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## The Exceptional Vulnerability of Humans to Alzheimer's Disease

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### Abstract

Like many humans, nonhuman primates deposit copious misfolded A $\beta$  protein in the brain as they age. Nevertheless, the complete behavioral and pathologic phenotype of Alzheimer's disease (AD), including A $\beta$  plaques, neurofibrillary (tau) tangles, and dementia, has not yet been identified in a nonhuman species. Recent research suggests that the crucial link between A $\beta$  aggregation and tauopathy is somehow disengaged in aged monkeys. Understanding why AD fails to develop in species that are biologically proximal to humans could disclose new therapeutic targets in the chain of events leading to neurodegeneration and dementia.

### Keywords

Abeta; amyloid; aging; dementia; neurodegeneration; nonhuman primate; prion; proteopathy; seeding; tau

### Alzheimer's Disease: A Uniquely Human Disorder?

The more similar animals are biologically, the more likely they are to manifest similar diseases. The full phenotype of **Alzheimer's disease** (AD), however, has not yet been found in any nonhuman species [1–5]. Recent research has reinforced the view that nonhuman primates – our closest biological relatives – are surprisingly resistant to an AD-like disorder as they grow old, despite the occurrence of AD-linked genetic, molecular, and cellular mechanisms that are quite similar to those in humans [5–8].

Central to the pathogenesis of AD is the aggregation, proliferation and spread of two misfolded proteins in the brain: **A $\beta$**  and the microtubule-associated protein **tau** (MAPT) [9]. The aberrant proteins propagate by a **prion**-like process [10] that is evident histologically, in the presence of extracellular A $\beta$  plaques, **cerebral A $\beta$ -amyloid angiopathy (CAA)** [11],

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and intracellular **neurofibrillary tangles** and **neuropil threads** consisting of **hyperphosphorylated tau** [12–14]. The relationship of histopathologic changes *per se* to dementia remains somewhat ambiguous, but a definitive diagnosis of AD requires the significant presence of plaques and tangles (Figure 1) in a patient with clinical signs and symptoms of cognitive change that typify dementia [15]. Indeed, both tauopathy and A $\beta$  **proteopathy** are necessary for the complete clinicopathologic expression of AD [16], but tauopathy is a particularly potent driver of neuronal dysfunction and cognitive decline [17–21]. Genetic and biomarker evidence, however, pinpoints the accumulation of misfolded A $\beta$  as the earliest obligatory event in the ontogeny of AD [9, 22].

Paradoxically, aged monkeys and apes can accumulate large quantities of A $\beta$  in the brain, yet in the species that have been analyzed, AD-like tangles are rare or absent (Figure 2). Furthermore, despite some decline in behavioral capabilities, a profound, dementia-like disorder has not been discovered in a nonhuman primate [2]. Aged dogs can also develop a degree of cognitive dysfunction and A $\beta$  deposition, but they do not present neurofibrillary tangles in the brain [23, 24]. In this article, we describe the comparative neurobiology of aging in humans and nonhuman primates, and then discuss how understanding this critical discrepancy – A $\beta$  plaques in the absence of tangles – could yield insights into the cascade of events leading from A $\beta$  aggregation to tauopathy and dementia in humans (Box 1).

## Aging and the Nonhuman Primate Brain

Over 300 species of nonhuman primates [25] today range from Africa and Asia (Old-World primates) to Central and South America (New-World primates). In addition to monkeys, the Old World is home to phylogenetically more distant primates such as lemurs and lorises (Strepsirrhini) as well as all species of our nearest biological relatives, the apes: chimpanzees, bonobos, gorillas, orangutans ('great apes') and gibbons ('lesser apes'). Humans are estimated to have diverged from the modern great ape lineage approximately 7–8 million years ago [26]. The Old-World monkeys and apes (Catarrhini) are genetically closer to modern humans than are New-World monkeys (Platyrrhini) [27, 28], which split into a separate branch of the primate lineage approximately 35 million years ago.

The lifespan of some representative nonhuman primates varies from around 18 years in mouse lemurs (*Microcebus murinus*, a strepsirrhine ['**prosimian**'] primate) [29] to 30 years in squirrel monkeys (*Saimiri sciureus*, a New-World monkey), 40 years in rhesus monkeys (*Macaca mulatta*, an Old-World monkey), and 60+ years in chimpanzees (*Pan troglodytes*, a great ape) [30]. In their later years, nonhuman primates display typical signs of advanced age, such as immune, cardiovascular, musculoskeletal and reproductive senescence, as well as changes in social engagement [31].

Various laboratories have sought evidence of an Alzheimer-like phenotype in nonhuman primates. Senile plaques were discovered in monkeys decades ago, and some of the earliest high-quality electron-microscopic images of plaques were obtained in aged rhesus monkeys [32]. Moreover, the complex neurotransmitter makeup of the abnormal neurites surrounding plaques was first established in aged monkeys [33, 34]. Structural magnetic resonance imaging (MRI) investigations indicate that, as in non-demented humans, **gray matter**

volume decreases with age in rhesus monkeys and chimpanzees, and **diffusion MRI** has disclosed signs of age-related deterioration of white matter integrity [35]. Atrophy of specific brain regions has also been detected by MRI in senescent mouse lemurs [36].

Behaviorally, performance on certain tasks declines in old monkeys [37–40] and prosimians [36, 41], but there is no clear evidence yet of severe cognitive and behavioral impairments comparable to those that characterize dementia [2, 42]. Cognitive capacity also weakens somewhat in normal aged humans, but (at least with regard to hippocampal function) the pattern of change differs from that in AD [43].

In comparing species, it is important to specify the functional changes that would constitute dementia in nonhuman primates, which lack some of the behavioral sophistication facilitating the detection of dementia in humans (such as language). Based on the criteria set forth in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [44], we here concisely define dementia due to AD as “the insidious onset and gradual progression of substantial impairment in learning and memory and at least one other cognitive domain (complex attention, executive function, language, perceptual-motor, or social cognition) that interferes with independence in everyday activities”. A key element of the DSM-5 definition is that the impairments are substantial, and thus, become debilitating for everyday life. The nature of cognition is likely to differ among species, but with the exception of language, all of these general domains can be objectively probed in nonhuman primates. Nevertheless, no evidence has yet been presented that multiple behavioral domains are impaired in senescent monkeys or apes to a degree that would be consistent with the dementia observed in humans with AD [2].

Furthermore, while the accumulation of aggregated A $\beta$  in the brains of aged simians sometimes exceeds that in AD [45], human-like neurofibrillary tangles with **paired helical filaments** have only been definitively identified in a chimpanzee [46] (the closest phylogenetic relative of humans). In this instance, however, the anatomic distribution of the tangles differed from the pattern in humans in that it was patchy, primarily neocortical, and spared the hippocampus.

We should emphasize that it is not uncommon to find some degree of hyperphosphorylated tau in the brains of aged nonhuman primates. Whether this is indicative of a pre-tangle state, or whether it is reversible and relatively benign (as in development [47] or hypothermia [48], for example), is not certain. In aged squirrel monkeys, hyperphosphorylated tau is present in occasional neurons and neurites [7], and it increases with age in neurons and dystrophic microglia in marmosets [49]. Mild tauopathy in the form of hyperphosphorylated tau and **silver-stained neurons** has been reported in very old macaques [50]; however, this tauopathy resembles **progressive supranuclear palsy/corticobasal degeneration** rather than AD [51]. In addition, an unusual type of focal glial and neuronal tauopathy occurs in aged baboons (*Papio hamadryas*) [52]. In none of these cases, however, do the lesions approximate the profusion of distinctive neurofibrillary tangles and neuropil threads in AD patients.

## Why Has AD Not Been Identified in Nonhuman Species?

The absence of a dementia-like syndrome and the paucity of neurofibrillary tangles in aged nonhuman primates with substantial A $\beta$  deposition currently defy explanation. Several factors might account for the differential vulnerability of nonhuman primates and humans to AD, including differences in lifespan, **apolipoprotein-E** subtypes, A $\beta$ , tau, or various other risk factors (Key Figure, Figure 3). We consider each of these issues in turn, but first we address the practical question of whether sufficient nonhuman primates have been analyzed to draw reliable conclusions about the presence or absence of AD.

### Have Too Few Nonhuman Primates Been Studied to Detect an AD-like Disorder?

It is possible that not enough aged primates have been examined to detect behavioral or neuropathologic signs of AD, which might simply be less common than in humans. In terms of the number of species examined, senescent brains have been scrutinized from animals across much of the primate order, including gorillas, orangutans, chimpanzees, green monkeys, baboons, guenons, mangabeys, squirrel monkeys, marmosets, tamarins, and lemurs (reviewed in [2, 6]; see also [8, 49, 53–56]), as well as tree shrews (*Tupaia belangeri*), close phylogenetic relatives of primates [57].

Relatively few representatives of some species have been studied (such as orangutans), but considerable work has been undertaken on aged macaques, and to a lesser extent, squirrel monkeys, marmosets, tamarins, and mouse lemurs [2]. All of these species develop senile plaques and CAA, as well as some degree of intracellular tau hyperphosphorylation with age, but AD *per se* has not been disclosed in any of them. It is, of course, impossible to prove that AD never occurs in nonhuman species. Indeed, we would not be surprised if an instance of human-like AD eventually is discovered in another primate, particularly a great ape. However, even if a naturally occurring AD-like condition is possible in nonhuman primates, present data indicate that it would be much less common than in humans.

### Do Nonhuman Primates Live Long Enough to Manifest AD?

In most instances, the onset of dementia in humans with AD occurs after the age of 65 years [9], a chronological age beyond the currently known lifespan of extant nonhuman primates (above). However, nonhuman primates age biologically more rapidly than do humans; in addition to manifesting many of the common systemic characteristics of human aging [6, 31], they develop A $\beta$  lesions in the brain at chronological ages that are approximately proportional to their lifespan [30]. Nearly one-third of humans aged 85 or older in the United States manifest AD [58]; based on their known maximum lifespan (above), roughly comparable biological ages in rhesus monkeys would be 28 years, and in squirrel monkeys, 21 years. Hence, if these species were equally susceptible to AD, we would expect to find evidence of incipient disease in one out of three animals beyond these ages; yet, neither AD-like neurofibrillary tangles nor dementia has been reported in aged monkeys with advanced A $\beta$  deposition. We certainly cannot exclude chronological age as a contributing factor to the species-specific development of tauopathy and AD, but the longer human lifespan alone does not seem to explain the apparent absence of AD in nonhuman primates.

### Do Variations in Apolipoprotein E (ApoE) Govern Species Differences in

**Susceptibility to AD?**—The most common genetic risk factor for idiopathic (sporadic) AD in humans is the presence of one or two apolipoprotein E- $\epsilon$ 4 alleles [59]. In the general population, ~14% of ApoE isoforms are ApoE4, whereas ~78% are ApoE3 and ~8% are ApoE2 [60]. How the ApoE type influences the risk of AD is still not entirely clear, but the *APOE $\epsilon$ 4* allele is associated with a significant lowering of the age at which A $\beta$  plaques and neurofibrillary tangles emerge in the human brain [61, 62]. Surprisingly, all nonhuman primates investigated to date are homozygous for *APOE $\epsilon$ 4* according to criteria for defining human ApoE subtypes [63], i.e., among primates, it seems that only humans can express ApoE3 and ApoE2. However, a threonine instead of an arginine at amino acid position 61 of ApoE, is thought to cause nonhuman primate ApoE4 to interact with lipids similarly to human ApoE3 [63]. Given the prominence of human *APOE $\epsilon$ 4* as a risk factor for AD, the exclusive departure of humans from the general (and presumably ancestral) primate form of ApoE4 could hold useful clues to the pathogenesis of AD.

### Does A $\beta$ in Humans Have Unique Pathogenic Properties?

In its most common manifestations, A $\beta$  is a 40- or 42-amino acid-long cleavage product of the A $\beta$ -precursor protein (APP) [64]. The amino acid sequence of A $\beta$  is the same in humans and all nonhuman primates studied thus far [2]. One conspicuous difference between humans and nonhuman primates is that humans with AD tend to deposit relatively more of the longer variant of A $\beta$  (A $\beta$ 42) than the slightly shorter, C-terminally truncated variant (A $\beta$ 40) [45, 65]. This is noteworthy because A $\beta$ 42 is especially prone to aggregate, and therefore, is believed to be important in the early development of AD [64]. Enzyme-linked immunosorbent assay (ELISA) studies confirm that A $\beta$ 42 predominates in most humans with AD compared to nonhuman primates with comparable A $\beta$  load, but some aged monkeys present A $\beta$ 42:40 ratios in the brain that are equivalent to those in humans with AD [45]. Furthermore, the A $\beta$ 42:40 ratio varies among humans with AD; indeed, an unusual case of AD has been described in which A $\beta$ 40 was far more abundant than A $\beta$ 42 [66], indicating that a preponderance of aggregated A $\beta$ 42 is not required for AD. Shorter and post-translationally modified A $\beta$  isoforms might also influence pathogenicity, but mass-spectrometric analysis failed to disclose C- and/or N-terminally truncated A $\beta$  fragments that were unique to either humans or monkeys [7].

Thus, there is no clear evidence yet that differences in the relative amounts of A $\beta$  isoforms might explain why nonhuman primates fail to progress from A $\beta$  deposition to the neurofibrillary tangles and dementia of AD. Nevertheless, ample experimental investigations have shown that the length of A $\beta$  affects its pathobiology and molecular structure. For instance, mice genetically engineered to express human-sequence A $\beta$ 40 do not exhibit amyloid pathology, whereas mice expressing human-sequence A $\beta$ 42 develop both A $\beta$  plaques and CAA [67]. In addition, A $\beta$ 42 and A $\beta$ 40 polymerize into amyloid fibrils with different molecular architectures that are likely to influence their functionality [68–70]. Hence, the factors that regulate the production, metabolism, aggregation and interactions of A $\beta$  isoforms in primates are worthy of further exploration.

Like **prion protein- (PrP) prions**, A $\beta$  misfolds and aggregates into structurally (and possibly functionally) distinct conformers [69, 71–74]. Evidence for differences in the architecture of misfolded A $\beta$  among primates has come from studies examining the A $\beta$  binding capacity of **Pittsburgh Compound B (PiB)** (a selective imaging agent for aggregated A $\beta$  in the human brain [75]). High-affinity binding sites for PiB are abundant in cerebral A $\beta$  deposits of AD patients [76], but in aged squirrel monkeys, rhesus monkeys, and chimpanzees (as in transgenic mice expressing human APP [76] and aged dogs [77]), A $\beta$  plaques and CAA almost entirely lack high-affinity binding sites for PiB. This unexpected finding suggests that structural variations in A $\beta$ , or the presence of associated molecules may alter or obscure the PiB binding site in nonhuman species [7, 45]. Intriguingly, the AD case described above in which the A $\beta$ 42:A $\beta$ 40 ratio was unusually low was also remarkably deficient in high-affinity binding sites for PiB relative to other cases of AD [66], underscoring the pathologic heterogeneity of AD in humans.

More studies are needed to establish the comparative molecular architecture of A $\beta$  in humans [70, 71] and nonhuman species, and we also need to determine whether conformational variants of aggregated A $\beta$  are linked to the particular pathogenicity of this peptide in humans, such as the induction of tauopathy [78–80]. In this regard, A $\beta$  oligomers – highly potent seeds for A $\beta$  aggregation [81] thought to be especially disruptive of neuronal integrity in the AD brain [82] – have yet to be characterized in nonhuman primates. How A $\beta$  proteopathy stimulates the development of tauopathy also remains a critical open question; does this happen directly, for example, by the cross-seeding of tau aggregation by A $\beta$  seeds [83], or does tau misfold and aggregate in response to non-specific stress to the cells? The latter possibility is supported by the presence of neurofibrillary tangles in a remarkable variety of brain diseases, including such diverse maladies as chronic traumatic encephalopathy, prion diseases, and viral encephalitis [16]. The nature of the pathologic relationship between A $\beta$  and tau, a key juncture in the AD cascade, remains poorly defined.

### Does Tau in Humans have Unique Biological Properties?

Independent of its putative connection to abnormal A $\beta$  in the AD cascade, tau itself may differ in ways that influence its pathogenic potential in nonhuman primates. In the electron microscope, the neurofibrillary tangles of AD are seen to consist mainly of paired helical filaments with a characteristic size and structure [84]. Identical paired helical filaments have been described in an older chimpanzee (discussed above), but not yet in any other primate species. Naturally occurring tauopathies have also been reported in several nonprimate species, including bears [85], cats [86], goats, and cattle [87, 88], but these conditions do not resemble AD pathologically.

Four general features of the tau protein have been recognized that might account for the paucity of tauopathy in senescent monkeys. First, differences in the primary sequence of tau could make the nonhuman primate protein less likely to misfold and aggregate [87]. The amino acid sequence of the longest brain isoform of tau is 98% identical in humans and macaques [87], and – perhaps significantly with regard to the formation of paired-helical filaments – 100% identical in humans and chimpanzees [89]. Additionally, the six tau isoforms found in the human brain have also been documented in nonhuman primates [87,



89]. However, some tau mRNAs in the rhesus neocortex include exon 8, which does not appear to be expressed in the human brain, nor is it expressed in non-primate species (such as goats) that are susceptible to tauopathy [87]. In addition, single amino acid substitutions in rhesus monkey tau, particularly in exon 3 or at position 220 of the longest tau transcript, have been hypothesized to diminish the pathogenicity of the protein by altering its charge or phosphorylation, respectively [87].

A second possibility is that the tendency of tau to develop neurofibrillary tangles is influenced by species-specific intronic *Tau* sequences [89]. Saitohin (*STH*), an unusual multiexonic gene in intron 11 of the tau gene (*MAPT*), differs among the primate species in which it has been shown to be present [89, 90]. The entire open reading frame of *STH* appears to be present only in humans and great apes, but not in gibbons (*Hylobates lar*) or cynomolgus monkeys [89]. *STH* thus bears further scrutiny with regard to AD and other tauopathies [90].

A third possibility is that different species display different patterns of tau phosphorylation. Hyperphosphorylation alters the properties of tau in multiple respects; for instance, by impeding the normal binding of tau to microtubules, hyperphosphorylation augments the tendency of tau to polymerize into assemblies such as neurofibrillary tangles [14]. Conversely, studies have shown that some types of tau phosphorylation may actually impede aggregation [91] and toxicity [92], indicating that not all phosphorylation of the protein is problematic.

Potentially relevant to species-specific differences in tauopathy is the hyperphosphorylation of tau in hibernating animals [48], a reversible state with few obvious aftereffects when animals return to **euthermia** [93]. Hamsters that hibernate do not exhibit plaques or tangles in old age [94], although aged bears can develop a tauopathy consisting of **straight tau filaments** [85]. Accordingly, it is conceivable that certain species (whether capable of hibernation or not) may be better able than humans to reverse the effects of acute tau hyperphosphorylation (which can occur, e.g., under conditions of stress [95] or injury to the brain [96]), rendering them less vulnerable to chronic tauopathy.

A fourth possibility is that putative extrinsic or posttranslational factors other than phosphorylation might govern the particular tendency of human tau to form paired helical filaments. In wild-type mice, tau is resistant to aggregation *in vivo* [97], but murine tau can be induced to accumulate in normal mice by exogenous tau seeds [98, 99]. Furthermore, mouse tau and human tau can be similarly assembled into paired helical filaments *in vitro* [97], even in the absence of phosphorylation [100]. Mouse tau is thus intrinsically capable of polymerizing into human-like paired helical filaments, so it could be fruitful to seek alternative, extrinsic determinants of species differences. Tau undergoes several types of post-translational modification besides phosphorylation [101], but to date, no such feature has emerged that would explain species differences in the susceptibility to tauopathy.

Since the publication of tantalizing molecular analyses of tau in various animals over a decade ago [87, 89, 97], surprisingly little work has been done to more fully define the pathobiology of tau in primates. Determining whether tau exon 8 is expressed in different

primate species, for example, would help to affirm or refute its hypothesized protective role [87], as would studies of exon 8-bearing tau in cell cultures, organoids [102], and genetically modified animal models. A comparative evaluation of specific types of neurons especially vulnerable to tauopathy in AD [103] could also be informative; brain regions giving rise to long axonal connections have expanded in the evolution of hominids, and it has been proposed that enhanced neuroplasticity of these areas may render cells more susceptible to tangle formation, possibly due to increased remodeling of synaptic membranes, or the cytoskeleton [4]. An in depth analysis of regional vulnerability, tau variants and posttranslational modifications in humans and nonhuman primates is clearly needed.

### Do Other Factors Differentially Modify AD Risk in Humans and Nonhuman Primates?

A $\beta$  and tau should remain central to future investigations of the origins of AD, but risk factors that increase the probability that these proteins will misfold and accumulate in the brain could variably modulate the trajectory of AD-like proteopathy in different species. For example, in a meta-analysis of studies seeking links between suspected environmental agents and the risk of AD in humans, moderate-to-strong potential associations were found for such factors as air pollution, aluminum, silicon, selenium, pesticides, vitamin D deficiency, and electric and magnetic fields [104] (although the list of potential environmental factors is much longer, and the ability of epidemiological studies to identify them with certainty is limited). Myriad genetic polymorphisms appear to influence the odds of developing AD [105], but (except for the *APOE* type, above) the impact of individual genetic variants is small. In addition, such factors as epigenetics [106], inflammation/immune activation [107], **proteostasis** [108], or posttranslational modifications of proteins such as glycosylation [109] have been linked to the risk for AD in humans, as have metabolic and cardiovascular disorders [110]. Other factors that can vary within and among species should not be overlooked, such as life-long activity levels [111], sleep patterns [112], head injury [113], psychosocial stress [114], diet [115], microbiome [116–118], and environmental exposure to microorganisms and viruses [119].

Finally, while the impact of the environment can be monitored and controlled in captive animals, it is important to determine whether captivity *per se* might affect AD-like pathogenic processes. In APP-transgenic mice, environmental enrichment has been shown to improve brain fitness [120] and lower cerebral A $\beta$  load [121]. Little work has assessed the effects of living conditions on AD-like pathology in nonhuman primates, but a recent study found that wild mountain gorillas (*Gorilla beringei beringei*) that spent their entire lives in natural habitats developed age-related changes in A $\beta$  and limited tau deposition similar to those of western lowland gorillas (*Gorilla gorilla gorilla*) that had lived in zoos [8].

### Concluding Remarks

Despite numerous biological commonalities and substantial deposition of A $\beta$  in the brain, aged nonhuman primates are remarkably resistant to the classic behavioral and pathologic phenotype that defines AD in humans. Even if a true AD-like condition is eventually discovered in a nonhuman species, current knowledge indicates that this is likely to be much less common than in humans. Given the key roles of aberrant A $\beta$  and tau in the pathogenesis



of AD, an important direction for future research would be a detailed comparative analysis of the molecular and cytologic characteristics of these proteins and how they interact in the brain to impair neuronal function. Differential modifiers of risk in different species might come to light from comparative investigations of genomic, transcriptomic, proteomic, lipidomic, metabolomic, epigenetic and environmental influences. Furthermore, examination of nonhuman species might shed light on the preclinical phase of AD pathogenesis [122] (see Outstanding Questions and Box 1). Specifically, why are some humans with abundant cerebral A $\beta$  deposition relatively intact cognitively? And is this a presymptomatic phase that will ultimately transition to AD, or a different manifestation of A $\beta$  proteopathy? Understanding how nonhuman primates manage to stave off dementia in the presence of abundant aggregated A $\beta$  could yield unexpected insights into the prevention and treatment of Alzheimer's disease.

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## Glossary

### Amyloid

generic term for abnormal accumulations of fibrillized proteins exhibiting birefringence under the light microscope following staining with Congo Red, as well as a typical cross- $\beta$  X-ray fiber diffraction pattern due to high  $\beta$ -sheet content in the constituent proteins. More than 30 distinct proteins can form amyloid in various organs, but the most common amyloids in the brain are formed by A $\beta$  and tau

### A $\beta$

Amyloid- $\beta$ , a normally generated cleavage product of the A $\beta$ -precursor protein (APP) that misfolds, multimerizes, and aggregates into senile (A $\beta$ ) plaques and cerebral A $\beta$ -amyloid angiopathy (CAA). Oligomeric forms of A $\beta$  are thought to be particularly pathogenic in the brain

### Alzheimer's disease

The most common cause of dementia in humans, classically characterized pathologically by the presence of senile (A $\beta$ ) plaques and neurofibrillary (tau) tangles

### Apolipoprotein E (ApoE)

The main apolipoprotein in the brain; ApoE is involved in lipid transport throughout the body. Humans can express any of three major isoforms (ApoE2, ApoE3, or ApoE4), of which the *APOE $\epsilon$ 4* allele is linked to a dose-dependent increase in the risk of AD

### Cerebral A $\beta$ -amyloid angiopathy (CAA)

The abnormal deposition of A $\beta$  in and around the walls of brain blood vessels. Some degree of CAA is present in the brains of most AD patients, and it is severe in approximately 20%

of cases. (Different proteins can cause CAA in other conditions, but A $\beta$  is the most common proteinaceous substrate for the disorder)

**Dementia**

insidious onset and gradual progression of substantial impairment in learning and memory and at least one other cognitive domain (complex attention, executive function, language, perceptual-motor, or social cognition) that interferes with independence in everyday activities

**Diffusion MRI**

(or diffusion-weighted MRI): type of magnetic resonance imaging (MRI) that can reveal neuronal fiber pathways in the nervous system by imaging the diffusion patterns of water molecules, constrained by surrounding tissue elements such as myelin

**Euthermia**

The state in which an organism has a normal body temperature; in this case, the temperature of the animal when not hibernating

**Gray matter**

Regions of the brain and spinal cord that are rich in neurons and glial cells and relatively poor in myelinated axons, such as the cortex on the surface of the cerebral hemispheres. White matter, in contrast, is rich in axons wrapped in fatty myelin, giving it a lighter appearance than gray matter

**Hyperphosphorylation**

In the context of tauopathy, a state in which excess phosphate groups are added to the tau protein. Hyperphosphorylation of tau is a putative early trigger for the development of neurofibrillary tangles

**Neurofibrillary (tau) tangles**

Intraneuronal accumulations of misfolded, hyperphosphorylated, polymerized tau protein. Ultrastructurally, tangles in the AD brain usually consist of characteristic paired-helical filaments

**Neuropil threads**

Abnormal accumulations of tau protein within neuronal processes

**Paired helical filaments**

Long, twisted ribbon-like structures consisting of two filaments of polymerized tau protein that twist with a half-periodicity of approximately 80 nm. Paired helical filaments are a common ultrastructural component of neurofibrillary and glial fibrillary tangles in AD

**Pittsburgh Compound B (PiB)**

N-methyl-<sup>11</sup>C 2-(4'-methylaminophenyl)-6-hydroxybenzothiazole; a radiolabeled imaging agent based on the histochemical dye thioflavin-T. As a tool to aid in the diagnosis of AD in humans, PiB is infused into the bloodstream, from which it crosses the blood-brain barrier and selectively binds with high affinity and stoichiometry to A $\beta$  plaques and CAA

**Prion**

Proteinaceous infectious particle; classical prions consist of misfolded prion protein (PrP, and they convey fatal diseases collectively known as spongiform encephalopathies or prion diseases. Prions convey their pathogenic properties to naïve PrP molecules by a crystallization-like process of molecular templating. The prion concept is expanding to include noninfectious diseases involving endogenous seeded protein aggregation (such as AD) as well as certain normal biological processes

**Prion protein (PrP)**

protein that, in a misfolded state, forms the prototypical infectious particles known as prions

**Progressive supranuclear palsy/corticobasal degeneration**

Neurodegenerative tauopathies in which the clinical and pathologic features show substantial overlap. Both disorders are characterized pathologically by abnormal inclusions of tau in neurons and particularly, in glial cells (astrocytes and oligodendrocytes)

**Prosimians**

group of primates evolutionarily more distant from humans than simians (e.g. monkeys and apes). Extant prosimians include strepsirrhine primates and tarsiers

**Proteopathy**

Disease caused by an abnormality of proteins, generally involving the misfolding and aggregation of disease-specific proteins. Amyloidoses are a common type of proteopathy

**Proteostasis**

Collective cellular mechanisms that support the viability of cells by regulating the production, folding, trafficking and elimination of proteins

**Senile (A $\beta$ ) plaques**

Abnormal accumulations of extracellular, misfolded A $\beta$  in the brain that can take various forms as seen with the light microscope; in many instances, plaques are associated with reactive gliosis, abnormal neurites, and a focal disruption of tissue integrity

**Silver-stained neurons**

neurons visualized with a silver-based histologic method that can be customized to detect abnormalities such as neurofibrillary tangles

**Straight tau filaments**

Single filaments (or tubules) of polymerized tau that are usually 9–18 nm in diameter; like paired helical filaments, they are involved in the formation of neurofibrillary tangles and glial fibrillary tangles in AD and other tauopathies

**Tau protein**

A protein that normally binds to, and stabilizes, cellular microtubules. In AD, tau misfolds, becomes hyperphosphorylated, and multimerizes into soluble oligomers and the  $\beta$ -sheet-rich polymers that constitute neurofibrillary tangles

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### Trends

The accumulation of misfolded, multimeric A $\beta$  and tau proteins in the brain is a defining pathologic feature of Alzheimer's disease, the leading cause of dementia in humans. Senescent nonhuman primates deposit abundant A $\beta$  in senile plaques and cerebral amyloid angiopathy, and mild intracellular hyperphosphorylated tau is sometimes present; however, the AD triad of significant senile plaques, neurofibrillary tangles and dementia has not yet been identified in a nonhuman species.

Establishing why species that are biologically similar to humans are resistant to Alzheimer's disease could reveal novel mechanistic objectives for the potential development of preventive measures and/or treatments.

### Outstanding Questions

What are the mechanisms by which abnormal A $\beta$  induces tauopathy *in vivo* (for example, by direct interaction of A $\beta$  and tau, or by an indirect mechanism such as cellular stress)?

Does A $\beta$  fold into alternative structural strains in nonhuman primates, and does the biological activity of these assemblies differ from that in humans?

How do A $\beta$  oligomers compare in humans and nonhuman primates? Is it possible that oligomeric A $\beta$  is more effectively sequestered (and thus neutralized) in nonhuman senile plaques?

Are neurons that are vulnerable in human AD somehow protected in nonhuman primates?

What behavioral tests or observational strategies would be most efficient in detecting a dementia-like disorder in nonhuman primates? Observations of aging animals in zoos, retirement facilities, and in the wild would be useful in the search for social and cognitive impairments that might portend dementia.

What environmental and general biological factors modulate the risk of developing tauopathy and AD? And is tau hyperphosphorylation always a precursor to neurofibrillary tangles?

What can be learned about the pre-symptomatic phase of AD pathogenesis by comparing aged nonhuman primates to high-pathology, but cognitively normal humans?

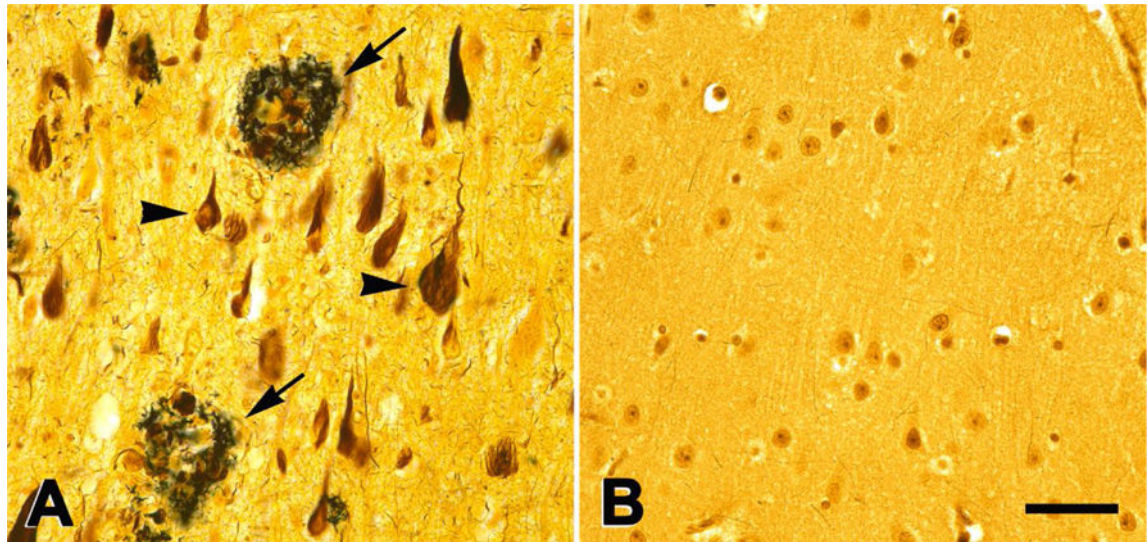
Can the effects of nonhuman primate ApoE (i.e., ApoE4 with a threonine at position 61) on A $\beta$  aggregation and tauopathy be modeled *in vitro* and *in vivo*?

What can be gleaned from comparative “-omics” analyses to illuminate the resilience of nonhuman primates?

**Box 1****Clinician's Corner**

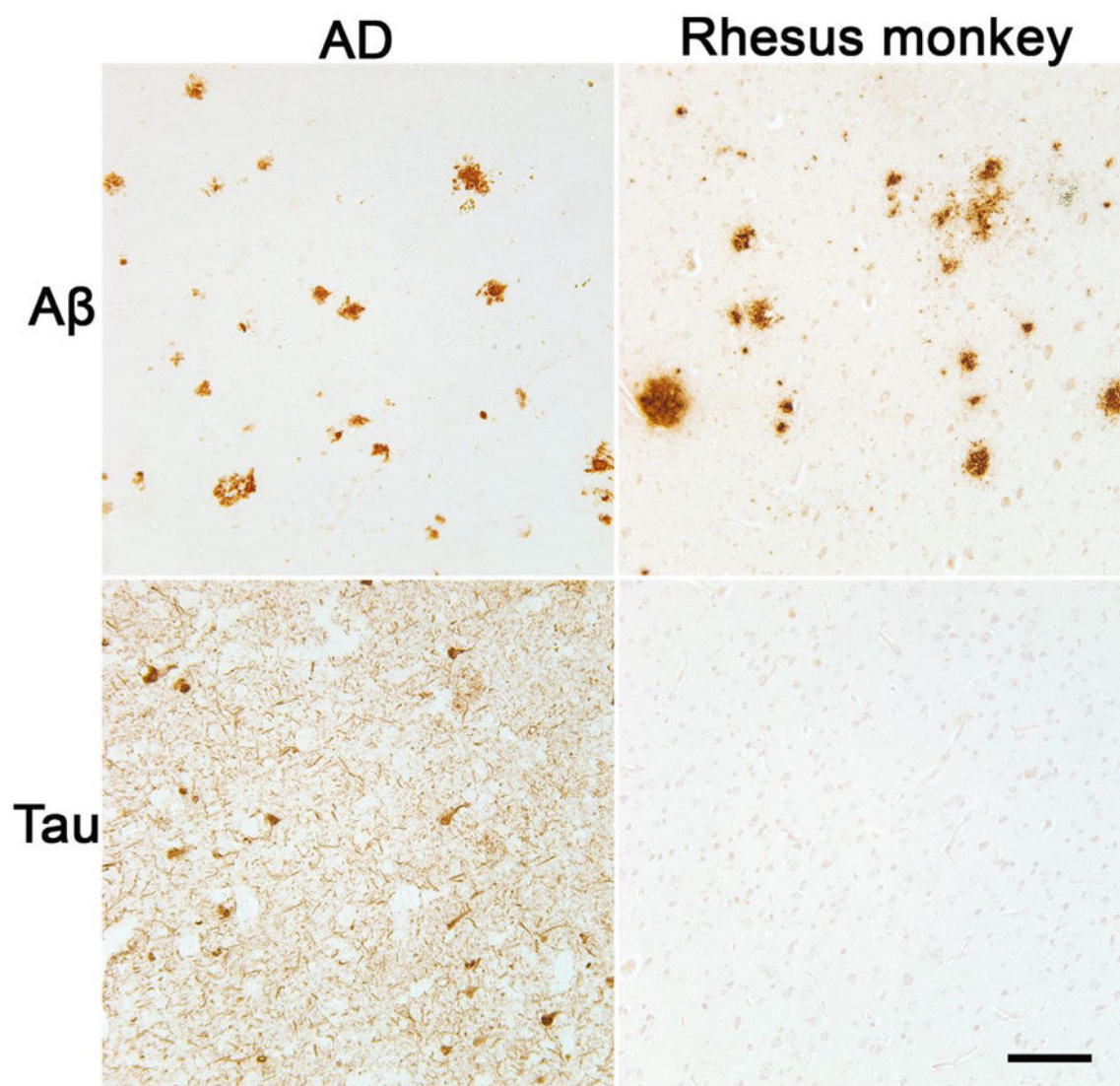
- Fundamental to the pathogenesis of Alzheimer's disease is the misfolding and seeded aggregation of A $\beta$  (a protein fragment that forms senile plaques) and tau (a protein that forms neurofibrillary tangles) in the brain.
- Genetic, pathologic and biomarker evidence currently favors a primary role of A $\beta$  in the cascade of events leading to AD, but the subsequent emergence of tauopathy is essential to the development of dementia in humans.
- Aged nonhuman primates develop copious A $\beta$  plaques, and they express A $\beta$  and tau that are quite similar to the proteins in humans, but the full clinicopathologic phenotype of AD has not been found in any nonhuman species.
- Establishing why aged nonhuman primates with abundant cerebral A $\beta$  deposition are protected from tauopathy and dementia could reveal new molecular pathways for the prevention and treatment of AD in humans.





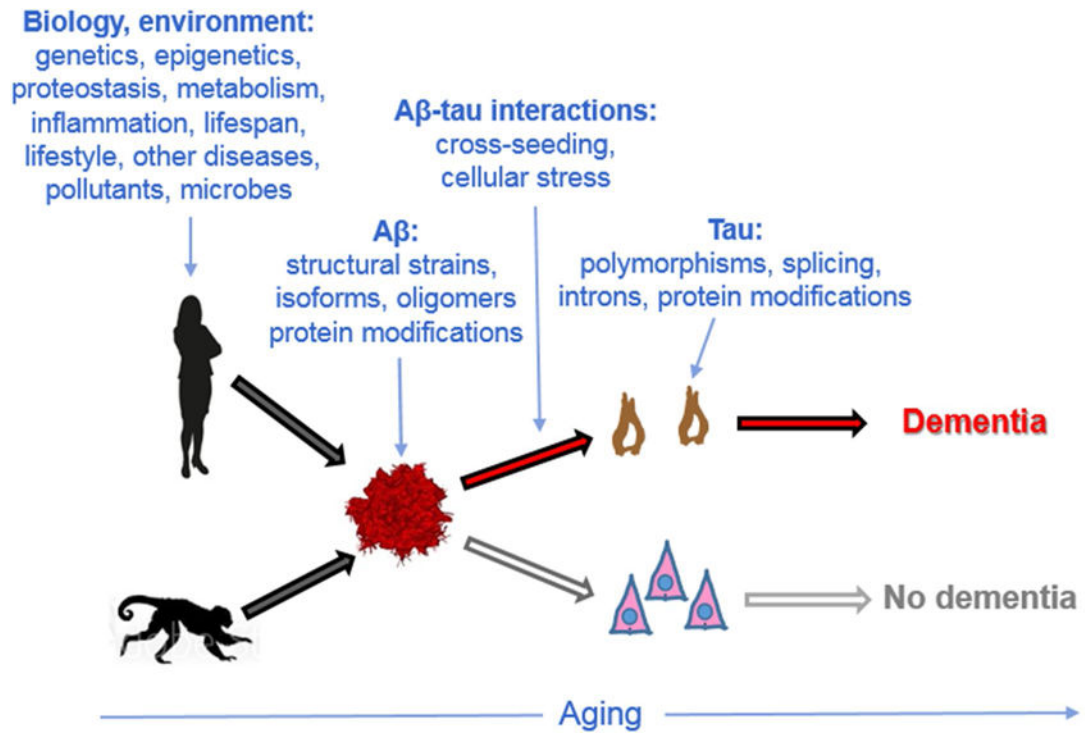
**Figure 1. Plaques and Tangles in Alzheimer's Disease**

Representative micrographs of histopathology of senile plaques (arrows) and neurofibrillary tangles (two are indicated by arrowheads) in the hippocampal formation of (A) a deceased individual harboring Alzheimer's disease (AD), compared to (B) a deceased individual without AD. (A) and (B) The tissue sections were stained with a silver-based histological method similar to that used by Alois Alzheimer to detect plaques and tangles in his index case. Scale Bar = 50 $\mu$ m.



**Figure 2. Comparative Histopathology of Aβ and Tau**

Representative micrographs of histopathology in a 72-year-old Alzheimer's disease patient (left column) and an aged (36-year-old) rhesus monkey (right column) are shown. The top row shows tissue sections of neocortex that were immunostained with antibody 6E10 to Aβ, and the bottom row shows the same region in nearby sections that were immunostained with antibody CP13 to hyperphosphorylated tau. Note the abundant neurofibrillary tangles and neuropil threads in the AD case (bottom left), but the absence of tauopathy in the aged monkey (bottom right). Scale Bar = 100μm and applies to all panels.



**Key Figure, Figure 3. Divergent Paths to Brain Aging in Humans and Nonhuman Primates**  
Abnormal A $\beta$  (red plaque) accumulates in the brains of aging humans and nonhuman primates, but only humans manifest the profuse neurofibrillary tangles (brown) and dementia that define AD. Neurons remain relatively healthy (pink triangles) in aged nonhuman primates despite pronounced A $\beta$  accumulation. Some potential factors that might influence the probability of developing AD, and their possible points of action in the pathogenic cascade, are indicated in blue. These include (from left to right) putative biological and environmental risk factors for AD, variations in the structure and function of A $\beta$ , influences on the induction of tauopathy by abnormal A $\beta$ , and differences in the biology of tau itself.