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Review

# The role of Aβ in Alzheimer's Disease as an Evolutionary Outcome of Optimized Innate Immune Defense

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## Abstract

Alzheimer's Disease is a progressive manifestation of aging associated with accumulated Amyloid β. It remains frustratingly unclear why this protein accumulates and how it contributes to Alzheimer's Disease pathology. In one recent hypothesis, Amyloid β is suggested to function as an antimicrobial peptide in innate immune defense within the brain, where Amyloid β gains toxicity when it becomes abundant. This essay proposes an evolutionary explanation for why Amyloid β expression is regulated at an optimum based on its function as a defense and how this leads to disease. Among its potential physiological functions, Amyloid β confers benefits to reduce direct pathogen damage while this simultaneously entails cellular cost of defense. Optimal Amyloid β expression occurs when the gain in fitness from an incremental increase is balanced by the marginal cost of this increase. It proposes that natural selection acting upon the young favored systems to maintain Amyloid β at an optimal level through mechanisms that induce the defense and repress its expression. With age, the force of natural selection declines and permits mechanisms of negative feedback repression to degenerate. Consequently, Amyloid β is expressed beyond its optimum. Age also elevates cumulative pathogen exposure, reduces pathogen barriers and reactivates latent pathogens. The net effect is elevated, chronic induction of Amyloid β in the brain. The model recommends attention to innate immune negative regulation in the brain to discover ways to restore these functions toward a youthful state in the elderly.

*Key words: Alzheimer's disease, Amyloid beta, signal detection, antimicrobial protection hypothesis, defense regulation.*

Alzheimer's Disease (AD) is a prevalent form of age-associated neurodegeneration. The incidence of AD accelerates each decade after age 65 years, while genetic factors predispose individuals to higher age-associated risk and to early-onset familial Alzheimer's Disease (1). Amyloid beta protein (Aβ), a recognized contributing factor to this pathology (2, 3), is a cleavage product of amyloid precursor protein (APP). Aβ is generated within the Golgi apparatus and endoplasmic reticulum through sequential cleavage of APP by BACE1 and γ-secretase. γ-secretase primarily produces the $A\beta_{1\text{-}40}$ isoform and secondarily the longer $A\beta_{1\text{-}42}$ species. Secreted from cells, these Aβ occur as monomers, low-molecular weight oligomers, protofibrils and mature β-sheet fibrils (amyloid plaques). $A\beta_{1\text{-}42}$ has greater propensity to form oligomers and higher order β-amyloid sheets (4). Given its phylogenetic prevalence and its distribution in many tissues, Aβ is likely to have positive functions (5-9). This essay proposes AD arises from the way natural selection has acted in the young to optimize the expression of Aβ based on its innate immune function relative to the costs of this defense. The concept helps bridge explanations between the mechanisms that cause AD (the 'how' of Tinbergen, (10)) and why evolution has produced this trait. 'Making sense' of this evolution (11) may suggest therapeutic approaches where the essential role of feedback is recognized to maintain optimized Aβ expression.

The negative consequences of Aβ are demonstrated when production is experimentally studied in mice. Animals expressing human forms of APP and a mutant presenilin γ-secretase proteolytic subunit have β-amyloid plaques, neuroinflammation and impaired cognition, although without tau neurofibrillary tangles (12-14). Neurofibrillary tangles are observed in human stem cell-derived neurons with familial Alzheimer's disease mutations (15). These and related data support a version of the amyloid hypothesis whereby age-dependent increase in Aβ induces tauopathy that leads to neurological decay (16). Nonetheless, it is unclear whether accumulated Aβ is sufficient to cause AD (17, 18). Recent clinical trials with monoclonal antibodies reduce the level of Aβ but have little effect on dementia (19, 20). Furthermore, some elderly individuals have high cognitive function despite widespread Aβ and NFT (21, 22). These outcomes may arise in part because Aβ has unrecognized properties. In particular, Robinson and colleagues proposed Aβ has physiological roles including to protect from infection, to repair the blood brain barrier, and to regulate synapses (5, 6). Emphasizing innate immunity, Moir, Tanzi and colleagues demonstrated Aβ can function as an antimicrobial peptide, positing the antimicrobial defense hypothesis of AD (7-9). Antimicrobial peptides are small peptides

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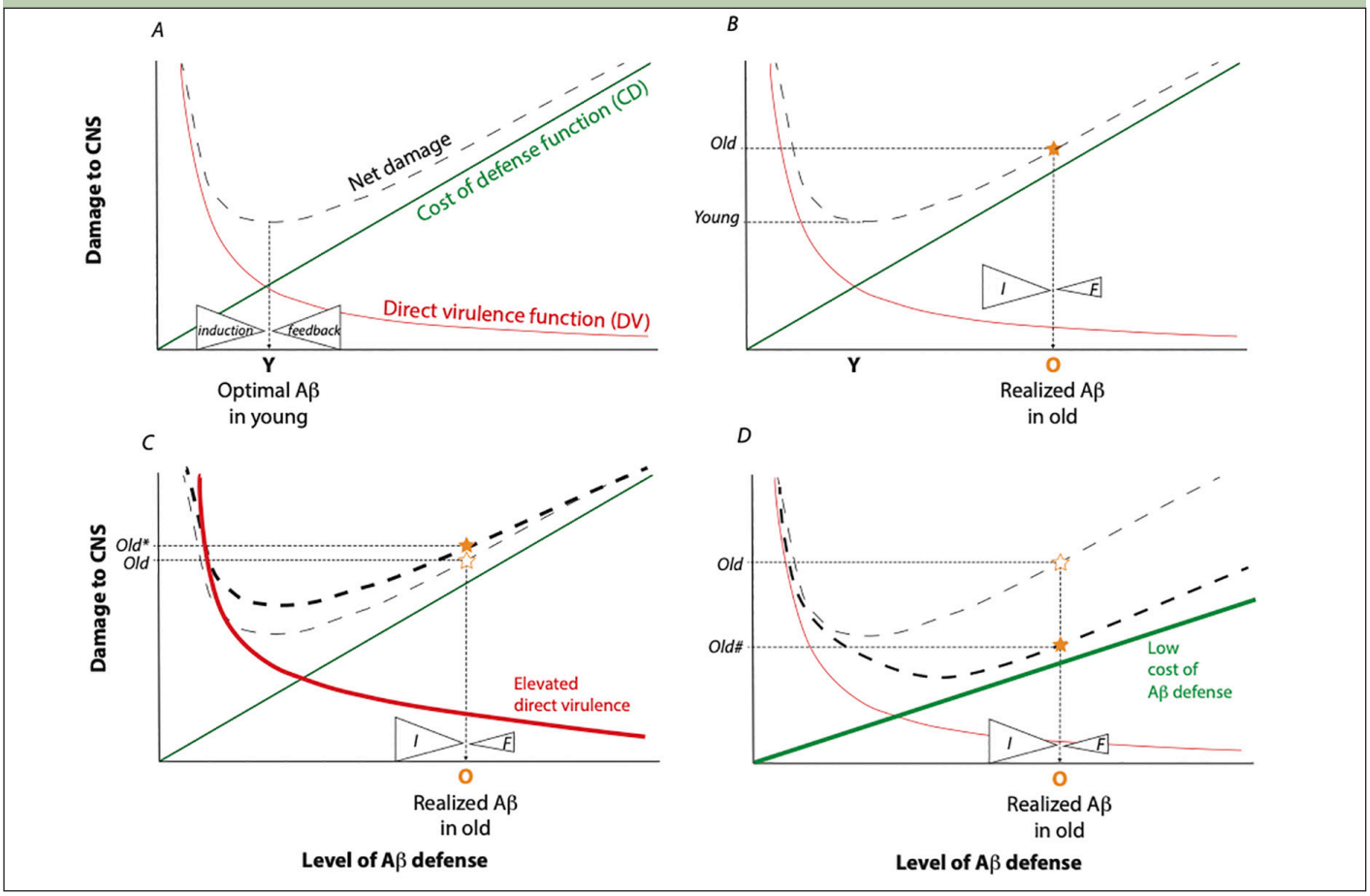
**Figure 1.** Model for the evolution of neurodegeneration as an outcome of defense optimization




Model built from the signal detection theory of Nesse (24). Each figure represents CNS net damage as a function of induced Aβ. Infection by bacteria, fungi, or viruses (or activated retrotransposons) produces direct damage to the CNS, represented as the Direct Virulence Function (DV), red lines. The DV is decreased in response to induced innate immune defense, here specifically by the level of Aβ. Expression of Aβ entails costs (damage) within the CNS, represented by the Cost of Defense function (CD) green lines. The sum of DV and CD yields the Net Damage (dashed lines). Fitness is maximized by strong selection acting in the young, which minimizes net damage. A) This model; proposes the optimal level of expressed Aβ in the young (Y) is maintained by counterbalanced mechanisms of Aβ induction (I) and negative feedback (F). B) In the aged, the force of natural selection is weak, permitting feedback mechanisms to degenerate such that ineffective feedback is less able to counterbalance the force of Aβ induction. Realized Aβ expression increases (O) and elevates the level of net CNS damage (star). This damage is manifest as neurodegeneration. C) Induction may also increase with age as old individuals acquire infection, experience reactivation of latent pathogens and loose pathogen barriers. This will elevate the DV function (heavy red line) and further increase the CNS net damage (Old*). D) Some individuals may have a low Aβ defense cost function (heavy green line). With lost capacity for negative feedback during aging, they still accumulate Aβ but the CNS net damage function is reduced (Old#). These old individuals would not present with Aβ-associated dementia yet their brains may have accumulated Aβ.

with amphipathic secondary structure produced by cells to defeat bacterial, fungal, viral and protozoan infections (23). Thus, Aβ may have evolved as a useful but dangerous defense system. From this perspective, the prevention of AD might be framed by asking what are the mechanisms that maintain the optimal level of Aβ activity and how do these mechanisms fail during aging? Understanding why Aβ has an optimal level of expression will suggest how cells maintain this level and what features may therefore degenerate as we age. I propose that Aβ expression is tuned in the young as an evolutionary compromise between its benefits and costs, and this optimal level is maintained by mechanisms of induction and negative regulation. When the force of natural selection weakens at advanced age, there is less selection to prevent degeneration of the negative regulatory system. Infection, viral reactivation or even 'sterile' agents may then stimulate Aβ beyond its optimal level. Aβ is always dangerous, even at young ages, but there is little fitness cost to its over-production at advanced age and we experience neurodegeneration. From this view, a potential strategy to maintain neuronal health in aging might seek ways to retain the negative regulatory network of Aβ at a youthful state.

## Aβ as an optimized innate immune defense

### *Defense system evolution*

Randolph Nesse applied signal detection theory to understand the evolution of defense systems (24). Fever, pain, fear, nausea, and immunity are defenses that protect individuals from acute injury, threats and infection. Such defenses are activated only when needed because they incur costs alongside their benefits. Nesse proposed defense activity is optimized to maximize

fitness based on the relationship between their costs and benefits. Fitness is the relative contribution to subsequent generations made by an individual or genotype. Thus, damage caused by a pathogen – its direct virulence – reduces host fitness. Host immunity mitigates the direct virulence by inhibiting the growth or action of the pathogen. Graphically, the direct virulence (DV) function describes how the fitness costs from pathogen damage is reduced by the expressed level of host immune defense (Figure 1A, adapted from Nesse (24)). The shape of this function depends on specific details of the pathogen and the efficiency of the defense, but in general it will reflect diminishing returns.

Defense mechanisms are expensive. Immune defense mechanisms incur fitness costs because they require physiological resources, and can also directly damage cells and disrupt tissue function (25, 26). As an example, pulmonary damage upon viral infection in humans includes effects from host immune-mediated responses that disrupt tissue architecture (27). In Drosophila, activated NF-κB induces an antimicrobial response but strongly represses fecundity, even when the activating stimulus is sterile (28). In mammals, TNF$\alpha$ induces a protective inflammatory response through degranulation yet this impairs vascular hemostasis (29). These costs are graded functions when they increase with the level of defense (Fig 1, cost of defense (CD) function). Nesse assumed a linear cost of defense although these functions may accelerate as occurs when fever produces hyperpyrexia or when highly activated macrophages produce systemic inflammatory disorders (30).

The shapes of the DV and CD functions specify the optimal defense activity. This point may sit where the level of defense minimizes the total cost, that is where the DV and CD intersect although Nesse emphasizes the optimum occurs where the marginal gain from additional defense is no longer positive. The optimum is determined by the relative rate of change between the DV and the CD, and it may be greater than expected for instance when DV declines quickly relative to the cost for increased defense (Fig 1A).

The aim is to understand how selection has shaped mechanisms to maintain defenses at their optimum in the context of this model. That is, what proximal mechanistic systems exist that satisfy the forces impacting defense evolution? I propose the optimum level of defense is controlled by counter-balancing induction and negative feedback, and this can maintain a quasi-homeostatic level of defense until an infection is cleared. The defense may be terminated in a gradual manner if the force of negative regulation decreases continuously when the inductive signals are reduced, as described for how inflammation is resolved by Dunster et al (31). If the negative regulation persists somewhat after inductive signals wane, the system may exhibit hysteresis whereby the defense abruptly terminates (32). Negative feedback, the essential 'how' in this model, occurs in many defense systems (29, 33). For instance, neutrophils produce arachidonate lipids that convert into proinflammatory leukotriene B4 at the site of injury. Arachidonate is subsequently converted by the affected tissue into lipoxins that block neutrophil intrusion into the tissue (34). In a second case, the A20 zinc finger domain protein is induced by TNF and TLR signaling via NF-κB where A20 subsequently ubiquitinates signaling elements of the NF-κB pathway to dampen inflammation (35). As a final example, experimental encephalomyelitis stimulates immunoglobulin OX2 within macrophages, which slows macrophage tissue influx and limits autoimmune damage (36). Maintaining an optimal defense level requires more than losing the inductive stimuli — it likely involves active systems of negative regulation. Thus, understanding the balance between the inductive and negative feedback systems of Aβ as a defense is an essential tool toward therapeutic management of AD.

## *Infection and immune defense of the brain*

The evolution of defense predisposes humans to neurodegeneration because the brain is exposed to pathogens (37) and the immune response of the brain provides protection with associated costs. Many defensive immune responses may contribute to neurodegeneration (38-40), of which amyloid as an antimicrobial peptide is one emerging hypothesized component. Here I consider this innate immune mechanism of Aβ as a model for how defenses are turned on and turned off. The principle is general to all defense systems of the brain and can inform new ways to manage neurodegeneration in aging.

The CNS copes with viral infections as well as bacterial and fungal pathogens. These can induce amyloid and associate with AD (41, 42). Herpes simplex virus-1 (HSV-1) is a frequently latent infection within the peripheral nervous system (43). Recent work with mice and cell culture show reactivation of herpes in the elderly can induce CNS amyloid pathology (44, 45). The neurotrophic protozoan *Toxoplasma gondii* is likewise argued to associate with AD etiology (46). Long-term infection by *T. gondii* in humans is widespread and largely benign except in immune compromised individuals (47, 48). Based on meta-analysis, the risk of AD is about 50% greater among *T. gondii* seropositive individuals (49). Human cytomegalovirus (HCMV) is also a common, latent pathogen, although data do not consistently associate it with AD (50, 51). Ancestral retrotransposable elements within our genomes such as LINE-1 can be activated with age in several tissues (52, 53). In cultured cells these LINE-1 elements may be perceived by the Type I interferon response system and thus induce an inflammatory response (53). Aside from viruses, subclinical fungal and bacterial infections occur in the human brain and associate with AD (54, 55). Candida protein and DNA has been detected in the brains of AD patients, while *Candida glabrata*, *C. albacans*, *Penicillium*

*notatum* and *Syncephalastrum racemosum* were seen in neurons of AD but not control brains (56). Whether these fungal infections cause AD or are secondary consequences of neurodegeneration remains unknown. *Chlamydia pneumoniae* is a ubiquitous, intracellular respiratory bacterial parasite. Initial reports found *C. pneumoniae* to associate with AD, while intranasal infection with *C. pneumoniae* activated astrocytes and produced Aβ deposits in the brain of wildtype mice (42, 57). Collectively these examples show that various microbes that associate with AD are available to stimulate defense systems in the CNS.

Upon new infection or pathogen reactivation, the brain is defended by the innate immune system. Microglia are innate immune sentinels of the CNS, coordinating phagocytosis and producing inflammatory cytokines (58-60). Glial astrocytes directly contribute to the innate immune inflammatory response and are likely the key source of amyloid production (61, 62). Neurons themselves generate Aβ when APP is processed within mitochondria-associated endoplasmic reticulum membranes (63). In these circumstances it is proposed with some debate (64) that Aβ acts in a defensive role where it provides antimicrobial activity (9). Synthetic Aβ kills *Streptococcus* and *E. coli* in vitro (7), while synthetic Aβ protects cultured cells from virus (65, 66). *C. elegans* engineered to express human Aβ42 are protected from *Candida albicans* infection, while 5XFAD mice resist cerebral *Salmonella* infection (8). Several mechanisms of protection by Aβ are proposed. Aβ oligomers bind microbe cell wall carbohydrates, cause agglutination and inhibit microbe adhesion to host cells (8). High concentrations Aβ porate microbes as do other AMPs (67). Aβ plaques may entrap viruses and bacteria, activating microglia migration (68-70). These studies suggest Aβ potentially acts within the brain as a defense to reduce the direct harm from pathogens.

Mechanisms are also proposed for how Aβ incurs costs (71). The oligomers of Aβ are considered to be toxic (72). Soluble Aβ oligomers may disrupt synaptic receptors (73). Aβ may also produce ion channels in liposomes and thereby disrupt cellular ionic balance (74, 75). Zaretsky and Zaretskaia (76) propose extracellular Aβ40 and Aβ42 enter cells by endocytosis into lysosomes where protein degradation produces Aβ fragments that porate the lysosome, the plasma membrane and mitochondria. As lysosomes are permeabilized, autophagy and mitochondrial function are disrupted, producing hallmarks of AD pathology (77, 78). Aβ oligomers may also cross-seed intracellular tau through the action of a common epitope, contributing to tau neurofibrillary tangles (79). There are many potential ways Aβ can be toxic, and these incur costs when Aβ is induced as a defense.

## *The balance of Aβ*

The costs and benefits of neuroprotective defense will be balanced by natural selection, where the impact of the pathogen on fitness is the sum of direct harm from the microbe plus damage caused by the induced defense. Aβ incurs defense costs when it acts as an induced antimicrobial peptide to limit microbe damage but the net CNS damage is less than would occur without the defense. I propose natural selection molds mechanisms of Aβ induction and negative feedback to achieve an optimal level of Aβ activity. If feedback systems involve hysteresis, this will generate a bistable equilibrium that abruptly activates Aβ to its optimum then abruptly terminates the defense once the infection is cleared. Appreciating these proximal requirements, many studies identify mechanisms for how Aβ is induced while others identify potential systems for negative feedback to stop production and clear Aβ.

Aβ is synthesized from the transmembrane amyloid precursor protein APP, which is processed by two related pathways (80). APP is made into non-amyloid P3 peptide via cleavage by $\alpha$-secretase followed by $\gamma$-secretase. Alternatively, in the amyloidogenic pathway APP is cleaved by β-secretase (BACE1) and $\gamma$-secretase to release Aβ peptides of 39 to 42 amino acids along with the APP intracellular domain protein. Points of control occur in APP processing when BACE1 activity is rate-limiting, although regulation of this step is not well understood (81). The transcription of β-secretase is induced by many stressors, including HSV infection (82). The enzymatic activity of BACE1 is stimulated by glycosphingolipids and glycerophospholipids (83), which may regulate the location of the enzyme within membrane lipid rafts (84). Following cleavage by BACE, Aβ is generated by the action of $\gamma$-secretase. $\gamma$-secretase is an assembly of four subunits including catalytic presenilin (85) where combined units are regulated by many partners (86) including the $\gamma$-secretase activating protein (GSAP) that alters the catalytic site of presenilin to enhance APP processing (87). Notably, viral infection induces interferon-induced transmembrane protein 3 (IFITM3) to directly activate $\gamma$-secretase and elevate synthesis of Aβ (88, 89). Overall, Aβ induction is regulated at many points in response to stimuli and cell-state sensors.

In a complementary way, Aβ is reduced by multiple mechanisms. Aβ is cleared across the blood brain barrier by chaperone-mediated transport (90, 91), while cerebrospinal fluid may enter the parenchyma to flush Aβ from the CNS (92). Within the parenchyma, soluble oligomeric Aβ is engulfed into cells, and then processed by autophagy, endosomes/lysosomes and the ubiquitin-proteosome. Peripheral monocytes infiltrate the brain to produce macrophages that phagocytize Aβ, as do microglia (93). Secreted by choroid plexus, the carrier protein transthyretin may act as an Aβ scavenger to export or neutralize amyloid (94, 95). Extracellular

soluble Aβ may also be catabolized by neprilysin, insulin degrading enzyme and angiotensin converting enzyme produced by neurons, microglia and astrocytes (96).

Neprilysin and transthyretin share an important feature. Their transcription is induced by the amyloid intracellular domain, which is generated when APP is cleaved by BACE (97). This action potentially provides negative feedback to regulate the quantity of extracellular Aβ. Amyloid and its precursors may also feedback upon the systems that lead to their production. The β C-terminal fragment (βCTF) generated by BACE cleavage contains a substrate inhibitory domain that negatively modulates γ-secretase (98). Within nonamyloidogenic processing of APP, the αCTF produced by α-secretase negatively modulates γ-secretase, potentially reinforcing production toward P3 and away from Aβ (99). The action of γ-secretase is also facilitated by interaction with γ-secretase activating protein (GSAP) and heat shock induction factor-1a (Hif-1a) (100, 101). Whether these proteins are inhibited in response to Aβ is unknown but if so, this could provide a further avenue for negative feedback regulation.

Overall, Aβ is balanced by mechanisms of synthesis and degradation that are mediated by negative feedback. I propose this system evolved to activate Aβ at an optimal level. Aβ entails benefits and costs, where the net effect on relative fitness (net damage) is exposed to natural selection, and this acts strongly at young ages. Thus, Aβ (and other defenses) always has its dark side but this is unavoidable in a world with pathogens. Aging, however, changes the balance.

## *Asymmetric regulation of Aβ in aging*

Reproductive value declines with age (102) and selection acting in the old therefore has little force to maintain defense regulatory systems if they are compromised. If the mechanism of negative feedback are degraded in aged individuals, the balance between induction and feedback will not maintain Aβ at its optimum. The loss of feedback may permit incremental accumulation of Aβ when negative regulation is a continuous mechanism. Alternatively, Aβ may accumulate precipitously if the negative regulatory system is based on hysteresis and aging increases the lag-time between inductive and terminating signals. In either case, the consequence is elevated Aβ in old individuals because the negative feedback (F) does not balance the level of induction (I) (Figure 1B). We experience high defense costs of Aβ in the form of neurodegeneration even while the elevated Aβ reduces the cost of direct virulence.

Unlike the processes of amyloid clearance (103-105), little is known about how age impacts mechanisms that terminated Aβ production, that is, how a proximal mechanism of AD will be shaped by declining force of natural selection. Central to my argument, innate immune systems can be controlled through negative feedback (106-108). Two examples illustrate the potential for this concept applied to AD. Type I interferon increases in the choroid plexus of aged mice (109, 110) and contributes to elevated expression of IFITM3, where IFITM3 activates γ-secretase (88, 89). Notably, Aβ suppresses microglial myocyte enhancer factors, which are positive regulators of Type I interferon (111). Thus, Aβ has the potential to negatively regulate its own production, and where there is a lag between induction and negative repression. It would be of interest to understand if components in this feedback network are impaired with age, and whether this increases the level of Aβ. In a second example some microRNA reduce NFκB, and this subsequently down-regulates innate immunity (112, 113). Potentially, microRNA secreted in exosomes from microglia (114) may be induced by Aβ and thereby mediate production of Aβ within the brain, while aging somehow interrupts this negative regulation.

Naturally, age will also increase exposure to stimuli that initiate Aβ production. Exposure to infection is cumulative in old individuals. Age also associates with decreased blood brain barrier function that increases pathogen entry to the CNS (115, 116). As well, latent infective agents such as HSV, HCMV or *Toxoplasma* are reactivated with age (45, 117, 118). Mechanisms that suppress LINE-1 retrotransposition may decline with age and thereby trigger Type I interferon (53, 119). Any of these age-dependent events will elevate the magnitude of direct virulence and further induce Aβ, increasing the net damage to the host (the point Old* in Fig 1C).

The defense model of AD may explain why high levels of amyloid are found in the brains of some people without dementia (Fig 1D). They may accumulate Aβ upon infection, and even have poor negative regulation of the response, but their cost function for this Aβ defense is inherently low; they experience little net damage from Aβ (the point Old# in Fig 1D). This explanation is difficult to explore within humans, but Aβ is thought to cause little damage in the naked mole rat where levels are similar to that of 3xFAD mice (120). Likewise, nonhuman great apes accumulate Aβ but lack measurable dementia (121). Conversely, APOE-ε4 (122) may alter the shape of the Aβ defense cost function such that cost is low relative to APOE-ε3 at young ages but accelerates more rapidly at late ages. APOE-ε4 carriers at late age may experience greater neurological damage per unit of Aβ expression. This model may account for the commonness of APOE-ε4 because young carriers of APOE-ε4 would incur a lower net fitness cost of Aβ upon infection than non-carriers. Consistent with this expectation, APOE-ε4 carriers appear to be better protected against early life infection among rural Ghanaians exposed to water borne pathogens (123).

This model also organizes thinking about familial- and sporadic-AD. FAD individuals carry mutations in genes involved in Aβ production such as presenilin. Consequently, the level of induced amyloid should be

elevated beyond the wildtype optimum even at young ages, as is observed in APP and PSEN carriers assessed for cerebrospinal fluid biomarkers (124). Unlike the explanation proposed for APOE-ε4, elevated Aβ in FAD carriers may be expected to have higher net cost than noncarriers. Cognitive impairment short of diagnosed AD may still impact the ability to care for children and grandchildren, and this may restrain the frequency of FAD alleles. As individuals with FAD age, their propensity to express Aβ advances the onset and penetrance of AD. Sporadic AD on the other hand arises from stochastic, age-associated events that induce defense expression (Aβ) -- new, cumulative or latent infection -- or impair the mechanisms of negative regulatory feedback. Unlike FAD, individuals that eventually develop SAD experience optimal levels of Aβ expression when young. The risks that induce Aβ in cases of SAD may be influenced by genetic polymorphisms, as when HSV-1 infection increases the incidence of AD among APOE-ε4 carriers (125). As well, this view suggests that polymorphisms affecting the negative regulation of innate immunity may be risk factors for SAD.

## Conclusion

### *Aβ in good health and bad*

Any negative consequences of Aβ are usually considered to arise only when the protein becomes abnormally abundant. The concept of defense optimization proposes Aβ is always costly, it is always a 'double-edged sword' (126). But when the activity of Aβ is at its optimum we cannot perceive its costs or benefits — we simply appear 'normal'. We observe costs when Aβ is elevated beyond normal, when the additional costs exceed the benefits. Overall, this defense model of AD is consistent with an underlying principle of how health and disease evolve (127): 'good health' is a compromise where the phenotype favored by evolution is less bad than the available alternatives.

My view emphasizes how Aβ is a proximal feature of a regulated defense, where natural selection shapes this regulation. Clearly, the CNS regulates many defenses, including other antimicrobial neuropeptides (128, 129), neuroinflammation (130), and cellular senescence (131). All defense mechanisms incur costs along with their benefits, and I propose each defense will be optimized through balanced systems of induction and negative feedback. As with Aβ, the regulatory mechanisms may become asymmetric in old individuals and contribute to neurodegeneration: strong induction with weak feedback. Furthermore, if negative regulatory systems control multiple defense mechanisms, mitigating the costs of one feature alone such as by removing Aβ may not resolve AD. Excessive costs from other defense systems can still drive AD pathology. Multiple inductive stimuli may also tip the balance of Aβ in older individuals, making it difficult to identify one etiological agent (132). In a translational context I suggest a practical perspective to address AD by understanding the events that reduce negative regulation of interlocking immune defense systems.

There are precedents for this theme. Nalivaeva (96) argued Aβ levels in the brain sit at a dynamic equilibrium between production and clearance. Puzzo (133) proposed AD arises when Aβ loses its ability to exert negative feedback through induction of alpha7 nicotinic acetylcholine receptors. Wick (134) suggested inflammation initially inhibits Aβ toxicity but persistent inflammation produces pathology. Here I emphasize how selection may have optimized the costs of Aβ relative its benefits, how negative feedback regulation may stabilize this optimum and how aging releases selection upon the maintenance of this feedback.

This thesis points to practice: understand how to preserve and restore negative feedback systems that regulate Aβ activity and defense systems in general. An aged brain may then induce an appropriate defense to a pathogen even when aging increases pathogen susceptibility, and then effectively terminate the defense as it does in young individuals. This perspective recommends explicit research on how Aβ production is negatively regulated through feedback, and more broadly how innate immunity and the inflammatory response of the brain is regulated to self-terminate.

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