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Perspective

Tipping points in neurodegeneration

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SUMMARY

In Alzheimer's disease (AD), Aβ deposits form slowly, several decades before further pathological events trigger neurodegeneration and dementia. However, a substantial proportion of affected individuals remains non-demented despite AD pathology, raising questions about the underlying factors that determine the transition to clinical disease. Here, we emphasize the critical function of resilience and resistance factors, which we extend beyond the concept of cognitive reserve to include the glial, immune, and vascular system. We review the evidence and use the metaphor of "tipping points" to illustrate how gradually forming AD neuropathology in the preclinical stage can transition to dementia once adaptive functions of the glial, immune, and vascular system are lost and self-reinforcing pathological cascades are unleashed. Thus, we propose an expanded framework for pathomechanistic research that focuses on tipping points and non-neuronal resilience mechanisms, which may represent previously untapped therapeutic targets in preclinical AD.

INTRODUCTION

A major shift in the burden of diseases has occurred over the last decades. Although infectious diseases have declined, the development of chronic, progressive, non-communicable diseases has increased dramatically.[1,2] Today, in Western societies, the leading causes of death are non-communicable diseases, among which neurodegenerative diseases, particularly dementia, play an important role. One feature these diseases have in common is that they are associated with aging, influenced by unhealthy lifestyles and vascular risk factors. Another defining feature is a long preclinical disease stage, in which pathological changes develop gradually without causing manifest clinical symptoms. In Alzheimer's disease (AD), neuropathologic features, characterized by amyloid plaques and neurofibrillary tangles, begin many years before cognitive symptoms appear.[3–6] The clinical disease slowly evolves into a late-onset dementia syndrome, with a prevalence of ~30% in people who are 85 years or older.[7] Less commonly, cognitive symptoms of AD occurs at an early age at onset, before the age of 65 years, in those with autosomal dominantly inherited mutations in presenilin 1, presenilin 2, or amyloid precursor protein. Longitudinal positron emission tomography (PET) and structural magnetic resonance imaging (MRI), together with biomarker analyses for amyloid beta peptide (Aβ), tau, and markers for neurodegeneration in plasma and cerebrospinal fluid (CSF), have revealed a chronological sequence of pathological events.[3,6] These studies consistently show that Aβ deposition begins two decades before the onset of clinical symptoms.[8–14] Tau pathology detected by PET ligands occur after Aβ deposition, at the onset of neurodegeneration but before the onset of cognitive symptoms. The initiation of Aβ deposition two decades before the clinical diagnosis and the hierarchical evolution of the major pathological events are remarkably similar in imaging studies performed on patients with sporadic and autosomal-dominant AD.[8] Previously, the importance of a complex cellular phase, evolving in a non-linear fashion over decades, has been highlighted as a key contributor to the pathology of AD.[15] An important task, therefore, is to identify the cellular mechanisms and dynamics involved in the transition from the preclinical to the clinical phase. One way to explain conversion is the gradual buildup of pathological events that eventually reach a critical level of accumulated neuronal damage at which symptoms appear. Another possibility is that clinical symptoms arise at a threshold level, and conversion occurs when resilience and resistance factors are exhausted and adaptation fails. The main differences between these two explanations lie in the kinetics with which neuronal function declines. The first model assumes a continuous and linear decline in neuronal function, whereas the second model is based a non-linear dynamics in which the decay occurs once a critical threshold is crossed. Dynamical models that incorporate non-linear interactions in a complex cellular environment are increasingly being recognized as essential for our understanding of AD.[16] Here, we borrow from the conceptual framework of the "tipping point" commonly used to describe how human activities can change the Earth's ecosystem.[17] The concept refers to a critical threshold at which small perturbations can shift a system into a new and often irreversible operation state. We propose that tipping points and their associated elements could serve as a useful theoretical concept for our understanding of the evolution of AD. To illustrate the concept and its underlying biology, we first explore the available evidence for non-linear dynamics in

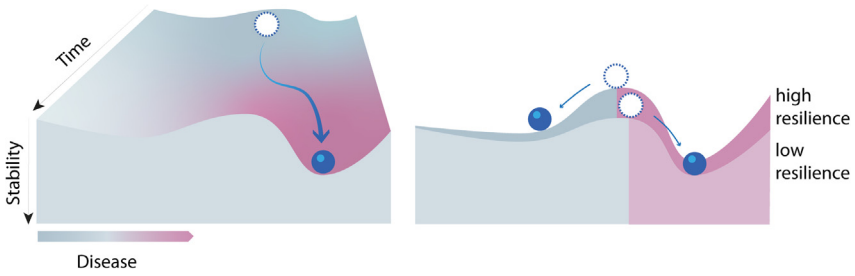


Figure 1. Schematic presentation of tipping points in the context of disease

The valleys represent stable attractors and the ball the state of the system. The left diagram shows how the ball moves over time along the blue arrow toward the disease state, depicted in violet. The basins of attraction are separated by a steeper hill when the system has high resilience and a lower when resilience is low.

AD. We discuss the chronological sequence of neuropathological hallmarks, neurodegeneration, and clinical symptoms, as well as the overarching resilience and defense strategies and possible positive feedback mechanisms in the disease process. We mainly focus on the functions of glial, vascular, and inflammatory modulatory units that provide stability in the early stages and runaway changes at a later stage in the disease.

TIPPING POINTS

Complex dynamical systems can undergo changes—at so-called tipping points that are often difficult to reverse (Figure 1). The term was first introduced in sociology in the studies of racial segregation, describing the conditions that led to the flight of the white population from a non-white neighborhood in the United States in the 1950s. Later, it has been frequently used in ecology.[17] Typical examples include lake ecosystems where tipping point is used to describe how gradual increases of nutrients cause clear water to become turbid or in forest systems to denote the point at which rainforest turns to savanna. What these examples have in common is that once a system has reached a critical threshold, relatively small changes can make a big difference. For a system to reach a tipping point, it is often moved to a new state by self-accelerating changes. The basis of such transitions is often positive feedback loops that are self-reinforcing and tend to exacerbate small perturbations as the transitions unfolds.[17,18] Tipping points usually occur in dynamical systems that consist of various stable attractor states into which the systems can evolve. Such attractor states are stabilized by negative feedback loops that reduce disturbances and sustain homeostatic set points. Complex dynamical systems, therefore, tend to be stable even when they are constantly perturbed, but once a critical threshold is reached, they reorganize irreversibly into a new state. The transition from health to disease exhibits characteristics of such behaviors. Neurodegenerative disorders, such as AD, can serve as an example to illustrate this point.

AD is characterized by a gradual, seemingly smooth disease process, in which neurodegeneration develops with characteristic spatial and temporal dynamics. Consequently, clinical symptoms develop slowly rather than abruptly as predicted for a complex dynamical system with critical transition points. Despite these features, there are characteristics that are inconsistent with linear dynamics. Structural neuroimaging with MRI can be used to assess atrophy as a measure of neurodegeneration in AD. Normal aging is already associated with a decrease in brain volume, occurring at a rate of ~0.2% per year until midlife and 0.3%–0.5% at the age of 70–80 years.[19] A number of studies have been conducted to determine the change point when atrophy begins to increase in AD.[20] These studies have shown that brain atrophy rates in AD do not increase linearly but gradually accelerate several years before symptom onset.[21–26] The time at which atrophy rates deviate from normal depends on the brain regions studied. For example, longitudinal structural MRI studies of patients with autosomal-dominant AD have shown pathological acceleration of hippocampal atrophy rates ~3 years before the expected onset.[24] Other longitudinal studies examining autosomal-dominant or sporadic AD concur with these observations, revealing increased atrophy rates a few years before diagnosis or expected clinical onset. The initial stages of atrophy appear to have a preference for brain regions with a high neurofibrillary tangle burden. In addition, the temporal sequence of brain regions with accelerated atrophy rates correlates with the Braak stages of increasing neurofibrillary tangle burden. Consistent with this pattern, atrophy progresses from the entorhinal cortex to the hippocampus to the neocortex.[20] The transition from the onset of atrophy to the development of the clinical syndrome is difficult to identify as the clinical syndrome develops over several years from a preclinical to a prodromal stage before dementia is diagnosed, and the time at which clinical symptoms appear may vary from person to person.[27,28]

The process of protein aggregation, which is based on a conformational autocatalytic conversion of misfolded proteins follows a non-linear kinetic.[29,30] Growing aggregates can fall into smaller pieces or form a surface for secondary nucleation, giving rise to further seeds for further aggregation. Such proliferations have the property of a self-propelling positive feedback loop.[31] Once the amyloid cascade is set in motion, there seems to be no cause and effect in the sense of classical logic. Indeed, current evidence does not support a causal dynamic of Aβ load and neurodegeneration.[32–34] There is a relatively poor correlation between Aβ load and neurodegeneration or the extent of cognitive symptoms.[35] Moreover, a relatively large proportion of cognitively unimpaired individuals have extensive Aβ plaque load at autopsy, suggesting that Aβ deposition is necessary, but not always sufficient, to trigger chronic progressive neurodegeneration. Preclinical AD is most likely a relatively stable condition in which various interconnected homeostatic circuits continuously correct perturbations by negative feedback mechanisms. For example, homeostatic mechanisms sense aberrant protein folding or aggregation and initiate countermeasures to improve protein homeostasis and aggregate clearance; glia may detect a noxious microenvironment and enhance their

defense, trophic, and metabolic support functions, and the neurovascular unit adapts blood flow to the altered metabolic requirement of the stressed neurons. These corrective, adaptive changes are necessary and capable of maintaining stable neuronal function over a relatively long time. What causes the system to tip?

COGNITIVE RESERVE

The notion of cognitive reserve represents an overarching concept to explain why some people retain cognitive ability despite neurodegeneration.[36–38] Reserve can be broadly classified as resilience based on brain or cognitive reserve, which may explain why clinical symptoms do not appear until years after neurodegeneration has started. High cognitive reserve indicates resilience to neuropathological damage, possibly due to optimized performance. Compensation may occur through more efficient use of the same brain network or by shifting operations to alternative circuits or cognitive strategies. Thus, the brain has multiple ways to cope with brain pathology and resist the development of clinical AD. With all these strategies, it is important to make a few distinctions. Brain and cognitive reserves refer to a threshold at which compensatory mechanisms are exhausted and the first symptoms appear. This threshold is defined by the brain structure already in place (e.g., number of synapses and connections) and by coping strategies. Cognitive reserve becomes relevant only when neuropathological changes have advanced to a level at which the function of some neurons is lost. Although this theoretical construct has severed as a useful explanatory approach for resilience mechanisms in neurodegenerative disorders, it is neuron-centric and therefore needs to be expanded to one that considers the contribution of other cell types.

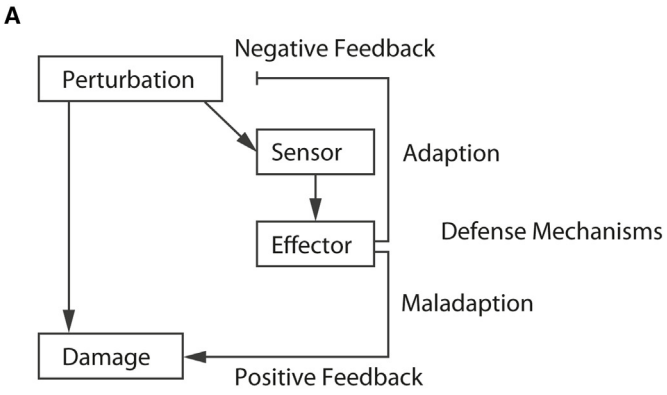
Here, we aim to extend the concept of resilience and resistance to non-neuronal factors. The resilience provided by glia, the vasculature system, and the immune system is of a different nature. According to the model we propose, they represent a defense system that is important in providing early resistance and adaptation to neuropathological changes. To understand how they operate, we will briefly introduce the concept of glial, vascular, and inflammatory modulatory units before discussing how their dysfunction can exacerbate pathology.

GLIAL, VASCULAR, AND INFLAMMATORY MODULATORY UNITS

Although constituting only 2% of the total body mass, the adult brain consumes about 20% of the total daily energy. The metabolic costs of neuronal transmission are high,[39,40] with about two-thirds of the energy consumed by neurons for action potential generation and synaptic transmission. Other functions required for neuronal transmission such as axonal transport, vesicle recycling, and neurotransmitter synthesis contribute to the high energy demands.[40] To generate the energy, neurons operate at a high rate of oxidative metabolism but cannot readily switch to glycolysis, which carries the risk of becoming vulnerable to hypoxia or ischemia. Other factors contributing to the poor tolerance of neurons to damage are their low regenerative capacity and their low functional autonomy. Even if neurons could be replaced after damage, they would need to be integrated into their circuitry at the correct location. The evolution of such a system, with cells operating at high energy and oxygen consumption within a complex circuit in which individual components cannot be easily replaced after damage, must have created an immense evolutionary pressure for the design of protective resilience in diseases.

To understand how the brain responds to disease, it is important to recall its basic design principle with the hierarchical arrangement of primary and secondary cellular functions. Although neurons perform primary brain functions, various supportive cells facilitate and optimize these functions. These supporting components consist of cells that form the protective barrier that surrounds the brain, the vasculature, and glia.[41,42] The division of cells into primary and supportive functions is not a ranking of the importance of tasks but rather reflects the specialized functionality of the organ. Primary cells are those that execute tasks beyond the organ boundary, whereas supportive cells have functions primarily within the tissue. The importance of supportive cells to brain performance is evident, for example, in glia, whose relative numbers have increased over the evolution of complex nervous systems. Glia are not only abundant but are also highly specialized for cell-type-specific, selective tasks within the nervous system. Oligodendrocytes primarily insulate axons by enwrapping them with myelin to enable fast, energy-efficient saltatory nerve conduction,[43,44] whereas astrocytes provide nutrients to neurons, maintain extracellular ion balance, recycle neurotransmitters, and shape synaptic circuits.[45–48] The functions of microglia are mainly related to immune response and maintaining brain homeostasis.[49,50] To perform these functions, supportive cells are equipped with sensors, which detect deviations in the concentration of various molecules such as oxygen, sugars, lipids, amino acids, ion concentrations, osmolarity, and extracellular matrix components. Perceived deviations of homeostatic variables are transformed into a specific response with the help of various effector mechanisms with the aim to restore homeostatic set points. Together, these various components consisting of sensors, effectors, and regulated variables with their specific set points constitute a homeostatic circuit.[51,52] Homeostasis is maintained by negative feedback loops that reverse deviations from the set point, which, in turn, keeps the regulated variables within their normal range (Figure 2). Thus, neurons are connected to each other not only to form neuronal networks but also to support cells to form multiple homeostatic circuits. This basic design principle is fundamental to our understanding of how neurons respond to disease.

Because supporting cells are primarily responsible for maintaining neuronal functions, it is not surprising that they undergo profound adaptive responses already early in neurodegenerative diseases (Figure 3). The neurodegeneration-induced reactivity of microglia to form so-called disease-associated microglia (DAM) is one example of such a process.[53–55] DAM represents a tissue injury program responsible for the upregulation of genes involved in lysosomal, phagocytic, and lipid metabolism pathways. Triggering receptor expressed on myeloid cells 2 (TREM2) is the key sensor, which is able to detect anionic lipid present on or



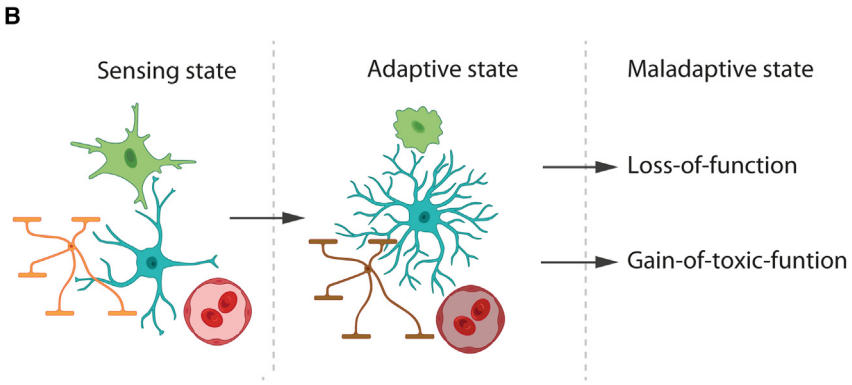


Figure 2. Homeostatic control circuit

(A) Perturbations constantly push homeostatic system away from their balance set points. Such deviations are sensed and translated into an effector program, which typically involves negative feedback loops that counteract changes and restore set points. Both negative and positive feedback loops can operate toward maintaining homeostasis. However, positive feedback loops can also amplify the initiating stimuli in such a way that they move the system away from its starting state toward new detrimental states.

(B) Glia, immune, and vascular modulatory units sense perturbations and execute effector programs that defend and preserve neuronal homeostasis. When these homeostatic mechanisms fail or the cells enter maladaptive alternative states, pathological processes can unfold.

released from damaged neurons or other cells and initiate the DAM effector response.[56] A remarkable feature of the DAM state is its universality, as it occurs in various neurological diseases. The conversion of astrocytes into a disease-associated astrocyte (DAA) state is another example of glial reactivity in the early stages of neurodegenerative disease.[57] Upregulated DAA genes are involved in development and differentiation, metabolic pathways, response to toxic compounds, and inflammatory signaling. Oligodendrocytes can also respond to injury by transforming into a disease-associated oligodendrocyte (DOL or DAO) state and upregulating molecular response pathways to damage, some of which are common with astrocytes (for example, upregulation of Serpina3n, C4b, and Ctsb).[58–61] Thus, together, glial reactivity can provide disease tolerance to neurons not only by providing defense against injury and toxic molecules but also by restoring deviation of essential homeostatic variables essential for neuronal functionality (Figure 4). The hierarchical arrangement of functions within the brain ensures that glia adapt rapidly to neuronal dysfunction at the expense of abandoning lower priority functions.

A second component of the support system is the vasculature, in which endothelial cells, pericytes, smooth muscle cells, and astrocytes regulate cerebral blood flow (CBF) in response to neuronal activity. The neurovascular unit functions to adjust CBF to neuronal energy demands[62,63] by integrating neuronal activity with vascular unit function in multiple homeostatic circuits. Neurons signal their metabolic state through transmitters that act on their receptors in the vasculature to trigger contraction or relaxation and modulate blood flow. For example, ATP and adenosine bind to purinergic receptors on pericytes and smooth muscle cells, causing hyperpolarization and vasorelaxation. Noradrenalin, neuropeptide Y, nitric oxide, and other modulators contribute to cerebrovascular regulation of blood flow. Astrocytes with their end-feet encircling the outer wall of the microvessels are part of the system and serve as a connecting link between neurons and endothelial cells. These observations show the extensive integration of neurons into a vast network of glial and vascular cells that together sense and respond to neuronal function within the framework of interconnected homeostatic circuits.

There is now overwhelming evidence for the contribution of non-neuronal cells in AD. Human genetic studies have been transformative broadening the previously neuron-centric view to include glia. The groundbreaking findings emerged from genome-wide association studies (GWASs) that identified genetic determinants of AD risk such as *APOE*, *SORL1*, *MS4A*, *SP1I*, *TREM2*, *ABCA7*, *CLU*, *CR1*, *INPP5D*, *CD33*, *EPHA1*, *BIN1*, *PICALM*, *PLCG2*, *ABI3,* and *PTK2B* in genome regions, harboring a large number of genes with non-neuronal expression patterns.[64–71] Among these, the variation found in *TREM2* is of exceptional importance because it triples disease risk and occurs in the coding region of a gene expressed exclusively in microglia in the brain.[72,73] The substantial effect size of the genetic variation enabled subsequent functional follow-up analyses of the role of TREM2 in AD pathology and led to strong evidence for microglia playing a key role in the disease,[56,74] a view further strengthened by the discovery of additional mutations in the coding region of microglia-enriched genes such as *PLCG2* and *ABI3*.[70,71] Assigning gene expression enrichment to cell types is not always straightforward. With advances in single-cell genomics, it has become clear that cellular heterogeneity and reactivity must be taken into account. For example, apolipoprotein (*APOE*), of which the e4 allele is the strongest genetic risk factor for sporadic AD, is a gene enriched in astrocytes under normal conditions but becomes one of the most upregulated transcripts

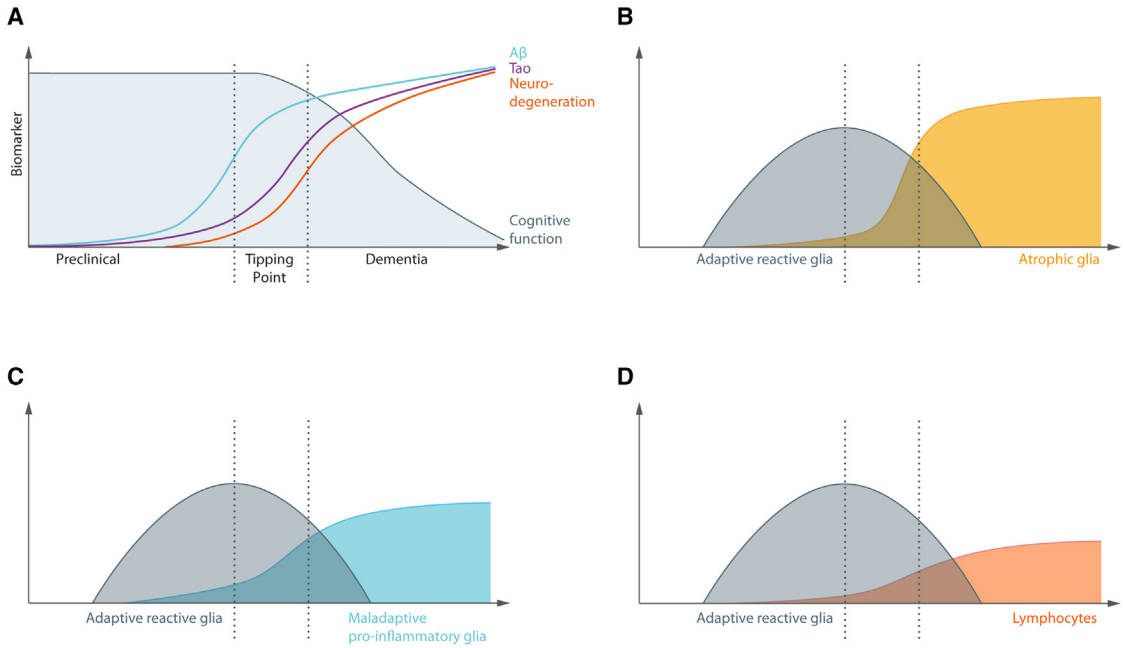


Figure 3. Proposed model of Alzheimer's disease progression

(A) Staging of Alzheimer's disease cascade with amyloid, tau, and neurodegeneration biomarkers according to Jack et al.[3] The tipping point between preclinical AD and dementia is marked by the two dashed lines.

(B) The proposed increase and decrease in the different glial states (depicted in different colors) are shown along the time axis. According to the proposed model, adaptive reactive glial response decrease and the number of atrophic glia increase at the tipping point.

(C) The proposed increase of maladaptive pro-inflammatory is shown.

(D) The proposed increase of lymphocytes is shown.

in microglia upon microglia activation and transition to DAM.[53] Likewise, *CLU* and *APOE* are activated as part of the disease-associated response in astrocytes and partially in oligodendrocytes.[57–59] Thus, reactive responses of glia share transcriptional features, of which immune- and lipid-associated modules overlap to some extent. Gene expression profiling of brain autopsy from AD patients has led to additional support for this notion, highlighting the role of immune, lipid, and endocytic pathways in microglia, oligodendrocytes, and astrocytes.[61,75,76]

GLIAL RESPONSES

Current models support a chronological sequence of pathological events, starting with Aβ plaque deposition, but over many years, the gradual deposition of Aβ plaques appears to have little effect on cognition. The question of how and when Aβ accumulation begins to exert pathogenic effects remains unresolved. It seems plausible that the formation of Aβ plaques is initially adaptive, or even protective, and only later becomes toxic. One possible event that could mediate this conversion would be the interaction with tau. Multiple studies have shown an association of tau pathology with future atrophy and cognitive decline, and there is evidence that neurons containing neurofibrillary tangles can release aggregated tau as ghost tangles.[77] Thus, Aβ-mediated self-propagating tau accumulation may represent a critical transition for initiating neurodegeneration. However, there are several reasons why this takes time to occur.[78] One reason could be the initial spatial segregation of tau and Aβ deposition, with tau pathology in the medial temporal lobe and Aβ pathology in the neocortex.[79,80] Several studies suggest that in the presence of Aβ, tau pathology spreads from the medial temporal lobe to the neocortex. This interaction is reminiscent of a self-amplifying positive feedback loop, in which more Aβ causes greater spread, and the next loop causes an even greater response. The molecular basis for this response may be cross-seeding and prion-like self-propagation of a "transmissible" amyloid conformation.[30]

Another reason for the long and variable time interval of amyloid-induced tau aggregation may be the glial responses to pathology. When microglia are depleted, tau seeding and spreading increases around amyloid plaques in mouse models of AD.[81,82] This preventive function of microglia depends on TREM2 and the conversion of microglia into the DAM state. DAM efficiently prevents tau pathology and brain atrophy in the presence of Aβ deposition. Thus, microglia appear to play a critical role in the prion-like spreading of tau pathology possibly by their ability to clear spreading tau species. Thus, one may speculate that exhaustion of microglia defense function may be one reason for the conversion of Aβ to tau pathology. Indeed, the discovery of rare coding variants in *TREM2* that increase the risk of AD several-fold has provided genetic support for a loss of microglia function in disease development. These variants, which result in single-amino-acid substitutions in the extracellular domain of the protein (R47H or R62H),[71,83] reduce ligand binding[84–86] for a variety of molecules, including negatively charged lipids, myelin debris, apolipoprotein E, and amyloid.[87–92] TREM2 is a versatile receptor that initiates not only

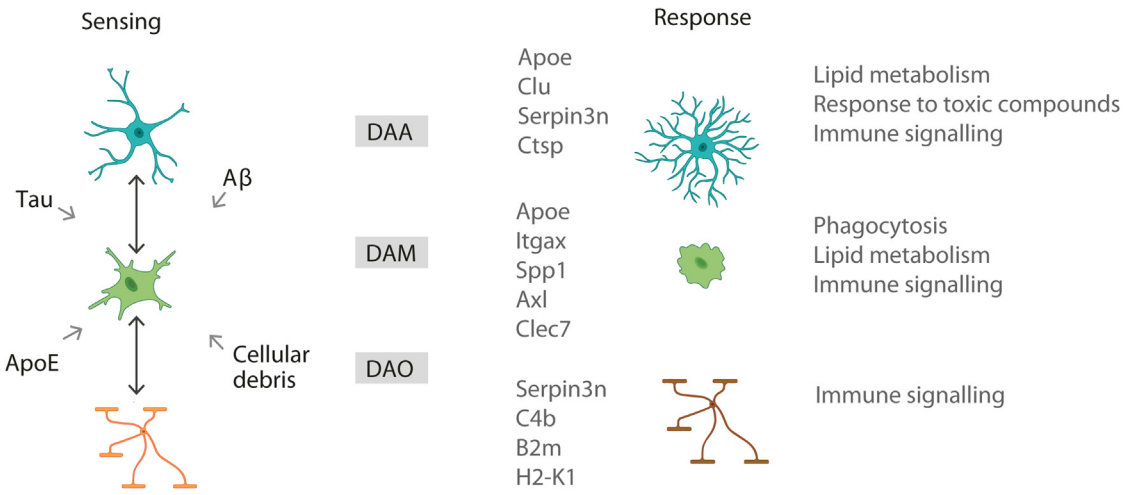


Figure 4. Disease-associated glia

Microglia (green) and possibly also astrocytes (blue) and oligodendrocytes (orange) are able to sense AD-associated pathology consisting of cellular debris (neurodegeneration) and aggregated species of tau and Aβ. As a response to AD pathology, microglia, astrocytes, and oligodendrocytes are converted into their disease-associated states, that is, DAA, DAM, and DAO, which execute effector programs with distinct but to some extent overlapping transcriptional responses. The primary goal of these responses is to counteract pathology and restore homeostasis.

phagocytosis but also a signaling cascade that ultimately culminates in the DAM state. DAM proliferate in the vicinity of amyloid plaques, where they participate in Aβ phagocytosis and plaque compaction, thereby reducing amyloid burden and limiting the spread of toxic species.[53,93,94] Even if there are conditions in which TREM2 can mediate maladaptive and detrimental microglia functions, it appears that the main function of DAM is to sense tissue damage and execute a defense program required for the protection of neurons from Aβ- or tau-related injury. PET imaging has shown that increased translocator protein (TSPO) signal correlates with improved cognitive function and slower disease progression in AD patients,[95] supporting the notion that microglial activation can be beneficial in the context of AD pathology. TREM2 is not the only microglial surface receptor that has been genetically linked to AD. CD33 (Siglec-3), a member of the sialic acid-binding immunoglobulin-like lectin (Siglec) family of receptors, is another example.[96] CD33 harbors an immune-receptor tyrosine-based inhibitory motif (ITIM), which upon ligand binding, mostly extracellular sialylated glycans, triggers an inhibitory signaling cascade leading to reduced cellular functions such as phagocytosis. Some of the CD33-mediated functions appear to control and occur upstream of TREM2. Deletion of CD33 increases TREM2-mediated activity, thereby promoting neuroprotection in mouse models of AD.[97]

Considering that one of the main functions of microglia is to sense changes in the brain environment and that more than 100 genes encoding for the microglial "sensome" have been identified,[98] it is likely that the microglial response to AD-related pathology requires the integration of signals from several additional receptors. Moreover, the transition to DAM implies a reorganization in the microglial sensome, such as the downregulation of purinergic and the upregulation of phagocytic receptors, so that disease-related tasks are prioritized at the expense of homeostatic functions. One question that arises is how long microglia can maintain the capacity to respond to the mounting pathology. There are two potential scenarios for how microglia may respond to exhaustion. One possibility is that they transition to a different activation state and exhibit heightened pro-inflammatory characteristics. Notably, specific subsets of activated reactive microglia have been identified that coexist with DAM and are characterized by the upregulation of interferon response genes.[55,60,99] Some of these subsets express high levels of MHC class II[99] or neurotoxic complement components.[100] When microglia enter such an overactivated state, they can cause damage by releasing cytotoxic factors such as reactive oxygen species (ROS), nitric oxide, and various cytokines. Another possible reaction to excessive pathology is microglia regression. Autopsy studies in people with AD have shown that microglia are unable to maintain their activated state into advanced disease stages and instead become dystrophic.[101] Microglia dystrophy is characterized by cytoplasmic fragmentation, lipofuscin accumulation, and de-ramified beaded or even fragmented processes.[102,103] One hypothesis is that increasing exposure to oxidative damage, toxic proteins, and lipid species that accumulate during disease progression leads to microglia exhaustion, eventually leading to a transition from DAM to a dystrophic or an interferon-responsive state. Loss of DAM could mark a tipping point at which key components of the defense system erode and dementia begins to unfold. Data from the Dominantly Inherited Alzheimer Network (DIAN) observational study, which includes families with a history of autosomal-dominant Alzheimer's disease, suggest that this could indeed be the case. Cross-sectional and longitudinal measurements of soluble TREM2 (sTREM2) in the CSF show that the levels are lowest in early preclinical AD, peak at the transition of dementia onset, and then decline in AD dementia.[104,105] Assuming that sTREM2 is a proxy for DAM, these data indicate that a partial loss of DAM activity marks the onset of clinical disease. Novel PET ligands that are able to discriminate the different microglia states would be necessary to substantiate these findings.

Much like microglia, astrocytes are critically involved in the response to AD-related pathology. A substantial number of risk genes associated with AD are highly expressed in astrocytes, including *APOE*, *CLU*, *SORL1*, and *FERMT2*. Although astrocytes are not considered a cellular component of the CNS innate immune system, they are able to sense tissue damage through Toll-like receptors or other types of pattern recognition receptors and to attract and instruct immune cells by the secreting immune mediators.[106–108] Reactive astrocyte subtypes include newly proliferated, border-forming astrocytes that arise from various progenitor cells and proliferating local astrocytes.[107,108] In addition, there are non-proliferative reactive astrocytes characterized by hypertrophy, that is, increased volume, thicker processes, and increased expression of glial fibrillary acidic protein (GFAP). A major overarching function of reactive astrocytes is their border-forming function, which is key for isolating pathology and limiting the spread of toxic molecules by their hypertrophic dense cellular processes and by the deposition of a network of extracellular matrix molecules. Not surprisingly, reactive astrocytes are found around plaques, where they participate in amyloid clearance by secreting apolipoproteins, α1-chymotrypsin, and α2-macroglobuline to promote transport across the blood-brain barrier (BBB).[109–111] In addition, reactive astrocytes function as phagocytes and are able to clear cellular debris and protein aggregates.[112,113] Astrocytes regulate neuronal network activity[114,115] and are also known to secrete neurotrophic or growth factors promoting survival of stressed neurons. One such factor is transforming growth factor β1, which protects synapses against Aβ oligomer-mediated toxicity.[116] Attempts to block astrocyte reactivity through inhibition of intracellular signaling cascades show inconsistent effects on pathological outcomes, pointing also to maladaptive functions in the disease.[117–119] Similar to microglia, astrocytes can adopt many different states in AD, including reactive neurotoxic astrocytes and atrophic astrocytes.[120–122] Reactive neurotoxic astrocytes lose several typical astrocytic functions, such as supporting neuronal survival, facilitating synapse formation and function, and phagocytosing synapses and myelin debris, and instead secrete neurotoxic molecules that promote oligodendrocyte and neuron death.[120] Astroglial atrophy is defined as a loss of surface area with a de-ramification of processes, including the reduction of perisynaptic processes resulting in diminished synaptic homeostatic support. Whether astroglial atrophy is the result of disease-induced exhaustion is unknown, but the consequence might be detrimental, as loss of both disease-associated reactive and physiological homeostatic functions likely exacerbates neuropathology.

Much less is known about oligodendrocytes, but recent single-cell transcriptomic analyses of AD brains have shown that oligodendrocytes exhibit pathology-responsive transcriptional signatures.[61,75,123,124] Oligodendrocyte signatures and myelin-related processes suggest impaired axonal myelination and metabolic adaptation to neuronal degeneration in AD. Interestingly, a spatial transcriptomic study analyzing the transcriptional changes occurring around amyloid plaques revealed early alterations in gene co-expression network enriched for myelin and oligodendrocyte genes, suggesting that the plaque microenvironment leads to oligodendrocyte reactivity.[124] Indeed, Serpina3n^{+}C4b^{+} reactive oligodendrocytes have been identified in AD,[58–61] but the function of these cells remains to be established. Future work will need to address whether this cell state has a specific function in protecting the brain from pathology. Of note, in later stages of disease with high amyloid accumulation, the plaque-associated oligodendrocyte-specific signature is lost. A reduction in oligodendrocytes and myelin in AD is consistent with several studies in both mouse models and postmortem AD brains.[125–128]

IMMUNE RESPONSES

Activation of the immune system is another factor that can trigger a self-reinforcing disease process.[129,130] Glial reactivity represents an essential adaptive defense mechanism, and when this becomes overwhelmed or insufficient, alternative defense mechanisms are needed.[15,110,131] That is, inflammation, which represents the second layer of adaptation. Inflammation is, in general, a response aimed at restoring homeostasis after infection or injury. However, it can also be the result of failed homeostasis, where the purpose of inflammation is to assist and correct tissue malfunction.[51] Several different inducers of inflammation have been described in the context of AD. Aggregated extracellular Aβ may represent an initial trigger for the activation of local microglia, which may be followed by secretion of signals from stressed neurons and release of intracellular proteins from damaged neurons containing neurofibrillary tangles. They all have in common that they send signals to the immune system that indicate neuronal dysfunction or homeostatic imbalance. The immune system's response to these perturbations occurs in a graded manner. Microglia are the first responders; however, when they and other glial cells are overwhelmed and the perturbing noxious molecules or signals cannot be turned down or eliminated, an inflammatory process may unfold.[130] This immune activation involves the recruitment of peripheral cells of the innate immune system, among which are neutrophils and circulating monocytes.

Such systemic chronic inflammation is often triggered when organ-intrinsic homeostatic responses become insufficient. Indeed, monocyte-derived macrophages that migrate into the brain can assist reactive glia in reducing Aβ amyloid burden,[132,133] and blocking infiltration of monocytes into the brain has shown to be detrimental in models of AD.[134,135] *In vivo* real-time imaging studies have revealed that monocytes crawl along the luminal walls of blood vessels where they remove vascular Aβ before re-entering the bloodstream.[136] Nevertheless, the inflammation that builds up in such a condition can take a detrimental course in which self-reinforcing inflammatory loops contributing to tissue destruction. For example, infiltrating neutrophils can induce neurotoxicity by releasing cytotoxic cytokines, promoting BBB breakdown, or by inducing oxidative damage.[137,138] Part of such maladaptive activation of the immune system is the stimulation of microglia and astrocytes into new pro-inflammatory states. The transformation could result in the induction of neurotoxic phenotypes. This can occur by the secretion of various inflammatory mediators including complement, cytokines, chemokines, and proteolytic enzymes that are released with the aim to revert the pathological condition; however, when accumulating at unconstrained levels, they cause collateral neuronal damage, which in

turn sustains the chronic, inflammatory reaction. For example, microglia have been shown to secrete complement that mediates synaptic loss in models of AD.[139] C1q is aberrantly elevated and deposited at synapses, triggering activation of the downstream classical complement pathway and its phagocytic removal.

Chronic inflammatory activation of microglia can lead to pyroptosis, which results in the release of apoptosis-associated speck-like proteins, which can act as seeds for Aβ deposition and thereby causing spread of pathology.[140] Inflammasome-activated microglia can also influence neuronal tau pathology. Genetic silencing of an essential inflammasome component, the NACHT, LRR, and PYD domains-containing protein (NLRP) 3, prevents Aβ-induced spread of tau pathology.[141] Activated microglia, in turn, are able to induce astrocyte activation by secreting interleukin (IL)-1α, tumor necrosis factor (TNF), and complement component 1q (C1q). Such astrocytes lose the ability to support neuronal viability and instead induce the death of neurons and oligodendrocytes.[120]

Increasing evidence suggest that in addition to innate responses, the adaptive part of the immune system also responds to AD neuropathology. Several studies have demonstrated infiltrations of $CD4^+$ and $CD8^+$ T cells in brains from patients and animal models of AD.[142,143] Single-cell T cell receptor sequencing and repertoire analyses have revealed clonal expansion of cytotoxic pro-inflammatory $CD8^+$ cells in the CSF of patients with mild cognitive impairment (MCI) or AD, some of which were specific to Epstein-Barr virus antigens.[144] $CD8^+$ T cells were also found adjacent to Aβ plaques and neuronal processes, but the functions of these cells remain unknown. Moreover, activated antigen-specific $CD8^+$ T cells have been detected in patients and mouse models of amyotrophic lateral sclerosis.[145] Although the source of the antigen remains unknown, these studies raise the intriguing possibility of lymphocyte-mediated auto-inflammatory responses directed against non-self or self-antigens within the CNS of patients with neurodegenerative diseases. Aging is another condition in which clonally expanded $CD8^+$ T cells have been found; they drive detrimental neuroinflammatory processes, mostly in white matter tracts.[60,146,147]

Taken together, these studies suggest that exhaustion of brain intrinsic glial defense mechanisms can give rise to peripheral innate and adaptive immune system activation. This additional layer of immune activation requires precise titration. If the response is set too high, the engagement of the peripheral axis comes at the price of collateral tissue damage. Thus, failure of resilience mechanism together with the self-magnifying inflammatory response could be another reason for how neurons shift from a healthy to a stressed state and eventually degenerate. Such cell death decisions occur in a switch-like binary manner and are executed only when all attempts to stay alive have been exhausted.

VASCULAR RESPONSES

The neurovascular unit, with its function of regulating CBF, promoting blood-barrier exchange of oxygen, metabolites, and nutrients and removing noxious substances from the brain, plays an important role in AD pathology. Vascular impairment is one of the earliest changes in late-onset AD as shown by the early reduction in CBF[148,149] and the early breakdown of BBB integrity in AD patients.[150] Thus, dysfunctional brain vessels actively contribute to the tipping point by limiting the delivery of substrate to the brain, impairing BBB function, reducing vascular clearance of Aβ and tau, and promoting cerebral amyloid angiopathy (CAA).[62] Notably, loss of BBB integrity contributes to APOE4-associated cognitive decline independent of AD pathology.[150] The importance of vascular factors in AD is supported by human genetic data and recent single-cell RNA sequencing data, showing that many of the major risk genes for AD are expressed in the human brain vasculature including brain endothelial, mural, and perivascular cells.[151]

There are various self-propelling mechanisms by which cross-talk between vascular dysfunction and neurodegenerative pathology could contribute to disease progression. Aβ induces endothelial dysfunction via ROS[152,153] and subsequent intracellular Ca^{2+} overload[154] that can be reversed by ROS scavengers.[153] Endothelial dysfunction may in turn lead to impaired Aβ clearance[155] and thus could further contribute to AD pathology, although this has not been convincingly demonstrated. Recent work further suggests that perivascular macrophages are another source of ROS and effector of the damaging neurovascular actions of Aβ.[156,157] Interestingly, GWAS genes associated with AD are enriched in protein endo- and trans-cytosis components of brain endothelial cells.[151,158] ROS production induced by Aβ oligomers further causes capillary constriction via endothelin-1 signaling to pericytes.[159] Pericytes regulate numerous vascular functions including BBB permeability, clearance of toxic metabolites, and blood flow. Patients with AD showed an early loss of pericytes[160,161] and genetic ablation of pericytes in mice leads to BBB breakdown, CBF reduction, and neuronal loss.[162] Moreover, pericyte loss in mice overexpressing APP has been shown to increase brain Aβ40 and Aβ42 levels and accelerate vascular and parenchymal amyloidosis by diminishing clearance of soluble Aβ40 and Aβ42 from brain interstitial fluid.[163] Another factor contributing to ROS production in the brain is hypertension. Recent work has shown a critical role of ROS-producing perivascular macrophages in mediating the neurovascular and cognitive dysfunction associated with hypertension.[164] ROS and oxidative stress in brain endothelial cells, pericytes, and perivascular macrophages may therefore be one convergence point where vascular and neurodegenerative processes overlap in a self-propelled mechanism. Another point of convergence could be the hemostatic system and the procoagulant state of Aβ.[165,166] For instance, Aβ binds to fibrinogen[167] and fibrin[168] and induces structural changes in fibrin clots that affect thrombosis and fibrinolysis.[169] Because of the leakiness of the BBB in AD, fibrinogen enters the brain parenchyma. Studies in mice have shown that fibrin(ogen) extravasation results in pericyte degeneration, amyloid accumulation, microglial activation, and neuronal dysfunction or loss.[169–171] Blocking the interaction between Aβ and fibrinogen has been shown to normalize thrombosis, reduce CAA, and improve cognition.[172] Some of the above vascular effects seem to depend on the presence of APOE4,[150,161,173] the strongest genetic risk factor for AD. APOE4 is also a risk factor for CAA,[174] and APOE immunotherapy reduces CAA and amyloid plaques while improving cerebrovascular function.[175] Overall,

these observations underscore the importance of vascular responses in AD.

AGING

Of all the risk factors for AD, age is not only the most potent but also the most elusive. Age may simply increase the time that is necessary for the pathology to build up, but there are observations that point to additional mechanisms. Several neuroimaging studies show an initial slow linear decline in brain volume; however, after the 6th decade of life, age-related atrophy accelerates and increases exponentially.[19] Curiously, the incidence of AD shows the same pattern, with an exponential rise after 65 years of age, when the number of cases starts to double every 5 years. The natural aging process is also linked to declines in specific cognitive abilities such as processing speed, memory, language, visuospatial skills, and executive functions. These age-related cognitive changes are accompanied by structural and functional modifications in the brain, which include alterations in neuronal structure, loss of synapses, and dysfunction in the neuronal network. Thus, aging may provide a fertile field for neurodegeneration by self-propelling positive feedback loops, in which erosion of resilience causes greater injury, and the next loop causes even more damage. This is made possible by the reciprocal interference of age-related neurodegeneration with glia, vascular, and immune responses. It is now well known that the glial responses described in AD models occur to some extent in normal aging of the healthy brain. For example, microglia in healthy, aged, white matter exhibit a DAM transcriptional profile, which is reminiscent of the reactivity observed in AD models.[91] DAAs and oligodendrocyte responses have also been described in both aging and in AD being surprisingly similar.[58–61] When these responses and those that arise in the vasculature or immune system converge in the aged AD brain, critical transitions may be triggered.

Conclusions

There is a substantial proportion of people that remain non-demented despite having amyloid plaques. Half of the amyloid and tau biomarker-positive individuals remain cognitively intact after ~15 years of follow, indicating a long and highly variable preclinical phase of AD neuropathology. We use the concept of tipping points to illustrate how self-propelled accelerating changes drive the disease from a preclinical to a clinical state and highlight the critical role of resilience and resistance factors, which we extend beyond the concept of brain and cognitive reserve to the glial, immune, and vascular system. We propose that loss of glial, immune, and vascular function initiates self-reinforcing pathological processes—such as tau spreading and inflammation that lead to neurodegeneration and dementia. The model we allude to is based on different stages of glial and immune reactivities that change over the course of the disease. We hypothesize that the process begins with an adaptive phase of reactivity, in which an effector program is initiated to defend and preserve neuronal function and viability. When these compensatory mechanisms become overwhelmed and maladaptive loss and gain of toxic pathological processes take over, neuronal function declines. Because different cells and regions in the brain are interconnected at multiple levels, it is likely that tipping points are also interconnected. Thus, crossing the threshold in one part of the brain may drive another system in another location closer to the tipping point. Such domino effects, or cascading tipping points, could be the basis of the known pattern of propagation along the Braak stages. An additional aspect to take into account is the spatial and temporal evolution of the cellular alteration. The pathology affects the brain in a staged manner, resulting in the simultaneous presence of early and late stages of the response in different brain regions at any given moment. Consequently, the glial, immune, and vascular responses described in this review are likely to coexist with diverse cellular compositions across brain regions. As a result, tipping points will be reached at varying time points across brain regions, providing one possible explanation for the gradual and relatively slow progression of clinical symptoms into the different cognitive domains. However, once the system has tipped and reorganized into this new and irreversible state, it becomes relatively independent of the pathological process that initiated the transition. This may explain why therapies targeting Aβ have so far proved ineffective or had relatively little effect in the symptomatic phase of AD.[176–178] Likewise, disease-modifying immunomodulatory therapies for the treatment of MS that are highly effective in the initial relapsing-remitting phase do not result in relevant clinical benefit when used in the secondary chronic progressive phase.[179] Thus, we might have to reconsider how we design disease-modifying treatments for AD and related dementia. Pharmaceutical intervention that targets the disease-causing pathological accumulation of amyloid must be used very early, possibly decades before the onset of clinical symptoms. Such therapies must be inexpensive and safe because they are administered to clinically healthy individuals, some of whom will never develop the disease. Because such therapies are not easy to implement, treatment of risk factors should not be overlooked. For the field of dementia prevention, it will be critical to understand the underlying biology of how risk factors influence disease development and progression and whether they do this by influencing resilience factors. Risk factor management is an established and successful approach to cardiovascular disease prevention but has not been adequately implemented for dementia prevention. One challenge is the accurate risk profiling of individuals at risk for dementia. Risk scores such as the Cardiovascular Risk Factors, Aging and Dementia (CAIDE) score have been established and, at least to some extent, allow prediction of subsequent dementia risk based on midlife assessment.[180] Such risk assessment could be combined with genetic testing for *APOE* alleles to determine the ε4 status, which is found in ~15% of the population but in ~70% of patients with AD.[181] In addition, risk stratification must include biomarker analyses for early assessment of amyloid, tau, and neurodegeneration. Despite the progress made in monitoring amyloid and tau deposition by biomarkers, these are still insufficient to predict the onset of dementia. Thus, additional biomarkers are needed to monitor vascular, immune, and metabolic functions and spot early warning signs for disease progression and conversion. In conclusion, we emphasize here the preclinical stage of AD,

which offers so-far untapped opportunities for intervention, which are lost once the disease has tilted into its irreversible clinical phase.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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