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Potential Models of Late-onset Alzheimer's Disease

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Abstract
Alzheimer's disease (AD) is a devastating illness with unknown etiology and no cure. The predominant model for studying AD has been transgenic mice with human mutant amyloid-ß (Aß) protein designed to reflect inherited familial forms of AD (fAD). However, this approach only reflects a small percentage of the AD population and has not lead to successful therapeutics. There is recent and compelling evidence that the Aß is not simply a misfolded protein that accumulates to eventual AD, but instead a protein with physiological roles that responds to several pathological contexts. If we better understand the contexts that stimulate Aß accumulation, and the character of its response, we can refocus research on targets upstream of Aß. In order to do this, the field needs models of late-onset AD (LOAD) that do not rely on human transgenes in mice. This perspective outlines models of contextually-driven Aß accumulation, animals with naturally elevated Aß and a potential human organ model that may be employed to better understand the role of Aß in AD.

Keywords: Alzheimer's disease, AD, amyloid protein, amyloid-ß, Aß LOAD, misfolded protein, fAD.

Introduction

AD is a debilitating progressive neurodegenerative disease with no cure that results in lack of cognitive function and extreme memory loss. AD may manifest relatively early due to inherited genetic susceptibility common in certain families. Approximately 5% of all AD patients have fAD; the remaining majority develops LOAD. Aß is a protein generally believed to be the driving etiology in AD, largely because genetic mutations related to fAD involve its production. There is yet no recognized etiological factor that can account for LOAD with certainty, though Aß is considered one of the best candidates. However, there are inconsistencies with an Aß-centered view of disease etiology. For example, nearly one-third of cognitively healthy individuals have sufficient Aß protein accumulation to be diagnosed with AD but remain cognitively normal, and a similar proportion of those diagnosed with AD do not have sufficient Aß accumulation to maintain an AD diagnosis after autopsy[1,2]. These data suggest that Aß is not sufficient or necessary to drive dementia, though it is required for the diagnosis of AD. This may be in part because Aß is not inherently pathological. For example, neuroinflammation is sufficient to drive AD-like memory impairment in wild type (WT) rats[3,4], and removal of microglia is sufficient to significantly improve memory in mice with three fAD human transgenes (3xTg-AD) without altering Aß levels[5]. While Aß might not be a singular causative factor in the development of AD, more than half of research in the field is devoted to the pathological consequences and elimination of Aß[6,7]. Therefore, to progress in our understanding of AD, we must learn more about the physiological role of Aß.

Aß is generally considered to be a toxic, misfolded protein. However, experimental data suggests that it plays a physiological role in immunity against microbes[8–13], the acute phase after injury[14,15], T cell regulation[16,17], cerebrovascular modeling[18], tumor suppression[19–21] and synaptic signaling[22]. These functions of Aß are consistent with adverse events reported in clinical trials that target Aß, including increased rates of infection[23–25], meningoencephalitis[26,27], microhemorrhages and edema[28–32], cancer[24,31] and seizures[29]. To better understand the physiological role of Aß in normal and pathological conditions, the

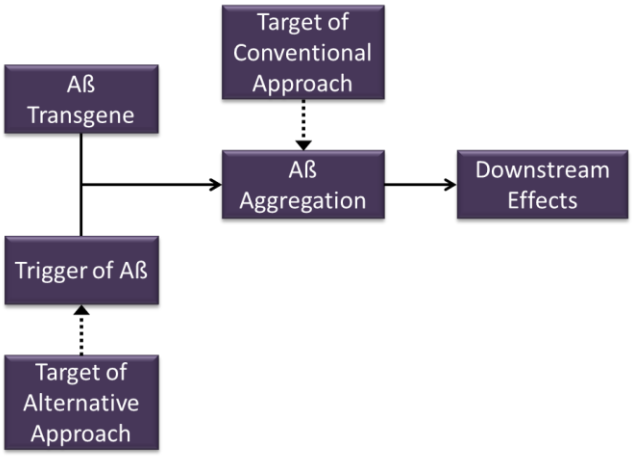

Figure 1. Targeting triggers of Aß alters the conventional approach. The conventional approach to Alzheimer's (AD) research is to investigate the downstream pathological consequences of Aß, primarily in mouse models that harbor a familial AD transgene, and to target the suppression or removal of Aß. However, this approach has not yet resulted in clinical efficacy. This review outlines models of triggers which elevate Aß levels and promote aggregation in wild type and transgenic animals. By investigating triggers of Aß, the therapeutic target is moved upstream, and diversifies our research strategy.

production of Aß should be contextually-driven. Unfortunately, mice with fAD transgenes that overexpress Aß (Tg-AD) are a poor model for the physiological role of Aß in normal conditions, and can represent the physiological role of Aß in pathological conditions only if challenged. This perspective will outline potential models of Aß accumulation that may better represent LOAD. If triggers of Aß elevation and aggregation are further characterized, then we will gain insight into the etiology of LOAD and can fundamentally alter our research strategy (see **Error! Reference source not found.**). Using new models to identify other targets will increase opportunities to achieve clinical efficacy in the large population of LOAD patients, the overwhelming majority of AD.

Experimentally-driven Aß

Aß can be driven in WT animals and potentiated in Tg-AD by experimental manipulations that include immune activation, cell-cycle reentry, traumatic injury and cerebrovascular injury (see **Error! Reference source not found.**). A number of factors amplify Aß production in cells, but this perspective concentrates only on *in vivo* animal models.

Lifetime infectious burden is increased in AD[33] and risk of AD is increased by the presence of viral and bacterial infections[34–37]. Evidence of microbial infection is found in AD plaque cores and brain tissue, including the presence of herpes simplex virus 1[38], spirochetes[39] and fungi[40]. Aß fluctuates during the course of infection in humans in a manner that suggests Aß is elicited by infection and subsides with resolution of infection[41–46]. A number of immune activators stimulate Aß production and related AD characteristics *in vitro*[47–55] and in rodents. Treatment with the viral mimetic polyinosinic:polycytidylic acid (Poly I:C) increases hippocampal Aß and memory impairment in WT mice[56] and increases extracellular Aß in Tg-AD mice[57]. The bacterial mimetic lipopolysaccharide has similarly been reported to increase Aß production in WT rodents[58–60] and to increase both Aß and phosphorylated tau (pTau) in aged Tg-AD mice[61–63]. Multiple live bacteria drive Aß production in rodent models as well. The bacteria *H. pylori* increases Aß and produces memory impairment in WT rats[64] and *B. pertussis* increases Aß in Tg-AD mice[65]. Similarly, infection with *C. pneumoniae* increases Aß production in a way that is synchronously tied with the course of infection in WT mice; when the infection abates, Aß resides[66–68].

Cell-cycle reentry is a process characteristic of cancer that should be absent in the terminally differentiated neurons of the AD brain but is instead common[69]. Activators of cell-cycle reentry stimulate Aß production *in vitro*[70] and in mice. Cell-cycle reentry can be initiated by conditional transgenic expression of simian virus 40 large T antigen oncogene produces Aß and tau deposits as well as neuronal loss in mice that do not harbor a human fAD transgene[71]. Impressively, this is the only known model to achieve the trifecta of AD-like pathology in the absence of fAD

transgenes, and thus may be more informative about the role of Aß than more popular Tg-AD models that do not faithfully recapitulate these aspects of AD.

Traumatic brain injury in humans suggests that Aß may respond to injury and reside during recovery[72–76]. Traumatic injury produced by controlled cortical impact (CCI) in rodents also drives dynamic production and recession of Aß. For example, CCI increases enzymes in the pathway to Aß production in WT rats[77]. CCI increases Aß in Tg-AD mice within one day and potentiates Aß deposition, though Aß levels return to normal over time[78,79]. Furthermore, the interaction between CCI and Aß are influenced by apolipoprotein E genotype[80], the strongest known genetic risk factor for LOAD. While traumatic injury is clearly not a model of LOAD, we can use it to learn about the physiological functions of Aß.

Models of increased Aß production and/or aggregation			
Species	**Aß Type**	**Trigger**	**Ref**
		Immune Challenge	
Mouse	WT	Poly I:C	56,57
Mouse	Tg-AD	Poly I:C	57
Mouse	WT	LPS	58–60
Mouse (Aged)	Tg-AD	LPS	61–63
Rat	WT	*H. pylori*	64
Mouse	Tg-AD	*B. pertussis*	65
Mouse	WT	*C. pneumoniae*	66–68
		Cell Cycle Reentry	
Mouse	WT	Simian virus 40 large T antigen oncogene	71
		Traumatic Injury	
Rat	WT	Controlled cortical impact	77
Mouse	Tg-AD	Controlled cortical impact	78,79
		Cerebrovascular Pathology	
Rat	WT	Needlestick lesion	83
Rat	WT	Hypertensive, stroke-prone	85,86
Rat	WT	MCAO	87–89
Rat	WT	Endothelin-1 and Aß combined injection	90
Mouse	WT	MCAO with transgenic Endothelin-1 overexpression	91
Guinea Pig	WT	Microhemorrhage induced surgically	92
Mouse	Tg-AD	Microhemorrhage induced by Bengal dye	94

Table 1. Models of increased Aß production and/or aggregation. The table outlines models discussed, listing the species, whether Aß is wild type (WT) or an inserted human transgene (Tg-AD), and the experimental manipulation used to increase Aß. In some cases the pathway to Aß production is elevated, there is evidence of increased Aß levels or Aß aggregation or deposition is increased. The specific effects on Aß of each trigger are described in the accompanying body of text.

Cerebrovasculature pathology is highly comorbid with AD and a likely contributor to AD etiology[81,82]. Cerebrovascular pathology also upregulates Aß production and draws Aß to the vasculature in animal models. For example, bleeding induced by needlestick lesions in WT rats transiently upregulates Aß and p-Tau near the lesion site and longer lasting deposition of Aß along the needle tract[83]. Stroke is a recognized driver of Aß and tau in WT and transgenic rodent models (reviewed[84]). Hypertensive stroke prone rats consistently present elevations in Aß[85,86]. Middle cerebral artery occlusion (MCAO) increases Aß production in WT rats that peaks in one month[87,88], and transitions from diffuse deposits to more dense plaque-like deposits within nine

months[89]. Blood-brain barrier damage generated by injection of endothelin-1 in combination with Aß potentiates Aß deposition beyond injection of Aß alone[90]. Blood-brain barrier damage induced by a transgenic model of endothelin-1 upregulation in combination with MCAO further enhances astrocytic production of Aß[91], as does surgically-induced microhemorrhage in guinea pigs[92]. Microhemorrhages induced by dietary hyperhomocysteinemia effect the distribution of Aß, drawing it to the cerebrovasculature[93]. Microhemorrhages also effect the rate of Aß deposition, as cerebrovascular amyloid angiopathy and plaque-like Aß depositions increase rapidly after microhemorrhage induction with Rose Bengal dye and return to the basal deposition rate within one week[94]. Together, these data suggest that cerebrovascular pathology may be used to promote Aß in WT animals and challenge Tg-AD models in a way that can help reveal the role of Aß in AD.

Naturally elevated endogenous Aß in animal models

More can be learned about the relationship between Aß and AD by evaluating models of naturally elevated Aß in addition to transgene-driven Aß. Brain Aß is conserved in other animal species[95], and some develop age-dependent Aß accumulation or high levels of Aß. These include, but are not limited to, non-human primates (Caribbean vervets and lemurs), canines (beagles) and rodents (octodon degus and naked mole rats) (see **Error! Reference source not found.**).

Vervet monkeys and lemur primates both develop age-dependent Aß deposition. Anti-Aß immunotherapy in vervets reduces the load of Aß plaques[96]. Lemur primates accumulate Aß deposition with age and their Aß sequence is more closely related to humans than the Aß sequence of mice. When treated with anti-Aß immunotherapy, aged primate lemurs develop microhemmhorages[97], consistent with outcomes of human clinical trials. Importantly, microhemorrhages were not predicted from pre-clinical work in Tg-AD mice, suggesting that this model of endogenous Aß may reveal important information about the physiological role of Aß.

Beagles have an Aß sequence with complete sequence homology to human Aß, though N-terminal modifications are distributed toward a more degradable form of Aß in beagles than humans[98,99]. Beagles develop diffuse amyloid plaques after ten years of age and additional dense Aß plaques over time[99–101]. By 15-18 years of age, 73% of laboratory-raised beagles had brain amyloid deposits[101]. Anti-Aß immunotherapy in beagles treated for approximately 2 years successfully reduced Aß load, but did not impact cognition[102]; similar to the effect these therapeutic approaches have had in human trials.

Octodon degus are a long-lived South American rodent with an endogenous Aß sequence that closely resembles human Aß, differing by only one amino acid whereas the Aß sequence in WT mice and rats differs by three amino acids[103,104]. Relatively young octodon degus develop vascular Aß accumulation, and aged octodon degus display a wide range of AD-like attributes, including intra- and extracellular Aß deposits, white matter pathology, intracellular tau, neuroinflammation, cell death, synaptic dysfunction and behavioral impairment[104–108]. Therefore, octodon degus may be a natural animal model of AD and can provide valuable insight into its pathogenesis[109].

In contrast, naked mole rats also have high levels of Aß but do not develop age-associated characteristics of AD. Naked mole rats also have naturally high levels of Aß that is only one amino acid removed from the human sequence and equally toxic to mouse neurons[110,111]. Though Aß levels in the naked mole rat are elevated throughout the lifespan at levels similar to 3xTg-AD mice that harbor multiple fAD genes, Aß does not increase with age and plaque-like aggregates are not observed in this rodent[110]. In fact, they have the longest longevity quotient of any known rodent, living approximately 30 years, and remain very

Models of naturally increased Aß production and/or aggregation			
Species	**Deviation from human Aß**	**Characteristics**	**Ref**
Vervets	Identical	Deposition increases with age	96
Lemurs	Identical	Deposition increases with age	97
Beagles	Identical	Deposition increases with age	98–101
Octodon degus	1 AA	Deposition increases with age	103–108
Naked mole rats	1 AA	Levels comparable to 3xTg-AD, however, deposition does not increase with age.	110,111

Table 2. Models of naturally increased Aß production and/or aggregation. Animal models of naturally-elevated Aß are outlined. This table is not an exclusive list of species that develop Aß, but lists models that lend themselves to research. In general, species that have naturally increased Aß levels and/or deposition have an Aß sequence identical to, or 1 amino acid (AA) away from, the human Aß sequence. In all cases, Aß has been documented to form aggregates with age with exception of the naked mole rat, which has high Aß levels but no evidence of AD-like deposits.

healthy[112–114]. The absence of pathology in the presence of high Aß over a lifetime suggests that Aß is not toxic in this model, and this is either because Aß is not inherently toxic or because naked mole rats are able to compensate for its presence. In addition to extreme longevity, naked mole rats are also known for maintained health and cancer resistence[115]. As discussed above, cell-cycle reentry associated with cancer is present in AD and stimulates Aß production. Yet, there is a strong inverse relationship between AD and cancer[116–118]. It is possible that Aß, which can be cytotoxic and suppresses tumor growth[19–21], is protective against cancer but permissive for AD. Therefore, the naked mole rat is a unique and relevant model for studying Aß.

Human

Ideally, the relationship between Aß and AD would be elucidated in humans, but imaging and post-mortem analysis can only give snapshot views. Aß can be induced in human cell lines. In particular, pluripotent stem cells derived from brain tissue better represent the size, function and context of brain than other human-derived cell systems and are becoming an extremely useful tool to investigate the effects of human Aß and AD-related genetic patterns[119]. Various triggers of Aß can be tested in these cell lines, and this can give us insight into the function of Aß. For example, various microbes induce Aß production and aggregation in animal cell lines and animal models. Furthermore, Aß has antimicrobial properties that have been demonstrated in culture systems. Evidence that Aß is triggered by and fights against microbial infection would be even more compelling in human brain cell systems, particularly if these effects are different in those derived from patients with AD or AD-related genetics. In addition to cell lines, Aß is found in various other human organs in the context of pathology[120–122], but only one is particularly suited for experimentation: the placenta.

Aß in the placenta is a newly discovered and relationship that deserves further exploration, because it may offer a unique way to model AD in a human organ. Recent evidence demonstrates that Aß accumulates in the urine of women with preeclampsia (PreE), a condition that effects 5% of pregnancies, and may be a better prognostic of clinical outcome than the current clinical standards[123]. Furthermore, enzymes that process Aß are increased in the placenta in addition to plaque-like Aß deposits. To date, it is unknown whether PreE is a predictor of later AD; clinical cohorts that have pregnancy records with reliable PreE diagnoses

(beginning in the 1960's) are just beginning to crest the age at which early AD will manifest. Like AD, PreE has no known etiology and no known cure.

PreE parallels some aspects of AD, albeit on the time scale of months instead of decades; making pregnancy and the post-partum period an unlikely but attractive time for testing Aß. Less contrived than a genetic mouse model of fAD, the placenta offers human Aß in a human organ experiencing a human environment. Aß can be evaluated in collected urine samples and in placentas after birth, which can be obtained readily and allow for testing that cannot be completed on postmortem brain tissue. Additionally, placentas from normal pregnancies can be sectioned into explants and tested *in vitro* using a within-subjects design. While people only get AD once, many women have multiple pregnancies. Interestingly, PreE is only repeated in approximately one third of subsequent pregnancies. This implies that there is either a trigger for Aß or a compensatory mechanism to protect against Aß in later pregnancies. For this reason, evaluating Aß during PreE offers a window of insight into AD that cannot be obtained from evaluating the human brain or transgenic mice.

Conclusion

Models exist that can be utilized to better represent LOAD, the form of AD that is by far the most common. These include experimental manipulations that stimulate Aß production, animals that naturally produce high levels of Aß and the human placenta, which has the potential to develop plaque-like deposits and is easily obtained. To date, all clinical trials for AD targeting Aß have failed, and some have been halted for serious adverse events in a subset of the population. This record of failure suggests that reducing Aß is consequential, potentially because Aß has important physiological roles in normal and pathological contexts. These roles will be better revealed with models that complement existent Tg-AD models.

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