Alzheimer’s and Parkinson’s diseases: The prion concept in relation to assembled Aβ, tau, and α-synuclein

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BACKGROUND: Alzheimer’s disease (AD) and Parkinson’s disease (PD) are the most common human neurodegenerative diseases. AD is primarily a dementing disease, and PD is a movement disorder. Together, they affect around 50 million people worldwide, with the vast majority of disease cases being sporadic. Their incidence increases with age. Like most neurodegenerative diseases, AD and PD are caused by the aggregation of a small number of proteins, with filament assemblies constituting the end-point of protein aggregation. AD is characterized by the presence of abundant extracellular plaques made of amyloid assemblies of Aβ peptides and intraneuronal inclusions made of assembled tau protein.

A pathological pathway leading from soluble proteins to insoluble filaments. This pathway is at the heart of human neurodegenerative diseases, including Alzheimer’s and Parkinson’s diseases. The formation of pathological seeds is a rare and energetically unfavourable event, which requires exposure of backbone amide groups and a high protein concentration. Once a seed has formed, single molecules can change shape and join the growing aggregates. Seed addition induces rapid assembly of the soluble protein. Fragmentation generates new seeds, accelerating the formation of aggregates. Filaments represent the endpoints of aggregation. They are typically unbranched, with a diameter of ~10 nm, and can be several micrometers long. This drawing is not to scale. [Adapted from S. K. Fritschi et al., in Protopathic Seeds and Neurodegenerative Diseases, M. Jucker, Y. Christen Eds. (Springer, Berlin, 2013), pp. 61–69].

Some dominantly inherited cases of AD are caused by mutations in the gene encoding the amyloid precursor protein (APP), the cleavage of which gives rise to Aβ. In these cases, dysfunction of APP precedes dysfunction of tau. In contrast, mutations in MAPT, the tau gene, give rise to dominantly inherited frontotemporal dementia and parkinsonism, with abundant tau inclusions in the absence of Aβ plaques. Extrapolation to the much more common sporadic cases of AD has given rise to the amyloid cascade hypothesis, which postulates that Aβ aggregation causes the formation of tau inclusions, synaptic dysfunction, nerve cell death, and brain shrinkage. However, tau inclusions correlate better with cognitive impairment, and Aβ may exert its effects through tau. Strategies targeting the formation of Aβ and tau assemblies are valuable for the development of mechanism-based therapies. Unlike AD, in which two distinct amyloid assemblies are present, PD is characterized by intracellular deposits, Lewy bodies and neurites, both composed of the protein α-synuclein. Dominantly inherited forms of PD are caused by mutations in SNCA, the α-synuclein gene. More than 95% of those diagnosed with PD have Lewy inclusions.

ADVANCES: For many years, the mechanisms underlying AD and PD were widely believed to be cell-autonomous. This implies that the same molecular events, such as the formation of tau and α-synuclein assemblies, occur independently in a large number of cells in an otherwise healthy brain. Recent findings have suggested instead that non-cell-autonomous processes play an important part in AD and PD. Inclusions are thought to form in a small number of cells and—if given enough time and, perhaps, a genetic predisposition—spread in a deterministic manner to distant brain regions. The formation of the first Aβ, tau, and α-synuclein inclusions is probably stochastic, with most seeds being degraded. Distinct molecular conformers of aggregated proteins (or strains) may underlie clinically different diseases. This is reminiscent of human prion diseases, such as Creutzfeldt-Jakob disease (CJD). However, there is reluctance to use the term prion for the inclusions of AD and PD. The main reasons are that in contrast to Kuru and CJD, transmission of AD and PD has not been demonstrated between individuals, and most experimental studies have used transgenic animals that overexpress disease proteins.

OUTLOOK: The prion concept appears to apply to all human neurodegenerative diseases with abnormal protein assemblies, including AD and PD. This has brought unity to the field and changed the way we think about these diseases. It has been known for some time that a seed can template aggregation of the homologous protein. However, the ability of protein aggregates to spread through the nervous system had previously been underappreciated. At a practical level, the new findings are helping to elucidate the mechanisms underlying disease, which may have therapeutic implications in all cases. It will be important to identify the molecular species of assembled host proteins responsible for propagation and neurotoxicity. ■
The pathological assembly of Aβ plaques and intraneuronal filamentous inclusions define Alzheimer’s disease, whereas intracellular inclusions of α-synuclein make up the Lewy pathology of Parkinson’s disease. Most cases of disease are sporadic, but some are inherited in a dominant manner. Mutations frequently occur in the genes encoding Aβ, tau, and α-synuclein. Overexpression of these mutant proteins can give rise to disease-associated phenotypes. Protein assembly begins in specific regions of the brain during the process of Alzheimer’s and Parkinson’s diseases, from where it spreads to other areas.

More than 100 years ago, Alois Alzheimer, Oskar Fischer and Friedrich Leydhecker described the inclusions of Alzheimer’s disease (AD) and Parkinson’s disease (PD), but their constituent proteins were only identified over the past 31 years (1, 2). In AD, these inclusions are amyloid plaques and neurofibrillary lesions, whereas in PD, they are Lewy bodies and neurites.

In the 1980s, β-amyloid (Aβ) peptides, cleavage products of the amyloid precursor protein (APP), were discovered as the major component of amyloid plaques and cerebral vascular inclusions, whereas tau protein was identified as the major component of the neurofibrillary lesions of AD. In the 1990s, α-synuclein was found to make up Lewy bodies and neurites. The study of rare, dominantly inherited cases was essential for understanding the aetiologies of AD and PD. Extrapolation to the much more common sporadic cases underpins most current thinking. In 1991, a missense mutation in the amyloid precursor protein gene (APP) that encodes Aβ was shown to cause AD (3), and in 1998, mutations in MAPT, the tau gene, were reported to cause frontotemporal dementia and parkinsonism (4–6). In 1997, a missense mutation in SNCA, the α-synuclein gene, was shown to cause PD (7). More recently, it has become apparent that AD and PD are caused by protein assemblies that adopt alternative conformations and become self-propagating, like prions (8, 9).

Alzheimer’s and Parkinson’s diseases

AD is the most common neurodegenerative disease. It is defined clinically by a progressive decline in memory and other cognitive functions, and neuropathologically by brain atrophy and the accumulation of abundant extracellular Aβ plaques and intraneuronal neurofibrillary tau lesions (Fig. 1A) (1). As shown with electron microscopy, plaques and neurofibrillary lesions are made of abnormal filaments with the fine structure of amyloid (Fig. 1B). They are unbranched and have a diameter of ~10 nm, with a length of up to several micrometers (10). Each amyloid filament exhibits characteristic dye-binding properties and consists of several protofilaments with β-sheet structures that are stabilized through hydrogen bonding. The in-register, parallel β-sheet organization predominates in amyloid filaments. The crystal structures of amyloidogenic peptides have shown that amino acid side-chains complement each other across the sheet-sheet interface and that the space between sheets is devoid of water (dry steric-zipper) (Fig. 1C) (11, 12). Nonfilamentous aggregates are also present (1, 8). They are β-sheet–rich but transient and are objects of intense investigation (13).

Aggregates formed by a given peptide or protein are polymorphic, in that they can adopt multiple molecular structures, which retain their properties after repeated passing between animals (14). Whereas abundant Aβ plaques and cerebral vascular deposits are specific for AD, filamentous tau inclusions are also characteristic of other neurodegenerative diseases, including chronic traumatic encephalopathy (CTE), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), argyrophilic grain disease (AGD), Pick’s disease, and frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17) (1). In some of these diseases, tau inclusions are also found in glial cells.

PD is the second-most common neurodegenerative disease and the most common movement disorder. Patients exhibit bradykinesia that worsens over time, in conjunction with one of three additional features: rigidity, resting tremor, or gait disturbance (15). PD is characterized by the widespread degeneration of subcortical structures of the brain, especially dopaminergic neurons in the substantia nigra. They contain Lewy pathology, which is made of abnormal filamentous complexes composed of α-synuclein (Fig. 1D). More than 95% of those who fulfill the clinical criteria of PD have Lewy pathology. PD-dementia and dementia with Lewy bodies (DLB) form part of the biological spectrum of PD. α-Synuclein is also the major component of glial cytoplasmic inclusions (GCI) (16–18), or Papp-Lantos bodies (19), filamentous inclusions that define multiple system atrophy (MSA), a movement disorder characterized by cerebellar ataxia, parkinsonism, and autonomic dysfunction. In MSA, unlike PD and DLB, many α-synuclein inclusions are also found in glial cells (oligodendrocytes and Schwann cells) (20, 21).

Links with prion diseases

Following radioinactivation studies, which suggested that the agent of scrapie may replicate without nucleic acid (22, 23), its purification led to the identification of the prion protein (PrP) and showed that the scrapie agent was devoid of nucleic acid (24). To distinguish protein pathogens from viruses, the term “prion” (proteinaceous infectious particle) was introduced (25). Human prion diseases include Kuru, Creutzfeldt-Jakob disease (CJD), Gerstmann-Sträussler-Scheinker (GSS) disease, and fatal insomnia. Scrapie, bovine spongiform encephalopathy (BSE), and chronic wasting disease (CWD) are the most common prion diseases in animals. A polymorphism at codon 129 of human PRNP, where M or V is encoded, is a susceptibility factor for prion diseases (26). Cases of variant CJD (vCJD), which humans acquire through the consumption of BSE-contaminated food products, have so far almost all been M/M (27).

With the identification of causative mutations in PRNP (Fig. 2A), a possible explanation for dominantly inherited and sporadic cases of CJD emerged (28–30). Mutations were surmised to lower the energy barrier for conversion of the cellular form of PrP (PrP(C)) to its scrapie form (PrPSc). Once a sufficient number of PrPSc molecules has formed, the conversion of PrP(C) to PrPSc occurs readily. Upon introduction into a new host, PrPSc seeds convert PrP(C) to PrPSc, which explains how prion diseases can be infectious. In some prion isolates, the majority of infectivity is protease-sensitive. Variable protease-sensitive prionopathy accounts for 2 to 3% of cases of sporadic disease (31). More needs to be learned about the sites of prion conversion and the mechanisms of intercellular propagation. The transfer of pathology from one neuron to another appears to occur trans-synaptically. The scrapie agent spreads through the visual system after retinal injection (32).

Findings from multiple studies have shown that strain-specific properties are maintained upon serial passage between animals and are encoded in the conformation of misfolded prion protein (33). Structural differences have been
demonstrated between two strains of yeast prions (34). In sporadic diseases, the formation of misfolded prion protein is hypothesized to be stochastic, with prions forming randomly but being usually degraded. The age-dependence of prion diseases, and neurodegenerative diseases more generally, may be the result of a decrease in the efficiency of protein quality-control systems (35).

Mutations in PRNP account for ~10% of cases of CJD, with 90% being sporadic. This is reminiscent of AD and PD, in which dominantly inherited mutations account for a minority of cases, with the majority being sporadic. Heterozygous G127V PrP confers resistance against Kuru, with V127 being only found in conjunction with M129 (36). Mice heterozygous for human PrP V127 are resistant to Kuru and CJD but not vCJD prions. Remarkably, homozygous mice are resistant to all prion strains (37).

Initially, the prion concept was confined to a small group of diseases, typified by scrapie and CJD, in which PrP, a glycolipid-anchored siglacyloprotein, adopts a conformation rich in β-sheet (38). Similar conformational changes have been observed for Aβ, tau, and α-synuclein assembles, as compared with misfolded prion protein, or to other properties. Yet in the brain (at least of overexpressing animals), many characteristics are shared with PrPSc. Thus, both PrPSc and assembled Aβ bound tightly to stainless-steel wires, and after their brain implantation, replication occurred, and prion-specific pathological changes ensued (41, 42). Assembled Aβ and α-synuclein were also resistant to inactivation by formaldehyde (43, 44).

For prion diseases, the molecular species responsible for infectivity and toxicity appear to be different (45–47). Subclinical states and large amounts of PrPSc have been described, as has neurodegeneration in the presence of small amounts of PrPSc. Removal of the glycosylphosphatidylinositol anchor of PrP reduces neurotoxicity, despite the accumulation of abundant extracellular PrPSc. It has been proposed that neurodegeneration is mediated by a toxic form of PrP, called PrPSc, that is distinct from PrPSc, but whose formation is catalyzed by PrPSc (47). Although the molecular species responsible for toxicity are not well defined, they may be crucial for activating one or more downstream pathways. Targeting the unfolded protein response in mice overexpressing PrP has been reported to prevent neurodegeneration (48).

Assemblies of Aβ, tau, and α-synuclein Aβ

APP encodes a widely expressed type 1 transmembrane glycoprotein that is alternatively spliced to produce three major transcripts: APP695, APP751, and APP770 (49, 50), with APP695 being the major isofrom in neurons. Aβ is produced from APP through sequential endoproteolytic cleavage, with its N terminus being located in the extracellular domain and its C terminus in the transmembrane region. The enzymes, which cut APP to produce Aβ, are the β- and γ-secretases.

γ-Secretase features in the initial and rate-limiting step, giving rise to the N terminus of Aβ. It removes the majority of the extracellular portion of the protein, leaving the C-terminal part of APP. BACE1 (β-site APP cleaving enzyme 1), a type I transmembrane aspartyl protease, which has its active site in the extracellular space, is the β-secretase.

γ-Secretase, which gives rise to the C terminus of Aβ, is a membrane-embedded aspartyl protease, which cleaves many transmembrane proteins, including APP and Notch. The γ-secretase complex consists of four proteins: presenilin (PS), presenilin enhancer-2 (Pen-2), anterior pharynx-defective (Aph-1), and nicastrin. PS, an aspartyl protease, forms the catalytic core of the complex. It comprises nine transmembrane (TM) domains, with the two catalytic aspartates located in domains 6 and 7. Upon assembly of the complex, PS undergoes proteolysis between these two domains to form the catalytically active γ-secretase. Pen-2 facilitates the maturation of PS, whereas Aph-1 stabilizes the complex. Nicastrin, which comprises two thirds of the 170-kD protein complex, may be a receptor for γ-secretase substrates. The human γ-secretase complex consists of a horseshoe-shaped domain of TM segments and a large

**Fig. 1. The assemblies of AD and PD.** (A) Light microscopic picture of Aβ plaques (blue) and neurofibrillary tau lesions (brown) in the cerebral cortex in AD. (B) Electron micrograph of a paired helical tau filament from AD. The cross-over spacing is ~80 nm. Paired helical filaments form the majority of tau filaments, with straight filaments being in the minority. [Reproduced with permission from (138)] (C) Steric-zipper crystal structure of the hexapeptide VQIVYK (residues 306 to 311) from the core of tau filaments, which is required for aggregation. Two β-sheets are shown (gray and blue), with the β-strands being parallel within each sheet, and antiparallel between sheets. A tau filament consists of thousands of β-strands, five of which are given for each sheet. The peptide backbones are shown as arrows. Protruding from each sheet are the amino acid side chains. The black arrow marks the filament axis. (D) Light microscopic picture of Lewy bodies and Lewy neurites made of α-synuclein (brown) in the substantia nigra in PD. [Reproduced with permission from (139)]
Fig. 2. Mutations in PRNP, MAPT, APP, and SNCA that cause human neurodegenerative diseases. (A) Missense mutations, truncation mutations, and changes in the numbers of octapeptide repeats in PRNP, the prion protein gene, cause dominantly inherited forms of CJD, fatal familial insomnia and GSS disease. Thirty-three missense mutations and six truncation mutations are shown. The number of octapeptide repeats (in yellow) can increase through insertion or decrease through deletion. The methionine/valine polymorphism at codon 129 is important. In human prion diseases with mutations P102L, P105L, P105S, A117V, D178N, H187R, T188R, F198S, E200K, D202N, Q217R, Y218N, Y226X, and Q227X, the sequence was valine at codon 129 of the mutant allele. In many cases with mutations P102L, D178N and E200K, the amino acid at codon 129 of the mutant allele was methionine. (Single-letter abbreviations for the amino acid residues are as follows: A, Ala; C, Cys; D, Asp; E, Glu; F, Phe; G, Gly; H, His; I, Ile; K, Lys; L, Leu; M, Met; N, Asn; P, Pro; Q, Gln; R, Arg; S, Ser; T, Thr; V, Val; W, Trp; and Y, Tyr. In the mutants, other amino acids were substituted at certain locations; for example, G127V indicates that glycine at position 127 was replaced by valine.) The signal sequence and glycosylphosphatidylinositol (GPI) peptide are indicated (in blue). (B) Missense, deletion, and intronic mutations in MAPT, the tau gene, cause dominantly inherited frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17T). Exons 1 (E1) and E9 to E13 are shown schematically (not to scale). E9 to E12 encode the four tau repeats, with E10 (in yellow) being alternatively spliced. Forty-four coding region mutations and nine intronic mutations flanking E10 are shown. (C) Duplication of APP, the amyloid precursor protein gene, as well as missense and deletion mutations (black box) in APP cause dominantly inherited AD and cerebral amyloid angiopathy. Twenty-eight missense and deletion mutations in APP are shown. The Aβ sequence is shown in brown, with the flanking sequences of APP shown in green (numbering according to the 770 amino acid isoform). (D) Multiplications of SNCA, the α-synuclein gene, and missense mutations (black box) in SNCA cause dominantly inherited forms of PD and dementia with Lewy bodies. Six missense mutations are shown. The black bars indicate the imperfect repeats in the amino-terminal half of α-synuclein.
extracellular domain (51, 52). Nicastrin, Aph-1, and the C-terminal part of PS are located at the thick end of the horseshoe, with Pen-2 and the N-terminal part of PS being located at its thin end. Because of the existence of two FS (PSI and PS2) and Aph-1 (Aph-1A and Aph-1B) variants, there are at least four different human γ-secretase complexes, cleavage by which results in different Aβ profiles (53). The processing of APP by γ-secretase is not restricted to a single site. It is cleaved several times, at the ε-, ϵ-, and γ-sites that are separated by approximately three amino acids. The final cleavage occurs between amino acids 37 and 43, giving rise to Aβ37, Aβ38, Aβ39, Aβ40, Aβ42, and Aβ43, with Aβ40 being the predominant species. However, Aβ42 is more aggregation-prone and believed to be the toxic building block of Aβ assemblies. The most abundant γ-secretase complex comprises PSI, Pen-2, Aph-1A, and nicastrin.

A third enzyme, α-secretase, cleaves between residues 16 and 17 of Aβ. ADAM10 (a disintegrin and metalloprotease) is the major α-secretase in neurons. Most APP is cleaved by the α- and γ-secretases, resulting in nonpathogenic fragments, but some is cut by β- and γ-secretases to generate Aβ. Cell-surface APP is endocytosed, resulting in the endosomal production of Aβ and its secretion into the extracellular space.

Once a Kuru-like syndrome had been transmitted from humans to chimpanzees (54), work was undertaken to determine whether AD and PD were transmissible. No convincing evidence of brain dysfunction was obtained (55). In the 1990s, the intracerebral injection of brain homogenates from AD patients was shown to cause deposition of Aβ in marmoset monkeys after 6 to 7 years (56). A separate approach used mice overexpressing human mutant APP, resulting in the formation of Aβ plaques. Intracerebral and intraperitoneal inoculations of AD brain homogenates accelerated the deposition of plaques (57–59).

Subsequently, assembled synthetic Aβ was injected intracerebrally into young transgenic mice, where it gave rise to Aβ amyloidosis (60). Strictly speaking, these experiments described the acceleration of a process that occurs anyway. However, the induction of Aβ deposition after the intracerebral injection of Aβ amyloid in transgenic rodents that do not normally develop pathology has also been described (61). In human brain, Aβ plaques are initially found in basal temporal and orbitofrontal neocortex (62–64). They appear later throughout the neocortex, as well as in hippocampal formation, diencephalon, and basal ganglia. In severe cases of AD, Aβ plaques are also found in brainstem and cerebellum (Fig. 3).

Modifying the conditions for peptide assembly resulted in different conformers of assembled Aβ, akin to prions (65). One strain of Aβ42 induced small plaques composed almost exclusively of Aβ42, whereas another produced large plaques composed of both Aβ40 and Aβ42. Moreover, transgenic mice injected with brain extracts from individuals with AD caused by different APP mutations formed distinct Aβ aggregates (66). These properties were maintained upon serial passaging in mice.

**Tau**

In adult human brain, six Aβ isoforms ranging from 352 to 441 amino acids are produced from one gene through alternative mRNA splicing (1). Three isoforms have three repeats each, and three isoforms have four repeats each. The repeats and some adjoining sequences constitute the microtubule-binding domains of tau. They also make up the core of tau filaments. In AD and CTE brains, all six isoforms are present in the filaments. In other diseases—such as PSP, CBD, and AGD—Aβ isoforms with four repeats are found. In Pick’s disease, three-repeat tau isoforms predominate in the inclusions. Unlike AD, these diseases lack Aβ pathology.

Despite the fact that mutations in APP, but not MAPT, cause inherited AD, neurofibrillary lesions are required for the development of dementia (62, 67). People with abundant Aβ plaques, but no or only few neurofibrillary lesions, do not have AD. The overexpression of mutant human tau in the brains of transgenic mice recapitulates molecular and cellular features of tauopathies, including filament formation and neurodegeneration. The crossing of lines expressing mutant tau with lines expressing mutant APP resulted in enhanced tau pathology (68). However, unlike in inherited AD, human tau was mutant. Three-dimensional cultures of human neural stem cells transfected with mutant APP have been reported to develop...
amyloid plaques and inclusions made of wild-type tau (69). Tau appears to be necessary for Aβ-induced toxicity, and the hyperexcitability of nerve cells caused by exposure to Aβ was reduced in the absence of tau (70).

The role of tau in neurodegeneration became clear with the identification of causative mutations in MAPT in FTDP-17 (Fig. 2B) (4–6). Filamentous tau inclusions are present, in the absence of Aβ deposits. Mutations fall into two largely nonoverlapping groups: those that influence the alternative splicing of tau pre-mRNA and those whose primary effect is at the protein level (7). Most missense mutations reduce the ability of tau to interact with microtubules. Some mutations also promote tau assembly into filaments. Intronic mutations and some coding region mutations lead to the relative overproduction of four-repeat tau.

In populations of European descent, MAPT is characterized by two haplotypes that result from a 900-kb inversion (HI) or noninversion (H2) polymorphism (77). Inheritance of the HI haplotype is a risk factor for PSP, CBD, PD, and MSA. The association between the HI haplotype and PSP had a higher odds-ratio than that between APOEε4 and sporadic AD (72).

Several lines of investigation have shown that assembled tau can behave like a prion. In the human brain, neurofibrillary lesions appear to spread along neural pathways from one brain region to another (62, 73). During the process of sporadic AD, they first appear in locus coeruleus and entorhinal cortex, followed by hippocampal formation and large parts of the neocortex (Fig. 3). Tau inclusions follow the opposite direction to Aβ plaques, which form first in the neocortex. The symptoms of AD are present when abundant tau inclusions and Aβ deposits are found in neocortex (74, 75). Tau deposition in entorhinal cortex and hippocampus is probably necessary, but not sufficient, for the development of AD (76). It remains to be determined whether Aβ plaques and tau inclusions form independently and when they become self-sustaining. It is also not clear whether one type of inclusion influences the spreading of the other. Interpretation is limited by the ability to visualize only a subset of aggregates. A pathological pathway leads from misfolded proteins to filaments, with a number of intermediates. The roles of the latter in the propagation of pathology and aggregate neurotoxicity need to be better understood. Positron emission tomography ligands can visualize Aβ and tau pathologies in living brains; if their spatial resolution can be improved, it will become possible to follow the sequential spreading of protein inclusions.

In AGD, tau inclusions are initially restricted to the ambient gyrus, from where the pathological process extends to the anterior and posterior temporal lobe, followed by septum, insular cortex, and anterior cingulate cortex (77). In CTE, tau inclusions form first in the depths of some cortical sulci, close to the perivascular spaces. They are later found throughout cerebral cortex, diencephalon, basal ganglia, brainstem, and spinal cord (78).

Intracerebral injection of human mutant tau inclusions into the brains of mice transgenic for wild-type human tau induced the formation of inclusions that spread to distant brain regions (79). Similar results were obtained when presymptomatic mice transgenic for human mutant tau were injected (80). Tauopathy was also observed in wild-type mice after seeding with human brain aggregates, although there was a lower density of aggregates than after seeding in transgenic human tau mice (81). A substantial species barrier was not present because human mutant tau seeds were reported to induce aggregation of wild-type murine tau (82, 83). Intraperitoneal injections of tau inclusions into presymptomatic transgenic mice promoted the formation of tau inclusions in brain, albeit less efficiently than after intracerebral injection (84).

Distinct conformers of assembled tau exist, reminiscent of prion strains (81, 85–87). This may explain the variety of human tauopathies. It is also supported by the presence of distinct tau filament morphologies in cases of FTDP-17 with different MAPT mutations (Fig. 4) (88). Network connectivity studies using functional magnetic resonance imaging have provided evidence that different tauopathies may be caused by distinct molecular conformers of assembled tau, akin to prion strains (89). This may explain the selective neuronal vulnerability characteristic of individual tauopathies, with different disease processes beginning in different brain cells, from where they spread to connected regions. Host factors may also play an important role (90).

Studies in cultured cells have shown the intercellular transfer of tau assemblies and the adoption of alternative conformations that became self-propagating (91, 92). Tau seeds were taken up and induced tau assembly in the cytoplasm. Monomeric tau was ineffective, and expressed tau could only be seeded if it was capable of aggregation (86). Internalization required the presence of sulphated glycosaminoglycans at the cell surface. Distinct seeded assemblies made of four tau repeats formed in human embryonic kidney (HEK) 293 cells (85); they could be distinguished upon injection into the brain of presymptomatic transgenic mice, from where they could be passed. When HEK293 cells expressing four tau repeats were seeded, inclusions formed that were identical to those initially present.

**α-Synuclein**

This is an abundant 140-amino-acid protein that is highly enriched in presynaptic nerve terminals (93). α-Synuclein binds to lipids through its amino-terminal part, when it multimerges and becomes α-helical. It can also self-assemble through this region, which forms the core of the β-sheet-rich disease filaments. In nerve
terminals, α-synuclein binds to the external surface of synaptic vesicles, where it is thought to play a role in neurotransmission. The membrane-bound form of α-synuclein is present in equilibrium with a cytosolic form. In nerve cells, membrane binding inhibits α-synuclein aggregation (94).

Like Aβ and tau, α-synuclein assembles into a β-sheet–rich conformation that is able to seed aggregation of soluble α-synuclein in transfected cells (92, 95). Neuropathological studies have shown that Lewy pathology spreads along neural pathways in the brain, beginning in the dorsal motor nucleus of the glossopharyngeal and vagal nerves, the olfactory bulb, and the anterior olfactory nucleus (Fig. 3) (96, 97). Lewy inclusions are also found in spinal cord, autonomic ganglia, and the enteric nervous system (2). It is not clear whether this is indicative of brain-to-gut or gut-to-brain spreading. The latter would be analogous to vCJD. In support of gut-to-brain spreading, vagotomcy has been associated with a reduced risk of PD (98).

In the 1970s and 1980s, some patients with idiopathic PD received intrastriatal grafts of human foetal dopaminergic neurons. After 10 to 22 years, a proportion of the grafted neurons had degenerated (99), and Lewy bodies were seen in the substantia nigra, nigrostriatal pathway, and other brain regions. In 1993, the first report appeared of patients with PD who had received intrathalamic transplants of human fetal substantia nigra tissue (100). However, in most patients, grafted dopamine neurons died within weeks (101). In vivo imaging of radioactively labeled dopamine neurons has shown that only a small proportion of grafted dopamine neurons remain intact up to 10 years after transplantation (102). In a recent follow-up study, only 30 to 50% of the original grafted neurons were found to be intact (103). These results suggest that the long-term survival of grafted dopamine neurons is limited.

Genetics of PD

MAPPING OF APP TO CHROMOSOME 21—TOGETHER WITH THE PRESENCE OF ABUNDANT PLASMA AND NEURROBLAIR L-quote;NS IN MOST ELDERLY INDIVIDUALS WITH Down’s syndrome caused by three, rather than the usual two, copies of chromosome 21—suggested an important role for Aβ in AD. In 1991, the first mutation in APP that causes AD was identified (3). Mutations in APP are located near the β- and γ-secretase cleavage sites, as well as within Aβ (Fig. 2C) (122). Mutations near the β-secretase cleavage site increase production of Aβ, whereas those near the γ-secretase cleavage site result in an increased ratio of Aβ42 to Aβ40. Mutations within Aβ increase rates of aggregation, suggesting that familial AD is initiated by the aggregation of Aβ. Dominantly inherited duplications of the APP locus also give rise to AD.

Mutations in PSEN1 and PSEN2 are the most common cause of inherited AD (113, 114). Mutations in the genes encoding the other γ-secretase components have not been associated with AD. Like the APP mutations near the γ-secretase cleavage site, PS mutations increase the ratio of Aβ42 to Aβ40, resulting in a gain-of-toxic function. Haploinsufficiency of the γ-secretase complex gives rise to autosomal recessive form of adrenal insufficiency, not AD (115). No disease-causing mutations have been identified in BACE1. However, the A673T variant of APP, which is located near the BACE1 cleavage site (position 2 of Aβ), is overrepresented in Icelandic controls when compared with AD (116). The A673T mutation interferes with the BACE1 cleavage of APP and causes a reduction in Aβ40 and Aβ42. Reducing BACE1 cleavage may thus protect against late-onset AD.

However, APP with the A673T mutation also appears to protect against cognitive decline that was not caused by AD.

Inheritance of the ε4 allele of apolipoprotein E (APOE) is the major risk factor for late-onset AD. It increases disease risk in a dose-dependent manner and lowers the age of onset, as first shown in 1993 (117). APOE comprises 299 amino acids and exists as three isoforms based on the presence of C or R at positions 112 and 158: APOE2 (C/C), APOE3 (C/R), and APOE4 (R/R) (118). One copy of APOE4 increases the risk of AD by about four-fold (compared with the more common APOE3) (119), whereas two copies of APOE4 increase the risk of AD by about 12-fold.

The mechanism by which the amino acid difference between APOE3 and APOE4 at position 112 (C vs. R) increases the risk of AD remains to be established.

Only ~40% of individuals with AD carry an APOEε4 allele, suggesting the existence of additional genetic risk factors. Genome-wide association studies (GWASs) have identified about 20 additional risk factors (119, 120). The effects of these common alleles are smaller than those of APOE. However, they make it possible to identify biological pathways involved in the pathogenesis of AD. Several loci play a role in the immune system, whereas others are involved in endocytosis and lipid biology.

There are also rarer risk alleles with large effects. Heterozygous missense mutations in the gene encoding triggering receptor expressed on myeloid 2 cells (TREM2) increase the risk of AD by about threefold (121, 122). APP and PSEN1 have so far not been identified in GWASs. This may be because Aβ clearance is impaired in sporadic AD (123), whereas Aβ species are overproduced in dominantly inherited AD (124).

Genetics of PD

Dominantly inherited forms of PD and DLB are caused by missense mutations in SNCAI (7) or multiplications (duplications and triplications) of the gene (Fig. 2D) (125). Six missense mutations have been described in the amino-terminal region of α-synuclein. Penetration in duplication cases was of the order of 40%, whereas it was close to 100% for triplications and missense mutations. Lewy pathology was present. Mutations causing MSA have not been identified, although the neuropathologies associated with some mutations in SNCAI have features of MSA (126, 127). Lewy body diseases and MSA are probably linked.

Heterozygous mutations in the gene encoding leucine-rich repeat kinase 2 (LRKK2) give rise to dominantly inherited PD (128, 129). LRKK2 is a protein of 2527 amino acids with three enzymatic activities (guanosine triphosphatase and protein kinase) and multiple protein-protein interaction domains. Disease penetrance is incomplete. In most patients, LRKK2 mutations are associated with the deposition of α-synuclein. LRKK2 is expressed at high levels in monocytes, suggesting a role in the innate immune system (130).

PD is a motor syndrome with levodopa-responsive parkinsonism, in conjunction with
α-synuclein–positive Lewy pathology and dopaminergic nerve cell loss in the substantia nigra (2). Because Parkinsonism can be present in the absence of Lewy pathology, multiple mechanisms may cause the degeneration of dopaminergic neurons of the substantia nigra. They can be associated with tau inclusions, as in FTDP-17 and postencephalitic Parkinsonism, or polyglutamine inclusions, as in spinocerebellar ataxias. A separate pathway involves primary mitochondrial dysfunction and defective mitophagy, as in juvenile-onset recessive Parkinsonism caused by loss-of-function mutations in PARKIN, PINK1, and DJ1.

Loss-of-function mutations in the gene encoding glucocerebrosidase (GBA) cause Gaucher’s disease and are characterized by the lysosomal accumulation of glucocereamide. Gaucher’s disease appears to predispose to PD (21). Heterozygous GBA mutation carriers without Gaucher’s disease have an increased risk of developing PD, and patients with PD are five times more likely to carry a GBA mutation than age-matched controls. GBA mutations enhance, but do not initiate, the aggregation of α-synuclein. They do not appear to predispose to MSA.

GWASs have shown that variability in SNCA, LRRK2, GAK (cyclin G-associated kinase), and MAPT are risk factors for sporadic PD (132, 133). Variants in SNCA probably increase expression. They are also a risk factor for MSA, as is variability in MAPT. The latter suggests an interaction between tau and α-synuclein that is probably independent of tau assembly.

Conclusion

Transcellular propagation of protein pathogens, reminiscent of the spread of viruses, represents an unprecedented concept of disease. It is now known to extend beyond CJD, to include AD and PD, which are the most common neurodegenerative diseases. For all three diseases, there is a long prodromal phase, during which neurodegenerative changes develop and eventually lead to brain dysfunction. The interval between the formation of the first protein inclusions and the appearance of disease symptoms may offer a therapeutic window, provided techniques able to detect small numbers of inclusions will be developed in order to diagnose and evaluate patients long before the appearance of clinical signs. On the basis of the progress described here, the prevention of neurodegenerative diseases using prophylactic therapies may become a reality in the not too distant future.

REFERENCES AND NOTES

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