients with Alzheimer disease. **a** | Experimental support that evolution of senile plaques starts with axonal swelling and varicosities (top row, arrows) and leakage from dystrophic axons (bottom row, arrows) in the cortex. **b** | Immunostaining of the cortex reveals small (left panels) and medium-sized (right panels) plaque-like accumulations (arrows) enriched for hyperphosphorylated tau (upper panels) and APP and/or amyloid-β (lower panels). **c** | Autophagic vacuoles (arrowheads) loaded with proteins accumulate in dystrophic neurites. **d** | Immunogold staining shows enrichment of cathepsin-D, the APP-degrading enzyme, in autophagic vacuoles in swollen neurites. **e**,**f** | Dense staining of cathepsin-D within late-stage senile plaques (e) overlaps with staining of accumulated amyloid-β (f). Abbreviation: APP, amyloid precursor protein. Parts a and b are reproduced, with permission, from Springer © Xiao, A. W. *et al. Neurosci. Bull.* **27**, 287–299 (2011). Parts c and e are reproduced, with permission, from Elsevier Ltd © Nixon, R. A. & Yang, D. S. *Neurobiol. Dis.* **43**, 38–45 (2011). Part d is reproduced, with permission, from Wolters Kluwer Health © Nixon, R. A. *et al. J. Neuropathol. Exp. Neurol*. **64**, 113–122 (2005). Part f is reproduced from Krstic, D. *et al. J. Neuroinflammation* **9**, 151 (2012), which is published under an open-access license by Biomed Central.

risk of AD.[37] This view is supported by two key findings from retrospective epidemiological studies: first, plasma levels of the inflammatory proteins C-reactive protein, α1-antichymotrypsin and IL-6 are increased long before clinical onset of AD and dementia;[38,39] and second, episodes of infections are strongly correlated with increased

likelihood of a diagnosis of dementia.[40] Randomized controlled trials, however, failed to show a beneficial effect of anti-inflammatory drugs in patients with symptomatic AD or mild cognitive impairment.[41,42] Nevertheless, extended treatment of asymptomatic individuals with the anti-inflammatory drug naproxen reduced the incidence of AD, supporting a beneficial effect of anti-inflammatory drugs only when administered in early, asymptomatic phases of the disease.[43]

Interestingly, patients with high plaque burden without dementia—so-called high-pathology controls[44,45]—show almost no evidence of neuroinflammation[46–48] and neurodegeneration.[46] These findings are in accordance with results from several transgenic mouse lines that express human versions of AD-inducing mutated genes, which show no evidence of strong neuroinflammatory responses nor widespread progressive neuronal cell death.[49] Of further interest, $A\beta_{1\text{-}42}$ levels in the brains of high-pathology controls were much higher than those in the brains of aged-matched patients with AD,[50] in agreement with a controversial proposal that $A\beta_{1\text{-}42}$ may be protective rather than toxic,[51] as further discussed below. In addition, PET imaging studies revealed that cognitive status in patients with AD is inversely correlated with microglial activation, but not Aβ load.[52,53] Finally, in accordance with the above mentioned genome-wide association studies,[7,8] chronic inflammatory diseases and conditions in humans, including atherosclerosis, obesity, diabetes, depression, and periodontitis,[54–60] all represent either risk factors for or correlate strongly with the risk of late-onset AD.

Aged and primed microglia

The increase in proinflammatory cytokines in the serum that accompanies systemic inflammation has been shown to play a fundamental part in communication between the brain and immune system. Such communication occurs through activation of central innate immunity and initiation of a behavioural response, known as sickness behaviour.[61] Apart from endothelial cells—which have an important role in blood–brain communication[62]—microglia seem to be crucially involved in regulation of the brain's response to systemic inflammation. For example, systemic inflammation in mice induced by the viral mimic PolyI:C,[63] the bacterial endotoxin lipopolysaccharide (LPS)[64,65] or by peripheral infusion of the proinflammatory cytokine IL-1β[66] was shown to activate microglia and induce the expression of brain-derived proinflammatory cytokines. In agreement with these findings, sepsis induces microglial activation in humans.[67] Moreover, chronic or repeated systemic inflammation in mice primes microglia to induce an exaggerated proinflammatory response to subsequent stimulations.[68]

Consistent with these findings, microarray data from aged human and murine brain tissue point to increased transcriptional activity of genes related to cellular stress and inflammation in the course of ageing,[10,69,70] a state that has been termed 'inflammaging'.[71] Hence, the observation that sickness behaviour at young age is relatively benign, whereas systemic inflammation in the elderly can lead to delirium,[72] could be explained by an age-associated priming of microglia.[73,74] In rodents, acute systemic infection in aged, but not young, animals leads to hippocampus-dependent cognitive impairments,[75,76] and exaggerated and prolonged upregulation of the proinflammatory cytokine IL-1β.[77,78] Chronic inflammatory conditions during ageing are, therefore, expected to profoundly affect the response of microglia towards damage signals that are released by degenerating neurons.

A broadly accepted view holds that microglia are recruited to clear Aβ aggregates,[79] but ablation of microglia does not influence the formation and maintenance of Aβ deposits in a mouse model of AD.[80] Similarly, after uptake of soluble and fibrillary Aβ by microglia, a large fraction of both species are released without degradation.[81,82] Microglia might instead be primarily recruited to clear the fragmented and/or apoptotic neurons and neurites within the senile plaques,[83] as occurs during neurodevelopment.[84] As proposed previously,[33] microglial involvement in internalization of Aβ aggregates could, therefore, be interpreted as part of the process of clearing degenerating neurites that contain misfolded and damaged proteins.

Finally, besides being hyperreactive in AD,[85] microglia may also become dysfunctional or senescent as disease progresses, as indicated by the association of fragmented microglia with tau pathology.[86] This observation would also explain the attenuation of neuroinflammation in AD patients with increasing age,[87] and supports the role of inflammation early in the pathogenesis of AD. Hence, in AD, a hyperreactive microglial state and increased secretion of proinflammatory mediators, combined with downregulated phagocytic functions, might lead to inefficient clearance of degenerated neurites. Impaired clearance mechanisms may produce not only a neurotoxic environment for surrounding neurons, but also a local 'hot spot' for accumulation of aggregation-prone peptides.

Early cytoskeletal impairments

Systemic administration of LPS, a potent inflammatory agent, induces hyperphosphorylation of tau in neurons[88]—a process that is mediated by activated microglia.[88–90] Similarly, a recent study showed that induced airway allergy in mice modified the brain inflammatory status and increased phosphorylation of tau.[91] Given that phosphorylation of tau is crucial for regulation of microtubule stability and axonal transport,[92] and that hyperphosphorylated tau not only affects the microtubule network but also induces accumulation of filamentous actin and formation of actin-rich rods,[93] these observations could provide a link between inflammatory processes and cytoskeletal abnormalities observed in postmortem examination of all AD cases.[94] As previously proposed,[95] these cytoskeletal abnormalities would affected axoplasmatic flow, as seen in patients with AD,[96,97] and would impair the function of the Golgi apparatus. Such an outcome could explain why this organelle has a fragmented and atrophic morphology in neurons of patients with AD.[98] Interestingly, overexpression of *APOE* ε4, as well as mutations in *PS1* and *APP*, also affect

tau phosphorylation, axonal transport, and neuronal dystrophy[99–102] in an Aβ-independent manner, which suggests a possible converging process underlying the familial and sporadic forms of the disease.

Finally, on the basis of analysis of an unbiased selection of postmortem human brains in the age range of 1–100 years, Heiko Braak and colleagues recently reported that tau-related neuronal changes appeared considerably earlier than did amyloid deposition, and that in more than half of investigated cases, abnormal tau protein occurred without the presence of Aβ deposits.[103] These observations indicate that impairments in neuronal integrity owing to hyperphosphorylation of tau could constitute an early neuropathological event that precedes deposition of the classical AD hallmarks, potentially by decades.

Inflammation and cellular stress

Numerous inflammatory stimuli, such as IL-1β and IFN-γ, induce an increase in protein synthesis through the mTOR (mammalian target of rapamycin) signalling pathway.[104] A large fraction of newly generated proteins, however, are defective in folding, translation, and/or assembly. This inflammation-induced pool of damaged proteins are selectively degraded through the immunoproteasome[105]—a fast-acting proteasome variant that protects cells from the damaging effects of neuroinflammatory processes associated with ageing.[106] In the brains of elderly individuals, aberrant, chronic elevation of inflammatory cytokines, which can result from persistent infections or inflammatory conditions, could conceivably impair or even inhibit immunoproteasome activity in ageing neurons,[107] thereby enhancing the intracellular accumulation of misfolded or damaged proteins.

Immune challenge either by the bacterial mimic LPS or by direct application of IL-1β results in pronounced increase in APP synthesis in primary cultured neurons[19,108] as well as in the brains of rats and mice.[19,109] Furthermore, several studies have provided experimental evidence that traumatic head injury in rodents and humans can result in significant elevation in APP levels,[110,111] as well as Aβ generation and amyloid plaque deposition.[112,113] In line with the high turnover, rapid anterograde transport, and processing of APP in distal compartments,[114–116] genetically induced fibre tract degeneration in the gracile axonal dystrophy mouse provokes rapid axonal accumulation of APP and Aβ.[117] Moreover, disruption of axonal and dendritic transport following impaired lysosomal proteolysis is accompanied by increased levels of C-terminally cleaved APP fragments,[118] which indicates that a combination of increased synthesis and impaired axonal transport of APP induces its rapid accumulation in neurites with subsequent aberrant cleavage. Notably, however, APP was recently shown to be required for maintenance of distal synaptic connections in APP/APLP2 knockout mice.[119] Hence, the increase in APP synthesis—so far exclusively considered as a trigger of accelerated production of 'neurotoxic' Aβ peptides—may be a physiological reaction of neurons to ensure stabilization of their synapses under stress conditions.

From varicosities to degeneration

The axonal enlargements described above that involve accumulation of multiple axonal cargoes and cytoskeletal proteins occur in transgenic AD mice,[120,121] aged monkeys,[22,122] and patients with AD,[123] and precede the typical disease-related pathology. Complementing these findings, Xiao and colleagues recently showed that extensively swollen axons and varicosities, accompanied by pronounced axonal leakage, are associated with the origin and development of neuritic plaques in patients with AD[28] (Figure 2a,b).

Swollen axons and varicosities in patients with AD contain high levels of APP[28] and autophagic vacuoles that are enriched in PS1,[123] cathepsin-D and cathepsin-B[124]—lysosomal proteases with β-secretase activity[125]—as well as other lysosomal proteins. It is plausible, therefore, that the release of intracellular contents into the extracellular matrix via axonal leakage[28] could bring APP into close proximity with APP-specific proteases. Aberrant APP processing at these locations is in agreement with the findings that Aβ plaques in patients with AD contain not only $Aβ_{1–40}$ and $Aβ_{1–42}$, but also substantial amounts of truncated Aβ peptides,[32] as well as large amounts of APP and its non-amyloidogenic fragments.[33,34] Interestingly, only truncated Aβ peptides isolated from the brains of patients with AD formed dimers,[32] which are suggested to be principal neurotoxic species of Aβ.[126] The proposed scenario of plaque formation could also explain the increase in aberrantly cleaved (by cathepsin-D) fragments of Apo-E that are observed in patients with AD.[127,128] Hence, in contrast to the familial form, in late-onset AD, aberrant processing of accumulated APP seems to be secondary to inflammation-induced axonopathy (Figure 2). In addition, physiologically produced $Aβ_{1–42}$ peptide may not represent the neurotoxic Aβ species, but an acute-phase reactant that is triggered by ongoing neurodegenerative processes, as suggested previously.[51]

Although axonal degeneration precedes and may precipitate plaque formation, pronounced cell death and progressive neurodegeneration are late features in AD. Therefore, certain transport processes might remain active at early stages of the disease, despite the overt axonopathy and amyloid plaque deposition. Indeed, in a transgenic mouse model of AD, dystrophic axons associated with Aβ plaques remained continuous and connected to viable neuronal somata.[129] Nevertheless, the lack of stabilizing presynaptic proteins, including APP,[119] is expected to trigger synaptic disconnection—a well-described feature of early-stage AD pathophysiology.[130] Secondary impairments in mitochondrial transport and energy supply,[131] and aberrant maturation of autophagic vacuoles,[30] are likely to further promote axonal degeneration and induce neuronal death.

Formation of neurofibrillary tangles

Dystrophic axons and dendrites associated with Aβ plaques are ideally placed to link Aβ with the microtubule-stabilizing protein tau and NFT neuropathology. Although NFTs can exist in the absence of Aβ accumulation,[103] a widely accepted view is that

amyloid-related changes precede the tau-associated neuropathology.[4] The direct or indirect mechanistic relationship between these two AD hallmarks, however, has not yet been resolved. Moreover, investigations into the molecular link between amyloid and NFTs have mainly, if not exclusively, centred on the involvement of Aβ peptides on tau localization and phosphorylation.[132]

The observation that neuritic plaques develop gradually in the projection areas of NFT-bearing neurons[133] indicates that NFTs develop in neurons whose neurites are involved in the formation of senile plaques. Support for this idea has been provided by immunolabelling and postmortem tracing studies in brain tissue from patients with AD, which showed that dystrophic and swollen and/or leaking neurites participating in plaque formation also contain hyperphosphorylated tau.[134,28] In addition, caspase activation was shown to precede the formation of tau aggregates, and caspase-cleaved tau was sufficient to induce the formation of NFTs.[135] Hence, similar to induction of caspase activation following axonal swelling during traumatic axonal injury,[136] caspase activation—and, thereby, NFT formation—might be triggered by axonal transport blockade or leakage.[137]

Notably, these data support the concept that NFTs form in response to the axonopathy with its aberrant accumulation and cleavage of APP and concomitant plaque formation, and not as a consequence of Aβ pathology. In line with this view, in mice over-expressing mutated human tau, NFT formation is preceded by axonopathy in the absence of amyloid plaque formation.[138] Moreover, genetic ablation of kinesin light chain 1, which induces an age-dependent axonopathy, is accompanied by tau hyperphosphorylation, as evaluated using several AD-specific tau antibodies.[138]

Conclusion

For the past two decades, the general assumption that the molecular mechanism underlying the genetically determined form of AD is identical to the one determining the late-onset variant of the disease has resulted in an almost exclusive focus of our experimental and translational research on Aβ species and its effects on neuronal integrity and functions. However, despite more than 66,000 publications, numerous clinical investigations, and innovative drug developments, we remain unable to even slow disease progression. Re-evaluation of our knowledge of the late-onset form of AD, which accounts for the majority of patients, is therefore of highest priority. In this article, we have integrated numerous experimental findings with a focus beyond Aβ to propose a sequence of pathological events that might lead to development of late-onset AD in humans. We suggest naming this integrated view of how the neuropathology evolves over decades 'the inflammation hypothesis of AD', as inflammation induced by infection, disease, or age-related changes could be the main cellular stressor after 80 or more years of life. In addition, traumatic head injury, micro-strokes and other vascular dysfunctions associated with increased risk of AD probably trigger the pathological cascade described here via secondary neuroinflammatory reactions.

In summary, in late-onset AD—in contrast to the familial form of the disease—chronic inflammatory conditions may represent a major trigger of pathology by inducing phospho-tau-related cytoskeletal abnormalities and concomitant impairments of axonal transport. These changes could lead to age-dependent formation of axonal swellings, focal accumulation of mitochondria, and transport and degradation of organelles. Membrane leakage at the sites of axonal swellings could serve as a seed for the formation of senile plaques, thereby triggering an innate immune response of the brain. Axonal transport impairments would also affect the stability of distal synapses and facilitate the formation of NFTs. Together with persistent neuroinflammatory reactions, these changes are expected to lead to prominent neurodegeneration and the spread of pathology. We argue, therefore, that extracellular Aβ plaques originate from intracellular APP accumulations and are secondary to degeneration of neurons. Consequently, therapeutic strategies to remove plaques using specific antibodies, or to prevent plaque formation through inhibition of β-secretase or γ-secretase, would have little—if any—effect on disease initiation and probably also progression. Finally, we propose that the primary pathological event in AD is inflammation-induced and stress-induced mislocalization and hyperphosphorylation of tau, with subsequent impairment of axonal transport.

We are aware that the experimental results and observations reviewed here represent only a fraction of all the published data on late-onset AD, and that further investigations are needed to fully delineate the molecular mechanisms that initiate and drive the pathology in late-onset AD. Hence we truly hope that scientists and clinicians will add their data to confirm, refine, adjust, and extend our proposed sequence of events. Nevertheless, we strongly believe that the proposed model with its solid experimental backup provides a first step for the initiation and support of new research directions in the AD field beyond Aβ.

Review criteria

Full-text, English-language articles were included in the search, without restrictions on publication date. We searched the MEDLINE and PubMed databases, and used the Google search engine, for terms including: "Alzheimer disease", "inflammation", "neuroinflammation, "ageing", "GWAS", "infection", "cognition", "dementia", "tau hyperphosphorylation", "amyloid precursor protein", "axonal transport", "cytoskeleton abnormalities", "oxidative stress", "lysosomes", "autophagy", "protein degradation", "microglia", "senile plaques", "neurofibrillary tangle", "neurodegeneration", and "caspases". Reference lists of selected articles were searched to identify further references. Our search for observations in AD was based on selected reviews on clinical and pathophysiological aspects of AD, and on PubMed searches using the above terms in combination with: "oldest-old", "nonagenarians", "without/no dementia", "high pathology", AND the filter "species: human".

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