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Mini-review

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

Adrianne F. Pike [a,*], Nynke I. Kramer [b], Bas J. Blaauboer [b], Willem Seinen [a,b], Ruud Brands [a,b]

[a] AMRIF B.V., Agro Business Park 10, 6708PW Wageningen, The Netherlands
[b] Institute for Risk Assessment Sciences, Utrecht University, P.O. Box 80177, 3508TD Utrecht, The Netherlands

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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-β 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-β 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.



**Contents**



*Abbreviations:* Aβ, amyloid-β; 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.

* Corresponding author. Tel.: +31 627905021.
*E-mail address:* A.F.Pike@uu.nl (A.F. Pike).

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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