

## Mini-review

# An alkaline phosphatase transport mechanism in the pathogenesis of Alzheimer's disease and neurodegeneration



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## ABSTRACT

Systemic inflammation is associated with loss of blood–brain barrier integrity and neuroinflammation that lead to the exacerbation of neurodegenerative diseases. It is also associated specifically with the characteristic amyloid- $\beta$  and tau pathologies of Alzheimer's disease. We have previously proposed an immunosurveillance mechanism for epithelial barriers involving negative feedback-regulated alkaline phosphatase transcytosis as an acute phase anti-inflammatory response that hangs in the balance between the resolution and the progression of inflammation. We now extend this model to endothelial barriers, particularly the blood–brain barrier, and present a literature-supported mechanistic explanation for Alzheimer's disease pathology with this system at its foundation. In this mechanism, a switch in the role of alkaline phosphatase from its baseline duties to a stopgap anti-inflammatory function results in the loss of alkaline phosphatase from cell membranes into circulation, thereby decreasing blood–brain barrier integrity and functionality. This occurs with impairment of both amyloid- $\beta$  efflux and tau dephosphorylating activity in the brain as alkaline phosphatase is replenished at the barrier by receptor-mediated transport. We suggest systemic alkaline phosphatase administration as a potential therapy for the resolution of inflammation and the prevention of Alzheimer's disease pathology as well as that of other inflammation-related neurodegenerative diseases.

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**Abbreviations:** A $\beta$ , amyloid- $\beta$ ; AD, Alzheimer's disease; AP, alkaline phosphatase; ASGP-R, asialoglycoprotein receptor; ATP, adenosine 5'-triphosphate; BBB, blood–brain barrier; CABG, coronary artery bypass graft; DAMP, damage-associated molecular pattern; FcRn, neonatal Fc (fragment crystallizable) receptor; GPI, glycosylphosphatidylinositol; IAP, intestinal AP; IgG, immunoglobulin G; LCFA, long-chain fatty acid; LPS, lipopolysaccharide; LRP-1, low-density lipoprotein receptor-related protein 1; NFT, neurofibrillary tangle; PAMP, pathogen-associated molecular pattern; P-gp, P-glycoprotein; PLAP, placental AP; PRR, pattern recognition receptor; RAGE, receptor for advanced glycation end products; SIRS, systemic inflammatory response syndrome; TNAP, tissue-nonspecific AP.

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## 1. Introduction

### 1.1. Inflammation and the proposed role of AP in its resolution

The inflammatory response of the innate immune system is a critical component of many acute and chronic diseases and is closely linked with other physiological processes including metabolism and neuroendocrine activation [1]. Generalized inflammation is the body's nonspecific reaction to a perceived inflammatory insult, whether endogenous or exogenous, in the form of either a damage-associated molecular pattern (DAMP) or a pathogen-associated molecular pattern (PAMP), respectively [2]. These molecular triggers disrupt tissue homeostasis by activating pattern recognition receptors (PRRs) on an assortment of cells such as macrophages and eliciting downstream responses. The nature and magnitude of these responses vary according to timing, duration, severity, identity, and location of the inflammatory insult.

Deviations from homeostatic conditions may be reversible or irreversible, with an apparent threshold level of danger signaling serving as the fulcrum between these outcomes. Immunosurveillance mechanisms of the immune system have been proposed increasingly to play a key role in the monitoring and maintenance of tissue homeostasis. These mechanisms are suggested to govern the balance between stages of disease initiation (i.e. reversible) and disease progression (irreversible) by acting on one side of the threshold to preserve or recover homeostasis and on the other side to amplify danger signals and thereby alert surrounding cells [3]. Such a theoretical framework has been applied specifically to pathologies including hepatic fibrosis, ischemic tissue damage, and various neurodegenerative diseases, among others [3]. It has been suggested that there is a nonspecific, systemic protective mechanism in place to monitor and defend against inflammatory insults that is only activated by a threshold concentration of an applicable molecular trigger. Concentrations exceeding the threshold overwhelm this defense mechanism, whereas super low concentrations may not be sufficient for its activation and instead aggravate toxicity [4]. An understanding of such a system would lead to breakthroughs in the treatment and prevention of uncontrolled inflammation and inflammatory diseases, but to date, this proposed protective immunosurveillance mechanism has not been elucidated [4].

Our research group has recently put forth a hypothesis describing such a protective immunosurveillance mechanism that involves the tissue-nonspecific isozyme of alkaline phosphatase (TNAP) [5]. TNAP is a GPI-anchored ectophosphomonoesterase with a notably high-pH biochemical catalysis optimum of 9–10, an alkalinity obtained *in vivo* only at niche environments that enable such favorable conditions by interaction of the enzyme with specific negatively charged substrates. TNAP is expressed at the apical membranes of epithelial and endothelial cell types including those of the liver and the blood–brain barrier. TNAP, like other alkaline phosphatase (AP) isozymes, sequentially dephosphorylates a wide range of substrates including DAMPs and PAMPs like extracellular nucleotides and LPS [6]. The resultant anti-inflammatory effects and immune gatekeeping role of APs have been widely documented [6–10].

For example, recent clinical findings by members of our group and others have shown that intravenously-administered AP

protected coronary artery bypass graft (CABG) patients from the spike in circulating proinflammatory cytokines that accompanies such a procedure and often escalates to systemic inflammatory response syndrome (SIRS) [8]. In a phase IIIa follow-up study involving patients undergoing cardiac valve replacement surgery either with or without CABG, AP treatment prevented mortality and significantly reduced the incidence of adverse events in comparison to placebo treatment. Both treatment regimens were carried out on top of standard care (Fret et al., personal communication [APPIREDII study]). Other studies have shown a similar protective and damage-reversing effect of AP treatment on localized and systemic inflammation associated with both chronic and acute conditions including metabolic syndrome [11], necrotizing enterocolitis [12], cystic fibrosis [13], and sepsis-induced ischemic injury [14]. While these studies specifically examined the protective effects of AP, it is also possible that other ectophosphatases such as CD39 or CD73 [6], among others, could have similar beneficial effects on barrier function.

Unexpectedly, systemic administration of exogenous intestinal AP (IAP) was observed to upregulate the expression and secretion into plasma of endogenous TNAP from liver [8], further enhancing dephosphorylation of systemic DAMPs and PAMPs. This is suggestive of an inflammation-induced regulatory mechanism for TNAP. However, the mechanism by which apically-localized TNAP could be delivered to circulation to achieve this goal despite intact tight junctions in the epithelial barrier remains unknown. According to our model, as illustrated for the liver [5], a rigidly controlled negative feedback process is initiated by a nonspecific inflammatory insult (ATP, LPS, etc.), triggering the transcytotic transport of TNAP from the apical (canalicular) hepatocyte membrane to the basolateral (sinusoidal) membrane as an immune complex with the immunoglobulin G (IgG) antibody. This transport is likely mediated in hepatocytes by the asialoglycoprotein receptor (ASGP-R). Dephosphorylation of inflammatory stimuli by this TNAP along with its release into the plasma by phospholipase D- or C-mediated cleavage of the GPI anchor and uptake of the substrate-associated TNAP-IgG immune complex by endothelial cells and macrophages leads to decreased inflammation while providing an early upstream signal for the induction of a number of anti-inflammatory gene products, including TNAP itself.

We propose that similar protective mechanisms are in place in other epithelial barriers besides the liver such as the intestine, airway, and placenta, and also in endothelial barriers such as the blood–brain barrier, though different mechanistic details apply in this tissue type. In non-hepatic tissues, the neonatal Fc receptor (FcRn) likely supplants the ASGP-R as the TNAP-IgG immune complex carrier. We suggest in this paper that a transport mechanism for TNAP, which may also apply to other ectophosphatases, across the blood–brain barrier (BBB) in particular may have important implications for linking inflammation to the pathogenesis of neurodegenerative diseases, including AD, which we highlight in this review.

### 1.2. Mechanistic background for an AP transport system

We previously proposed a ‘rescue AP’ mechanism for the liver involving AP and IgG binding as an immune complex to the ASGP-R [5]. The activity of AP isoforms at the apical membranes

of polarized cells at epithelial barriers including those of the liver, intestine, and airway is suggested to be regulated by a highly sensitive, pH-dependent negative feedback mechanism involving P2Y receptor stimulation by extracellular nucleotides [15–18]. TNAP, located by default at the canalicular hepatocyte membrane, is known to be a ligand for the ASGP-R in the liver [19]. Liver TNAP also has the capacity to serve as an antigen for IgG, which itself binds to the ASGP-R in a carbohydrate-independent manner and is present in high concentrations in bile [20–24].

We proposed the interaction of TNAP-IgG immune complexes with ASGP-Rs that have relocated to the canalicular hepatocyte membrane [25] in response to local extracellular ATP/ADP increases caused by the early stages of inflammation [26,27]. The rising pH and  $\text{Ca}^{2+}$  release due to anti-inflammatory P2Y signaling would be consistent with appropriate conditions for optimal ASGP-R ligand binding [28], amplified TNAP catalytic activity [29], and induction of apical-to-basolateral  $\text{Ca}^{2+}$ -wave directed transcytosis [30–32]. This would result in the transport of liver TNAP-IgG complexes to the sinusoidal membrane of the hepatocyte. Dephosphorylation of circulating DAMPs and PAMPs could occur and phospholipase D or C cleavage of the GPI anchor could release the TNAP-IgG complexes from the membrane surface. These complexes subsequently could be taken up by known IgG receptors such as FcγRIIb on nearby endothelial cells and macrophages, stimulating anti-inflammatory signaling cascades. As this process continues, expression of liver TNAP would be upregulated in an attempt to keep canalicular ATP levels under control, explaining the observed increase in endogenous production of the enzyme. Importantly, in non-hepatic tissues, FcRn would most likely serve as the IgG complex carrier instead of the liver-specific ASGP-R.

This protective mechanism would utilize AP as a nonspecific antigen for early acute-phase danger signaling [20]. Administration of exogenous AP could provide a ‘head start’ to such a system through the formation of immune complexes with circulating IgG and activation of anti-inflammatory signaling pathways including upregulation of endogenous AP. On the other hand, insufficient levels of AP would likely lead to accumulation of extracellular inflammatory insults like ATP, overwhelming the protective P2Y-mediated mechanism and allowing proinflammatory P2X signaling to take place. This would promote further cell damage and the release of additional nucleotides. This AP-dependent system is thus positioned at the threshold between reversible and irreversible inflammatory responses and tissue damage, and it may represent a key immunosurveillance mechanism and a defense against unchecked inflammation and inflammatory disease progression.

In endothelial barriers such as the BBB, FcRn-mediated TNAP transport may take place in response to systemic inflammation as well, but with somewhat different mechanistic details from those in epithelial tissues. We discuss in the following sections how these differences may come into play with special importance in the progression of AD pathology. Cultivating an understanding of AP transport across epithelial and endothelial barriers may open major possibilities for new means of prevention and treatment of inflammatory pathologies like AD.

## 2. Inflammation and protein accumulation in neurodegeneration

In their progression, all of the major neurodegenerative diseases exhibit both an inflammatory component (reviewed in [33]) and a pathological accumulation of intra- or extracellular proteins (reviewed in [34,35]). This is true for Alzheimer’s disease (AD) [36–39], amyotrophic lateral sclerosis (ALS) [40], Parkinson’s disease (PD) [41–43], Huntington’s disease (HD), Lewy body dementia (LBD) [44,45], Niemann-Pick Type C disease [46], and others.

Though inflammation itself may not necessarily serve as the causative factor of pathology, and the primary initiators of inflammation may vary between these diseases, there is a high degree of overlap between their downstream inflammatory mechanisms [33,47,48]. Also, similar patterns of misfolding, aggregation, and spreading of various proteins including amyloid-β (Aβ) peptide, the microtubule-stabilizing protein tau, and α-synuclein, each of which are soluble under normal conditions [49–52], occur across the spectrum of neurodegenerative diseases. Despite these commonalities, the definite identity of the initial pathological stimulus remains elusive [37,39,53]. It is unknown whether inflammation leads to protein accumulation, or vice versa, or if there is some other interplay between these two processes.

Matters are further complicated by the fact that both systemic inflammation (peripheral) and neuroinflammation (within the CNS) are associated with neurodegenerative diseases [33,37,39,54]. Systemic inflammation and neuroinflammation occur on opposite sides of the BBB, which is a layer of endothelial cells lining the vasculature in the brain. The BBB is so carefully structured, selectively permeable, and tightly controlled that for many years it was thought to confer ‘immune privilege’ on the CNS by preventing communication between peripheral and central immune cells [55–57]. However, it is now known that peripheral immune cells occasionally can penetrate the BBB for immunosurveillance purposes, and pro-inflammatory activity by these cells is suggested to be involved in the progression of neurodegenerative diseases [57]. Increased BBB permeability is associated with various neurodegenerative diseases, including AD [58,59]. Importantly, however, communication between the periphery and the CNS also takes place prior to BBB breakdown while the barrier appears to remain intact [48,54,60].

The resident immune cells of the CNS are known as microglia, and they are analogous to macrophages in circulation. Inflammatory insults switch these microglia from a quiescent, anti-inflammatory state known as M2 into one of several possible M1 activation states [33,37,61]. These stimuli may emanate from within the brain itself or they may be communicated from the periphery [48]. Activated microglia impact BBB integrity via modulation of the expression of tight junction proteins [62], and they also produce a variety of pro-inflammatory cytokines including TNF-α and IL-6 that further promote inflammation within the brain [60]. A ‘two-hit’ hypothesis for neuroinflammation has been proposed [47] in which the first ‘hit’ is an initial inflammatory insult such as neurodegeneration-associated proteinopathy, infection, inflammatory cytokines, injury, or ischemia, which activates microglia. Damage to neurons by this activation results in large-scale neuronal release of the intracellular DAMP ATP, which is the second ‘hit’. The high extracellular concentration of ATP activates P2X receptors and potentiates the inflammatory process [47]. Microglial activation is reversible with the resolution of inflammation, but this resolution can be overwhelmed by the prolonged or chronic presence of the initial inflammatory stimulus [33,48]. Bringing ATP concentrations back down to P2Y-activating levels could thus help to prevent or reverse the neuroinflammatory process and promote anti-inflammatory signaling.

## 3. Pathophysiology of AD

In AD in particular, two characteristic hallmarks of pathology are evident in the brains of affected patients, typically originating within the hippocampus and the cerebral cortex. One of these is the presence of ‘senile plaques’ composed mostly of Aβ due to the post-synaptic aggregation and rapid fibrillization of monomers and oligomers of this 4 kDa peptide [33,38,49,63]. The other is the intraneuronal deposition of hyperphosphorylated tau protein to

form 'neurofibrillary tangles' (NFTs) [33,38,49,63]. Activated microglia are often found in the areas surrounding senile plaques in AD [36,37,55,64,65]. The physiological function of A $\beta$  in the healthy brain has not been identified, though it has been suggested that the peptide may play a role in normal synaptic plasticity [49]. Tau, on the other hand, has been implicated in maintaining axonal transport in the neuron by associating with and stabilizing microtubules, and also in indirectly regulating the function of the neuronal N-methyl-D-aspartate (NMDA) receptor via targeting of Fyn kinase to the synapse [49,66,67]. This latter action of tau has been shown to be responsive to administration of A $\beta$  [66], but the specific manner in which A $\beta$  and tau are linked, and why these proteins in particular are affected in AD, remains unknown.

#### 4. Application of a TNAP transport model to the BBB and AD

##### 4.1. TNAP at the BBB and the synapses

TNAP is expressed at high levels at the luminal (circulation) side of the BBB and also at neuronal synapses, particularly within the two major sites of AD pathology, the hippocampus and cerebral cortex [68–70]. Synaptic expression is evident in neurons across various cortical regions, which suggests a possible function for the enzyme in neurotransmission [69–72]. TNAP is overexpressed in BBB endothelial cell models whose barrier functionality has been 're-induced' by co-culture with glial cells, indicating a very important role for TNAP in the maintenance of barrier integrity [73]. The primary activities for TNAP in the BBB and neurons have not yet been established definitively. However, in tissues apart from the brain (e.g. the intestinal enterocyte barrier and microvascular endothelia), the intestinal and tissue-nonspecific isoforms of AP (IAP and TNAP) regulate the long-chain fatty acid (LCFA) transporter CD36, activating it by dephosphorylation to increase uptake of LCFAs across the barrier [74,75]. CD36 is also expressed in the human BBB, where it transports LCFAs into the brain [76], so TNAP in this location may also regulate this process.

AP isoforms have been suggested to play a role in transport systems in the duodenum, jejunum, kidney, and liver as well as in cultured hepatocyte and Caco-2 intestinal epithelial cell lines [77,78]. This is based on the high correlation of AP expression levels with the amount of exchange surface area in each tissue type [78]. Importantly, BBB TNAP has been implicated specifically in the saturable transport of insulin across the barrier from the periphery into the brain by a yet-unknown mechanism [77]. Insulin has been shown to have neuroprotective effects via multiple mechanisms, indicating its integral role in maintaining normal brain function and cognition (reviewed in [79]). Insulin is a known noncompetitive inhibitor of TNAP activity at the BBB [68], which implies a molecular binding relationship to the enzyme. Thus, insulin binding to TNAP may be involved with insulin transport into the brain.

Insulin-like growth factor 1 (IGF-1) is an important modulator of neuronal function [80]. Passage of IGFs from circulation into the brain across the BBB is regulated by IGF binding proteins (IGFBPs), which are present in high levels at this barrier [80–82]. The binding affinity of IGFBPs is regulated by their phosphorylation state, and this has been shown in the placental syncytiotrophoblast barrier to be controlled by the membrane-bound placental isoform of AP (PLAP) [83]. Analogously, TNAP could control the phosphorylation state of IGFBPs at the BBB as well, thereby impacting IGF-1 transport. Under baseline conditions, then, TNAP may participate in and/or regulate the critical uptake of LCFAs, insulin, and IGF-1, among other neurotrophic factors, into the brain.

For these reasons, we suggest that TNAP is essential for proper BBB maintenance, and that under inflammatory conditions, barrier functionality is lost at least in part through the release of TNAP into

circulation from the luminal microvessel membrane in an anti-inflammatory effort to eliminate plasma DAMPs and PAMPs. Phospholipases C/D could cleave the GPI anchor of the enzyme from the membrane, resulting in a detrimental loss of TNAP function at the apical BBB surface. An ensuing lack of sufficient uptake of LCFAs, insulin, IGF-1, and other neurotrophic factors, along with a shortage of DAMP/PAMP dephosphorylation activity at cell membranes, would have disastrous consequences for the brain that could contribute to increased permeability. This implies a crucial need for replenishment of TNAP to keep the barrier intact.

##### 4.2. Transport of IgG and A $\beta$ across the BBB

The neonatal Fc receptor (FcRn) is also expressed at the BBB endothelium, and transcytosis of IgG immune complexes by this receptor, particularly those with A $\beta$ , is extremely important for the normal functioning of the brain [84]. As described in Section 3, aggregation of A $\beta$  in the hippocampus and frontal cortex is well known to be associated with AD [84–86]. Transport of A $\beta$  in both directions across the BBB is critical in the regulation of levels of A $\beta$  within the brain itself, and Zlokovic et al. [84] have proposed in their 'neurovascular hypothesis' that impaired efflux of central A $\beta$  from the brain is a key factor in the pathological accumulation of this protein in the tissue [84–87]. Circulating A $\beta$  in the plasma is imported across the BBB in the luminal-to-abluminal (blood-to-brain) direction primarily by the receptor for advanced glycation end products (RAGE), a member of the immunoglobulin superfamily [84,88,89]. A $\beta$  is cleared from the brain by transport in the abluminal-to-luminal (brain-to-blood) direction by three separate known receptors. The first is the low-density lipoprotein receptor-related protein 1 (LRP-1), located both in neurons and on the abluminal surface of the BBB [84,86,89–91]. The second is P-glycoprotein (P-gp) at the luminal surface of the BBB [85,86,90]. It is proposed that LRP-1 and P-gp act in cooperation to transfer A $\beta$  from the brain to the plasma, with LRP-1 transporting the protein into the BBB endothelial layer at the basolateral membrane and P-gp transporting it out into circulation at the apical membrane [86,90].

The third receptor is FcRn, which is a recycling endocytosis receptor that also can undergo bidirectional transcytosis [84,92–95] in an indirectly Ca<sup>2+</sup>-dependent manner via calmodulin binding [95]. FcRn-mediated A $\beta$  efflux requires the peptide to interact as an antigen in an immune complex with IgG for transport [84,87]. FcRn binds IgG with high affinity between pH 5 and 6.5, with rapid release of ligand occurring as physiological pH is approached [96]. Thus, transport of IgG immune complexes requires their initial internalization by another means prior to association with FcRn within acidic endosomes intracellularly. It is commonly accepted that general fluid-phase endocytosis is responsible for this initial uptake [96,97], but this is still an uncertainty. A major known function of FcRn in epithelial cells is immunosurveillance, as the receptor carries luminal antigens bound to IgG across barriers for presentation to immune cells [93,94,96,98–103]. Due to the FcRn's pH dependence, the directionality of this transport can be dictated by a pH gradient between plasma membranes [104]. In endothelial cells, on the other hand, the major function of FcRn appears to be maintenance of IgG homeostasis by recycling the antibody to the plasma, which is also a pH-dependent process [97,105,106]. However, in BBB endothelial cells, the FcRn also removes central A $\beta$  as an IgG complex transcellularly, depositing it in the plasma for uptake by the liver [84,87].

Under physiological conditions, LRP-1-mediated amyloid clearance is very rapid and appears to be the predominant mechanism for A $\beta$  efflux across the BBB [84,87,107]. However, in animal models, brain capillary expression of both LRP-1 and P-gp has been shown to decline with age and under systemic inflammatory



conditions [84,86,87,90]. Strikingly, while LRP-1 is also downregulated in AD brains, FcRn-mediated clearance of A $\beta$  continues at normal levels independently of aging or AD conditions, and has even been shown to be higher under such conditions in comparison to younger, wild-type control animals [84,87]. In addition, RAGE expression increases with age, contributing to higher brain concentrations of A $\beta$  [84,89]. These observations suggest that during the course of aging and/or the pathogenesis of AD, the brain relies increasingly heavily on FcRn for A $\beta$  clearance across the BBB. The Zlokovic group has proposed amplification of FcRn expression at this barrier as a potential AD therapy [84]. They found that brain perfusion of A $\beta$ -specific IgG in AD-model mice decreases central A $\beta$  levels and RAGE-mediated import of A $\beta$  into the brain from circulation.

To explain this observation, the group put forth a “sink theory” in which the association of A $\beta$  with exogenous IgG in the plasma generates an immune complex concentration gradient across the BBB, facilitating efflux of A $\beta$  from the brain. Meanwhile, a portion of this A $\beta$ -specific IgG enters into the brain, where it complexes with A $\beta$  and engages in the FcRn-dependent efflux thereof across the BBB, a process which is related to IgG concentration [84]. Since, in contrast, depletion of peripheral A $\beta$  via enzymatic degradation by the type II metalloproteinase neprilysin did not result in the enhanced clearance of central A $\beta$  [108], such an effect may be mediated specifically by an IgG-related mechanism rather than by a simple diffusion gradient.

#### 4.3. TNAP-IgG immune complex transport and accumulation of A $\beta$

During the course of their investigations, the Zlokovic group encountered upon analysis of the BBB abluminal membrane a single ~55 kDa protein that binds to A $\beta$ -IgG complexes. They proposed that the FcRn-mediated, IgG-assisted transport of A $\beta$  may require further binding to an additional IgG receptor for initial internalization, represented by this protein band. This finding corroborates the concurrent report by the Ashe group of the presence of significant quantities of an unidentified, soluble ~55 kDa protein in their studies of the effects of soluble and insoluble A $\beta$  on neurodegeneration [109]. This group found via A $\beta$  immunoprecipitation that the unknown protein was not a higher molecular weight aggregate of A $\beta$  and was not responsible per se for the disruption of cognitive function, which they observed in their AD rat model [109]. In later experiments, however, the Ashe group identified an A $\beta$  dodecamer which they designated A $\beta$ \*56 as the entity responsible for this band [110]. While it appears from the data of these authors that there is indeed an A $\beta$  dodecamer present in the ~55 kDa protein band isolated from AD brain tissue, and that this A $\beta$ \*56 species has been observed by others [111], the reason why this band did not initially respond to A $\beta$  immunoprecipitation is unclear.

We propose that this is because in addition to A $\beta$ \*56 in these tissue samples, a different ~55 kDa protein may also be transported by FcRn as an immune complex with IgG, namely TNAP. It remains to be seen whether or not this is the case, but it is tempting to speculate upon since TNAP-IgG immune complexes have been detected in the plasma of patients with various diseases [23,112]. Also, PLAP has been suggested to be involved with binding of IgG from the maternal plasma for transport of the antibody across the placental syncytiotrophoblast barrier due to the observation of PLAP-IgG immune complexes at this membrane [113]. The actual transcytosis of IgG across this barrier is widely regarded to be FcRn-mediated [114–116].

As mentioned in Section 4.1, TNAP is highly expressed at the BBB [68,72] and at neuronal synaptic contacts [70–72]. BBB microvessel TNAP, being found primarily at the luminal membrane of the barrier, is likely not accessible to abluminal IgG/FcRn, particularly

not if it is being solubilized into plasma in an anti-inflammatory measure. However, upon BBB insult, some TNAP has been found at the abluminal membrane of the barrier in association with increased pinocytotic vesicles and channel-like structures in the endothelial cells [117,118]. This TNAP may be able to associate with IgG within the brain, reflecting the relationship between AP and IgG in the syncytiotrophoblast barrier. TNAP-IgG immune complexes may then engage in FcRn-mediated transport to the luminal BBB membrane and/or plasma in a restorative effort to maintain TNAP activity and barrier function. Also, if the normal role of TNAP at this barrier involves insulin transport into the brain [77], it may be that TNAP recycles constitutively between the luminal and abluminal surfaces of the endothelium to a small extent, though this remains to be shown. Alternatively, vesicular neuronal TNAP may be able to associate with IgG for this purpose, accounting for the presence of TNAP at the abluminal membrane. Perivascular and periaxonal spaces within the brain have been predicted to be sufficiently wide for the diffusion of large molecules like antibodies [119].

In any case, it may be that under inflammatory conditions, TNAP-IgG complexes are competing with A $\beta$ -IgG complexes for valuable FcRn binding sites at the abluminal BBB membrane for transport across the barrier. This could interfere with normal efflux of A $\beta$ -IgG complexes from the brain, causing a backlog of A $\beta$  oligomers. Sustained activation of this mechanism by chronic, low-grade inflammation, such as that associated with AD [55,120], may thus be involved in both the loss of BBB integrity and the accumulation of A $\beta$  in this disease. This model may explain the previously mentioned success of A $\beta$ -specific IgG administration in decreasing brain A $\beta$  accumulation [84] and the failure of neprilysin in the same regard [108] with the favoring of A $\beta$ - over TNAP-IgG immune complexes for FcRn-mediated transport due to higher concentrations of the former.

Inflammatory insults and elevated proinflammatory cytokine levels have been related specifically to increased influx and decreased efflux of A $\beta$  across the BBB and consequential amyloid accumulation in the brain tissue [86,91,121]. Peripheral LPS administration has been shown to result in significantly increased circulating proinflammatory cytokine levels and hippocampal A $\beta$  levels by 7 days of daily exposure. Interestingly, while mice develop tolerance to LPS beyond this time point, displaying restored cytokine levels despite continued treatment, A $\beta$  levels remain persistently elevated [122,123]. Peripheral inflammation induced by LPS results in downregulation of brain endothelial LRP-1 despite an increase in neuronal LRP-1 [91]. This increase in neuronal LRP-1 leads indirectly to enhanced amyloid precursor protein (APP) processing into A $\beta$  in brain tissue, while decreased BBB LRP-1 is associated with impaired A $\beta$  efflux and an increase in net A $\beta$  influx [91,124]. These changes collectively promote A $\beta$  accumulation within the brain. Furthermore, they are accompanied by a decreased uptake rate of plasma A $\beta$  into the liver, which is the primary site for its LRP-1-mediated clearance and subsequent degradation [86]. These observations are attributed to an inflammation-associated decrease in LRP-1 expression in the BBB and liver. As mentioned previously in this section, it appears that decreased LRP-1 expression, in aging and in AD at least, is partially compensated for by increased reliance on FcRn-mediated A $\beta$ -IgG complex efflux [84,87].

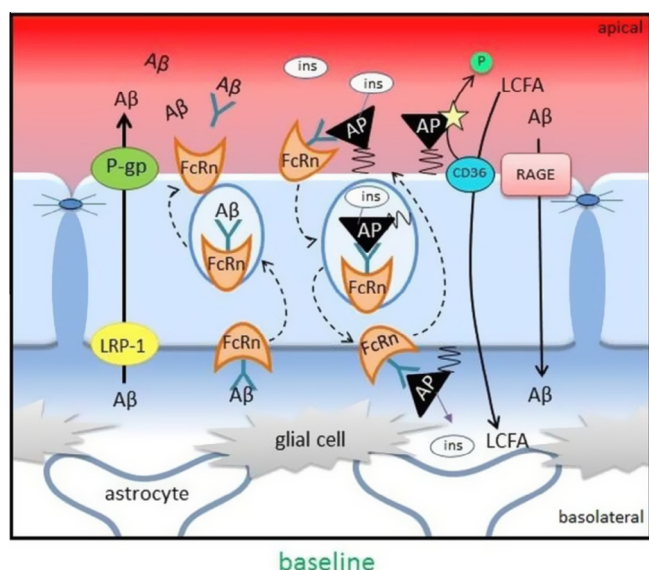
These observations, taken together, support our proposed model in which inflammatory stimuli engage FcRn-mediated transport of displaced TNAP as a complex with IgG in an acute phase immune mechanism. Prolonged low-grade inflammation would lead to continual TNAP immune complex delivery to the plasma with gradual A $\beta$  accumulation as a result. As sustained FcRn-mediated export thus becomes a dominant pathway for anti-inflammatory purposes, LRP-1 expression at the BBB may be

downregulated in response. It may be that the cell executes this immune measure in an attempt to restore homeostasis and resolve inflammation by increasing circulating TNAP concentrations and anti-inflammatory signaling, but that this occurs at the expense of A $\beta$  efflux from brain because LRP-1 is expressed insufficiently and many FcRn binding sites are occupied. It may be that this resolution measure is useful in the short term, but when in operation for an extended period of time, it could underlie the observed relationships between long-term inflammation and the deposition of A $\beta$  in AD.

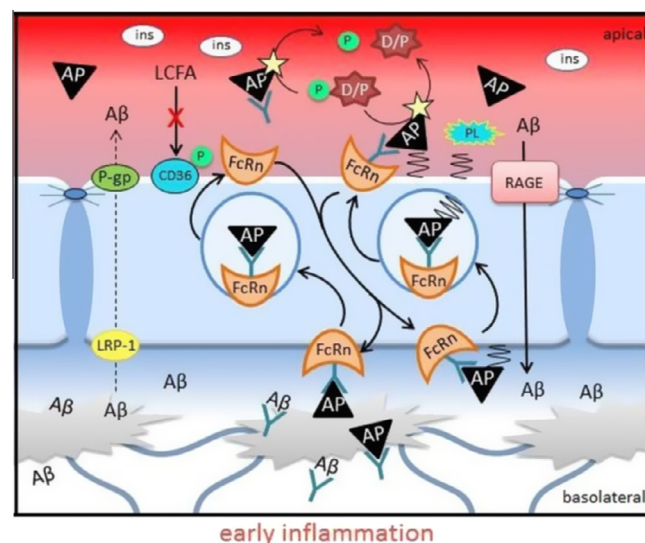
#### 4.4. TNAP-IgG immune complex transport and accumulation of hyperphosphorylated tau

Moreover, such a mechanism simultaneously may offer an explanation for the other hallmark molecular occurrence in AD: the extracellular deposition of hyperphosphorylated tau protein in the brain leading to the formation of intraneuronal neurofibrillary tangles (NFTs). Tau pathology appears to occur downstream of A $\beta$  buildup [125,126]. However, the specific nature of the relationship between phosphorylated tau, originally accumulating intracellularly in the neuronal somatodendritic compartment [52,66], and A $\beta$ , accumulating extracellularly at the postsynapse, remains unknown given their initial spatial separation in the brain tissue [66]. It is only upon degeneration of the neuron that phosphorylated tau is released into the extracellular space [70].

Neuronal membrane-bound TNAP has been shown to be one of the primary tau dephosphorylating enzymes in the brain and a



**Fig. 1. Baseline conditions:** under normal non-inflammatory conditions where there is a fully functional blood–brain barrier (BBB) endothelial layer with intact tight junctions (dark blue ovals), the apical and basolateral sides of the barrier remain completely separate from one another. Transport of molecules from one compartment to the other is tightly regulated. Here, the receptor for advanced glycation end products (RAGE) transporter (pink) imports A $\beta$  from circulation into the brain. GPI-anchored TNAP (black) at the apical membrane serves to dephosphorylate CD36 (turquoise; dephosphorylation activity is indicated by a star). This facilitates uptake of long-chain fatty acids (LCFA) into the brain. Anchored TNAP also functions to bring insulin (ins) into the brain, possibly via neonatal Fc receptor (FcRn)-mediated transcytosis of a TNAP-IgG immune complex as illustrated. Thus, TNAP is found primarily at the apical membrane but a small amount can be found basolaterally at any given time as it recycles. IGF-1 transport is not illustrated. Meanwhile, FcRn (orange) also transports A $\beta$  out of the brain as an IgG complex, but the primary route for A $\beta$  efflux is through the combined activities of low-density lipoprotein receptor-related protein 1 (LRP-1) and P-glycoprotein (P-gp) (yellow and green, respectively). Solid lines indicate primary pathways; dotted lines indicate secondary pathways. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

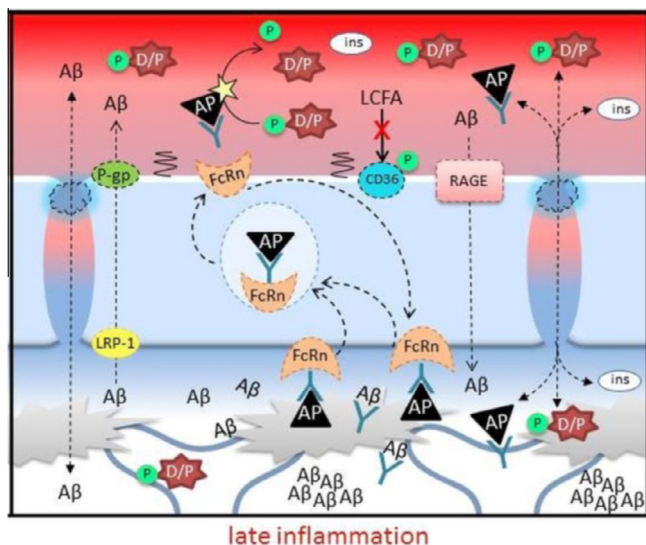


**Fig. 2. Early inflammation:** in the early stages of systemic inflammation prior to BBB breakdown, tight junctions and transport systems are still intact. Phosphorylated damage- and pathogen-associated molecular patterns (DAMPs and PAMPs [D/P, red]) are present in circulation. The primary function of TNAP (black) at this point becomes dephosphorylation (star) of these systemic inflammatory stimuli. TNAP is released from the membrane into circulation for this purpose via cleavage of its GPI anchor by phospholipase C/D activity (PL). Brain uptake of insulin (ins), LCFA, and IGF-1 suffers as a result of insufficient apical membrane-bound TNAP. To make up for this loss, transport of TNAP by FcRn (orange) to the apical membrane is increased at the expense of A $\beta$ -IgG complex efflux. LRP-1 and P-gp (yellow and green) activities decrease under inflammatory conditions while RAGE (pink) activity increases, and A $\beta$  begins to accumulate extracellularly at the brain side of the BBB. The source of TNAP for transport may be the small stock of basolaterally-anchored TNAP or, alternatively, solubilized neuronal TNAP. Sustained transport of TNAP from the brain leads to increased neuronal TNAP expression to maintain tau dephosphorylation activity at the neurons (not illustrated). Eventually, the increased TNAP expression is unable to keep up, and hyperphosphorylated tau begins to accumulate as a result (not illustrated). A $\beta$  and tau pathologies thus can be linked mechanistically to inflammation in AD via a TNAP transport mechanism. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

pivotal mediator of the tau neurotoxicity cycle [70,127]. In an *in vitro* human neuron model, TNAP-dephosphorylated extracellular tau was found to be required for the induction of sustained intracellular calcium increases through membrane muscarinic receptor activation leading to protein kinase rephosphorylation of intracellular tau in the cycle of neurodegeneration [70,127]. This dephosphorylated tau-induced rise in intracellular calcium precedes an increase in TNAP expression, suggesting a regulation of TNAP in neurons by tau protein [70]. Furthermore, the expression and activity levels of TNAP are enhanced in brain tissue from familial and sporadic AD patients independently of aging, and AP dephosphorylating activity is also increased in the plasma of these patients, with plasma activity correlating inversely with cognitive function [70,128]. Continual removal of TNAP from the neuronal membrane and/or the abluminal BBB surface due to increased efflux across the barrier by FcRn in an anti-inflammatory strategy could account for this increased plasma TNAP activity. Neuronal TNAP expression may be increasing in compensation, but eventually unable to keep up with the rate of efflux. Phosphorylated tau would then accumulate in the brain as a result despite increased TNAP expression and activity.

#### 5. Conclusion: AP as a therapeutic agent for the prevention and treatment of AD and other neurodegenerative diseases

In our model (illustrated for AD sequentially in Figs. 1–3), an inflammation-induced switch in the role of TNAP from its baseline



**Fig. 3.** *Late inflammation:* as inflammation progresses, tight junctions break down between the BBB endothelial cells, allowing mixture of the blood and brain compartments. As a result of this free passage, transport pathways decrease in efficacy (indicated by dotted lines). Insufficient TNAP (black) at the apical membrane prevents controlled uptake of insulin (ins) and LCFA, and insufficient TNAP in circulation cannot cope with the high plasma levels of phosphorylated DAMPs and PAMPs (D/P, red). Phosphorylated D/P cross the deteriorating BBB into the brain compartment, where they can activate microglia (gray), leading to neuroinflammation. Meanwhile, FcRn (orange) continues to deliver TNAP to circulation in an anti-inflammatory effort, but suboptimally as the mechanism becomes overwhelmed by phosphorylated D/P. TNAP from within the brain can presumably diffuse paracellularly to plasma as well, but this contributes to insufficient TNAP within the brain. Prolonged inhibition of A $\beta$  efflux furthers the buildup of A $\beta$ , and while monomers and small oligomers can cross the BBB paracellularly, aggregating fibrils cannot do so and remain trapped in the brain. The same is true for aggregates of hyperphosphorylated tau. Circulating AP can enter the brain through the leaky BBB and help to dephosphorylate ATP released from damaged neurons. This would help to halt the progression of inflammation and restore BBB integrity; the same applies to other neurodegenerative diseases even when A $\beta$  and tau specifically are not present. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

involvement in the uptake/transport of molecules at the BBB to a stopgap anti-inflammatory function would mean the release of TNAP from the barrier's luminal surface. Loss of TNAP from the BBB into circulation under these conditions would mean the loss of its inherent activities at the barrier. This would lead to decreased functionality and integrity of the BBB through impaired uptake of LCFAs, insulin, and IGF-1, among other neurotrophic factors. To offset this, and to further promote the anti-inflammatory defense mounted by TNAP, the transport of TNAP from the abluminal BBB surface and/or the neurons may occur through FcRn-mediated transcytosis of the enzyme to the luminal membrane as an immune complex with IgG. This in turn could lead to both accumulation of A $\beta$  and decreased tau dephosphorylating activity within the brain. Sustained activation of this system by chronic, low-grade inflammation could explain the pathology of both A $\beta$  and hyperphosphorylated tau observed in AD. If so, interference with this mechanism to provide sufficient anti-inflammatory AP in circulation, leaving endogenous TNAP to perform its normal functions at the BBB and synapses, could circumvent the need for TNAP transport and thereby maintain barrier integrity. This would prevent accretion of A $\beta$  and tau as well as the downstream neurodegeneration associated with these events.

We thus suggest systemic administration of AP as a therapeutic intervention against the pathology of AD, and that of other neurodegenerative diseases as well. While A $\beta$  and tau pathologies are associated primarily with AD, chronic inflammation and eventual loss of BBB integrity are common across the range of these

diseases. At the point during inflammation that endogenous TNAP is already overwhelmed, and BBB permeability begins to increase and transport systems such as those involved with AD pathology begin to break down as a result, the presence of sufficient AP in circulation could allow for its entry into the brain through the leaky barrier to dephosphorylate the 'second hit' ATP released by neurons damaged by microglial activation. This would then help to prevent and even reverse the progression of inflammation and loss of BBB integrity in neurodegenerative diseases in general. Hence, supplementation of systemic alkaline phosphatase would serve two functions: (1) to overcome/detoxify inducers of chronic systemic inflammation, thereby reducing their impact on BBB TNAP availability, and (2) to combat ongoing neuroinflammatory processes by detoxifying DAMPs and reversing microglial activation to an M2 state as well as deactivating any circulating immune cells which might penetrate the leaky BBB as a consequence of hyper-permeability, tight junction loss, and/or basal lamina degradation.

An AP transport mechanism also would have fundamental implications in terms of insulin signaling in the brain and other tissues under inflammatory circumstances that would relate to insulin-resistant conditions other than AD, including type II diabetes. This possibility for a unifying mechanism between diseases involving both inflammation and impaired insulin signaling with TNAP, other AP isoforms, or even other ectophosphatases at its core provides a very appealing field for further study, and our group is pursuing research to test this hypothesis.

## Conflict of Interest

The authors declare that there are no conflicts of interest.

## Transparency Document

The [Transparency document](#) associated with this article can be found in the online version.

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In loving memory of Wm. B. Pike.

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