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REVIEW ARTICLE

Alkaline phosphatase: a potential biomarker for stroke and implications for treatment

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Abstract

Stroke is the fifth leading cause of death in the U.S., with more than 100,000 deaths annually. There are a multitude of risks associated with stroke, including aging, cardiovascular disease, hypertension, Alzheimer's disease (AD), and immune suppression. One of the many challenges, which has so far proven to be unsuccessful, is the identification of a cost-effective diagnostic or prognostic biomarker for stroke. Alkaline phosphatase (AP), an enzyme first discovered in the 1920s, has been evaluated as a potential biomarker in many disorders, including many of the co-morbidities associated with stroke. This review will examine the basic biology of AP, and its most common isoenzyme, tissue nonspecific alkaline phosphatase (TNAP), with a specific focus on the central nervous system. It examines the preclinical and clinical evidence which supports a potential role for AP in stroke and suggests potential mechanism(s) of action for AP isoenzymes in stroke. Lastly, the review speculates on the clinical utility of AP isoenzymes as potential blood biomarkers for stroke or as AP-targeted treatments for stroke patients.

Keywords Stroke · Alkaline phosphatase · Biomarker · Tissue nonspecific alkaline phosphatase · Blood-brain barrer

Stroke: Current biomarkers and therapeutics

Stroke

Stroke is one of the leading causes of death and disability in the U.S., accounting for approximately 1 in every 19 deaths (Benjamin et al. 2018). When stroke occurs, oxygen and glucose perfusion are restricted in specific brain regions, leading to cell death and the subsequent loss of memory and motor function. The size of the stroke often correlates with the extent of disability, assessed through a simplified modified Rankin scale questionnaire (Bruno et al. 2013). There are two different types of stroke. Hemorrhagic strokes occur when a weakened blood vessel leaks out into the brain tissue. The second, and most common type of stroke, is known as ischemic stroke, where blood flow to a certain area of the brain is blocked from a blood clot or plaque lesion. Ischemic stroke can be embolic, where a clot or plaque lesion forms in another area within the body then travels and gets stuck in the brain, or thrombotic, where a clot forms within one of the vessels that supplies blood to the brain (Dirnagl et al. 1999).

Strokes commonly occur in the elderly and occur more often in women than men. Risk factors for stroke include: hypertension, high cholesterol, atherosclerosis, smoking, excessive drinking, and diabetes. Although reperfusion of the ischemic brain is the goal for treatment, intense inflammation and further tissue damage occurs during the reperfusion process. Clinical evidence shows that an evolution of brain injury often occurs in the hours to days following a stroke, which allows only a small time-frame for successful therapeutic intervention. Within minutes of a stroke, the neurons at the core of the infarct that are closest to the region of oxygen or glucose deprivation undergo necrotic cell death. The necrotic core is surrounded by an area of tissue, the penumbra, that is less severely impacted by the lack of blood flow and remains metabolically active; functionality of the penumbra may be lost, but is salvageable. Clinicians focus on restoring the functionality of the penumbra region as part of their stroke treatment (Dirnagl et al. 1999; Dirnagl and Endres 2014; Benjamin et al. 2018).

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Stroke biomarkers and therapeutics

Although numerous biomarkers have been assessed for their use in stroke, none so far have proven to be reliable enough to use as a standard in the clinic. Several current or emerging stroke biomarkers are described in Table 1. There is a critical need to develop faster and less expensive diagnostic testing tools for stroke, such as the use of blood biomarker panels. Despite growing efforts to identify blood biomarkers that may be useful for the determination and differentiation of stroke, there are no current specific biomarker recommendations for use in the clinic. Likewise, stroke therapeutics are limited. Since the approval of recombinant tissue plasminogen activator (rtPA) in 1996, no other drug has received FDA approval to treat stroke (The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group 1995; Adams et al. 1996; Report of the Quality Standards Subcommittee of the American Academy of Neurology 1996). The quest for new stroke therapeutics has been plagued by numerous clinical trial failures, due in large part to the discrepancy between the positive results in preclinical animal models of stroke, and the subsequent negative findings when the same therapeutics are tested in human clinical trials (Bushnell et al. 2006; Jickling and Sharp 2015). One possible candidate for use as a diagnostic and prognostic marker for stroke is alkaline phosphatase (AP). Several studies have indicated that AP may be actively beneficial or detrimental in many inflammatory and ischemic settings (Heemskerk et al. 2009; Davidson et al. 2012; Shimizu et al. 2013a; Liu et al. 2016; Gdara et al. 2018). This review will discuss the practicality of exploring AP as a potential marker for stroke and how AP can be manipulated for therapeutic purposes.

Alkaline phosphatase

Alkaline phosphatase genetics and cell biology

Alkaline phosphatase (AP) was first discovered in 1923, when Dr. Robert Robison described the presence of an enzyme abundant in animal bone that rapidly hydrolyzed hexosemonophosphoric acid into phosphoric acid (Robison 1923). AP has since been shown to play a significant role in human bone mineralization, confirmed by many cases of hypophosphatasia, a rare metabolic inherited disease caused by a mutation in the *ALPL* gene (Moore et al. 1990; Whyte et al. 2009; Barvencik et al. 2011). There are four isoenzymes of AP in humans, i.e. intestinal (IAP), placental (PLAP), germinal (GCAP), and tissue nonspecific (TNAP) (Millan 1986; Weiss et al. 1986; Berger et al. 1987; Millan and Manes 1988), which can be reviewed in (Van Hoof and De Broe 1994; Buchet et al. 2013). The first three isoenzymes are expressed in the tissues for which they are named and each is encoded by a unique homologous gene loci in humans: *ALPI*, *ALPP*, *ALPPL2*, and *ALPL* (Harris 1990; Buchet et al. 2013). The TNAP protein, also known as bone/liver/kidney AP, is expressed by a variety of tissues including multiple cell types in the brain. TNAP is the most abundant isoenzyme collected from blood, where approximately 50–60% is derived from bone, 30% from the intestines, and 10–20% from the liver (Moss 1982).

APs belong to the ectophosphatase enzyme family and are localized in multiple mammalian cells and tissues (Bannister and Romanul 1963; Kang and West 1982; Paiva et al. 1983; Mori and Nagano 1985; Van Hoof and De Broe 1994; Champion et al. 2003). This class of enzymes is anchored on the cell plasma membrane surface by a glycosylphosphatidylinositol (GPI) moiety which allows them to act on substrates in the extracellular space. APs can be localized in the lipid rafts of the plasma membrane outer leaflet via the C-terminus to the GPI, found as a soluble protein in the serum, or as a vesicle-associated protein in the extracellular space. GPI-anchored AP proteins can be shed from the plasma membrane by cleavage from phosphatidylinositol-phospholipases to take on the soluble form in blood (Low and Zilversmit 1980; Low 1987).

Abnormal levels of AP can result in hypophosphatasia (Waymire et al. 1995; Razazizan et al. 2013; Sebastián-Serrano et al. 2016). Thus, AP has a well-characterized role in skeletal mineralization, and speculation into other physiological function(s) of AP enzymes has generated the most interest with regard to host defense. The role in inflammation is due, in part, to its ability to neutralize endotoxins through dephosphorylation of the lipid-A moiety converting it to the non-toxic monophosphoryl product, and it may target bacterial components like CpG DNA and flagellin (Poelstra et al. 1997a, b; Chen et al. 2010). Similarly, AP also deactivates ATP, which when upregulated can act as an immunological danger signal, while maintaining homeostasis of gut bacteria (Poelstra et al. 1997a; Malo et al. 2010; Peters et al. 2015). Figure 1 summarizes AP's actions in the periphery.

Another complication of abnormal AP serum levels in *Akp2* (mouse TNAP gene) null mice is epilepsy. Nearly three decades after its initial discovery, Shimizu showed histochemical evidence of TNAP in the nervous system of several animal models (Shimizu 1950). However, the roles of TNAP in neurological disorders remains poorly understood. Since TNAP has been shown to interact with multiple substrates and molecules, it is highly likely that TNAP exhibits multiple functions in the brain (Waymire et al. 1995; Whyte et al. 1995; Ermonval et al. 2009). Depending on the cell type, TNAP can be transiently or constitutively expressed within the central nervous system,

Table 1 Current or potential biomarkers as diagnostic or prognostic tools for stroke

Biomarker Group	Molecule or Cell	Diagnostic Ability	Prognostic Ability	Reference
Neurotropic Factors	Brain-derived neurotropic factor (BDNF)	↑ at stroke onset	↓ = poor prognosis	(Gandolfi et al. 2017)
Myokines	Irisin		↑ = good prognosis	(Gandolfi et al. 2017)
	Myostatin	↑ = muscle wasting		(Gandolfi et al. 2017)
	Follistatin-like 1 (FSTL1)		↑ = good prognosis	(Gandolfi et al. 2017)
Cytokines	IL-6, TNF-α, IL-10, IL-4, IL-17, IL-23, TGF-α, IL-15, IL-19, IL-33, IL-1β	↑ at stroke onset	Varies	(Beghetti et al. 2003; Sonderer and Katan Kahles 2015; Bonaventura et al. 2016; Gandolfi et al. 2017)
Chemokines	C-X-C motif chemokine (CXCL)12; C-X3-C motif chemokine ligand (CX3CL)1; and monocyte chemoattractant protein (MCP)-1	↑ at stroke onset	Varies	(Bonaventura et al. 2016)
Neuropeptides	Neuropeptide Y		↑ = good prognosis	(Gandolfi et al. 2017)
	Proenkephalin		↑ = poor prognosis	(Gandolfi et al. 2017)
Growth Factors	Vascular endothelial growth factor (VEGF)	↑ at stroke onset		(Gandolfi et al. 2017)
Immune Cells	$CD4^+CD28^-$ T cells		↑ = poor prognosis	(Gandolfi et al. 2017)
	Regulatory T cells (Tregs)	Peripheral pattern changes after stroke	↑ = good prognosis	(Gandolfi et al. 2017)
	Natural Killer (NK) cells	↑ in brain at stroke onset		(Gandolfi et al. 2017)
	T and B Lymphocytes; $CD4^+$ & $CD8^+$ T cells; γδ-T cells	↑ at stroke onset; peripheral pattern changes after stroke		(Gandolfi et al. 2017; Bonaventura et al. 2016)
	Microglia	↑ at stroke onset		(Bonaventura et al. 2016)
	Neutrophils	↑ at stroke onset		(Bonaventura et al. 2016)
	Dendritic cells	↓ during stroke		(Gandolfi et al. 2017)
Protein & Enzyme	CRP, GTT, GPT, bilirubin	↑ at stroke onset	Varies; typically ↑ = poor prognosis	(Beghetti et al. 2003; Pineda et al. 2008; Tang et al. 2013; Luo et al. 2013; Muscari et al. 2014; Sonderer and Katan Kahles 2015; Bonaventura et al. 2016)
	AP	Usually ↑ at stroke onset, but some variation	↑ = poor prognosis	(Cheung et al. 2008; Metwalli et al. 2014; Muscari et al. 2014; Ryu et al. 2014; Lee et al. 2015; Schiff et al. 2016)
MicroRNAs	miRNA-320b	↓ = ↑ risk factor of carotid atherosclerosis		(Gandolfi et al. 2017)
	miRNA-146a, −181b, and -30a	Varies	↓ = ↑ neuroprotection	(Martinez and Peplow 2016; Gandolfi et al. 2017; Khoshnam et al. 2017)
	miRNA-107, −128b, and − 153	↑ at stroke onset		(Martinez and Peplow 2016; Khoshnam et al. 2017)
Reactive Oxygen Species	Antioxidant enzymes	↑ at stroke onset = redox imbalance		(Bonaventura et al. 2016; Khoshnam et al. 2017)
Damage Associated Molecular Patterns (DAMPs)	Toll-like receptors (TLRs); neutrophil calcium influx	↑ at stroke onset		(Bonaventura et al. 2016)

Key: ↑ = increase; ↓ = decrease

which suggests multiple mechanisms of gene expression across the many cell types in the brain and spinal cord (Narisawa et al. 1994; MacGregor et al. 1995; Fonta 2004; Langer et al. 2008). Some data suggest that TNAP may play a role in neurotransmitter metabolism (Fonta 2004; Fonta et al. 2005; Balasubramaniam et al. 2010), and Hanics et al. used TNAP null mice to show that TNAP deficiency leads to decreased brain myelination and synaptogenesis. These findings suggest that TNAP plays an important role in brain development and that TNAP deficiency can contribute to many forms of neurological dysfunction, including epilepsy (Hanics et al. 2012). Figure 2 depicts numerous presumed functions of AP in the CNS.

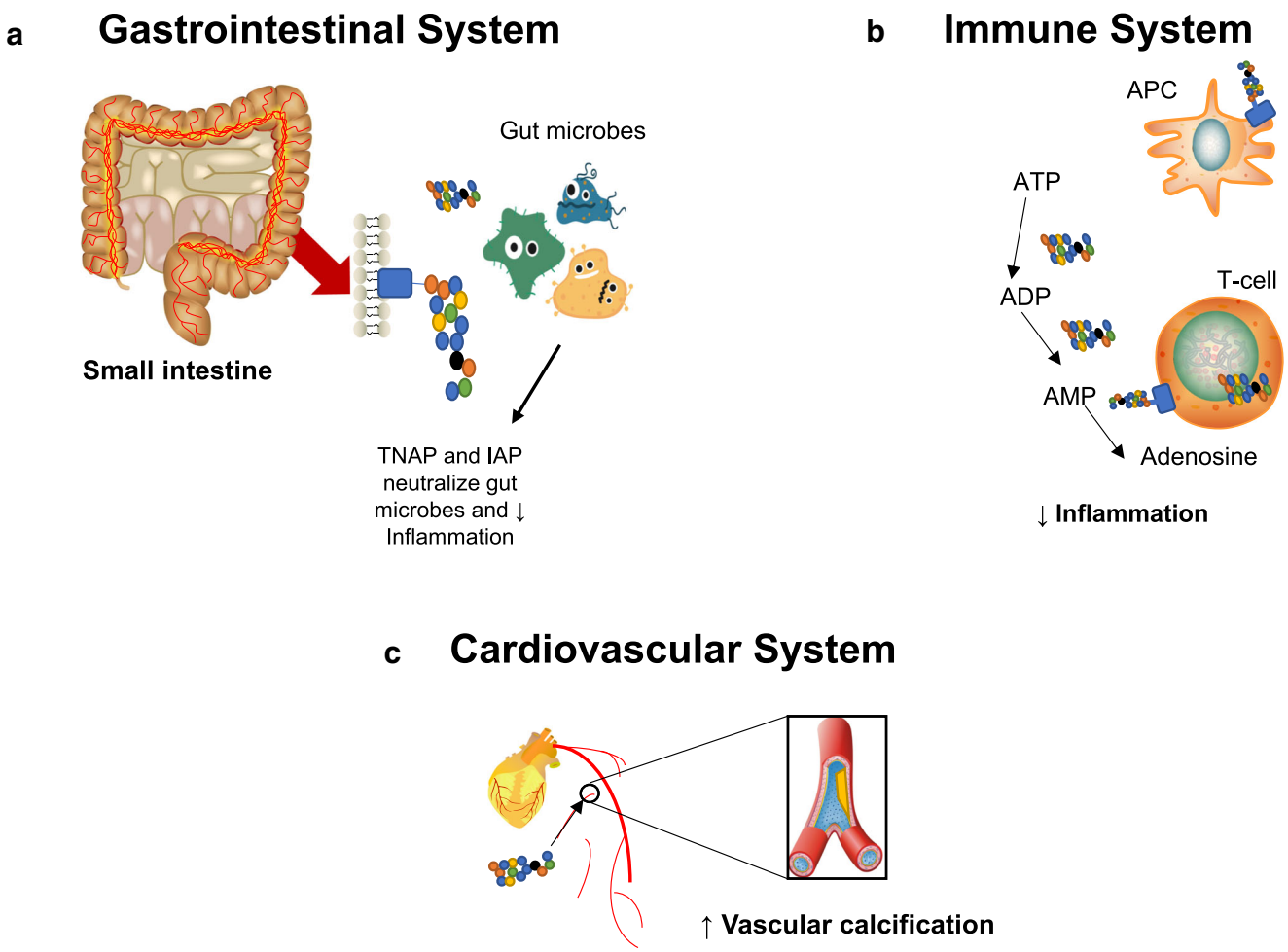

Fig. 1 Role of alkaline phosphatase isoenzymes in the periphery: AP plays an important role in the physiology and pathophysiology of many organ systems. AP's actions in the gastrointestinal, immune, and cardiovascular systems are most relevant to the systemic immune response in ischemic stroke. **a** In the gastrointestinal system, both TNAP and intestinal AP play an important anti-inflammatory role by neutralizing gut microbes. **b** Immune system: Numerous peptides, lipids, and other molecules are recognized by antigen-presenting cells (APC) to activate T cells in the periphery. During T-cell activation adenosine triphosphate (ATP) is released, contributing to the inflammatory environment. TNAP can convert ATP to the anti-inflammatory molecule adenosine through stepwise conversion of ATP to adenosine diphosphate (ADP) and adenosine monophosphate (AMP). **c** Cardiovascular system: An excess of bone AP contributes to vascular calcification, leading to stiff muscle walls and, eventually, atherosclerosis

Alkaline phosphatase as a biomarker for stroke

Serum alkaline phosphatase as a diagnostic tool

Normal blood AP levels vary depending on sex and age, although AP levels typically display a wide range within these respective groups (Fenuku and Foli 1975; Lester 1977; Molla et al. 1990; Magnusson et al. 1995; Zierk et al. 2017; Wanjian et al. 2017; Li et al. 2018). For example, naturally high levels of AP are seen in children because their bones are still growing. Thus, clinicians and researchers rely on an average range of "normal" AP levels rather than a specific number. In general, abnormal AP levels are indicative there is some condition or disorder that has disrupted homeostasis. Some temporary conditions may also affect AP levels, including pregnancy, bone fractures, and taking specific medications (Herbeth et al. 1981; Rodin et al. 1989; Okesina et al. 1995; Choi and Pai 2000; Sadighi et al. 2008). For example, pregnancy can cause AP levels to be elevated 2–3 times that of normal due to an increase in placental AP (Okesina et al. 1995; Choi and Pai 2000). Alternatively, a patient's serum total AP levels can also be increased following a meal due to an increase in the intestinal isoenzyme; however, this is typically a very transient elevation that quickly returns to normal levels if the patient is otherwise healthy (Sukumaran and Bloom 1953; Khan et al. 2016).

Elevated levels of AP are also indicative of numerous disorders including excessive skeletal mineralization, Paget's disease, tumors, and, potentially, Alzheimer's disease (AD) (Naik et al. 1977; Lampl et al. 1990; Vardy et al. 2012). The magnitude of AP elevation tends to reflect the extent of dysfunction. Typically, AP tends to be most markedly elevated

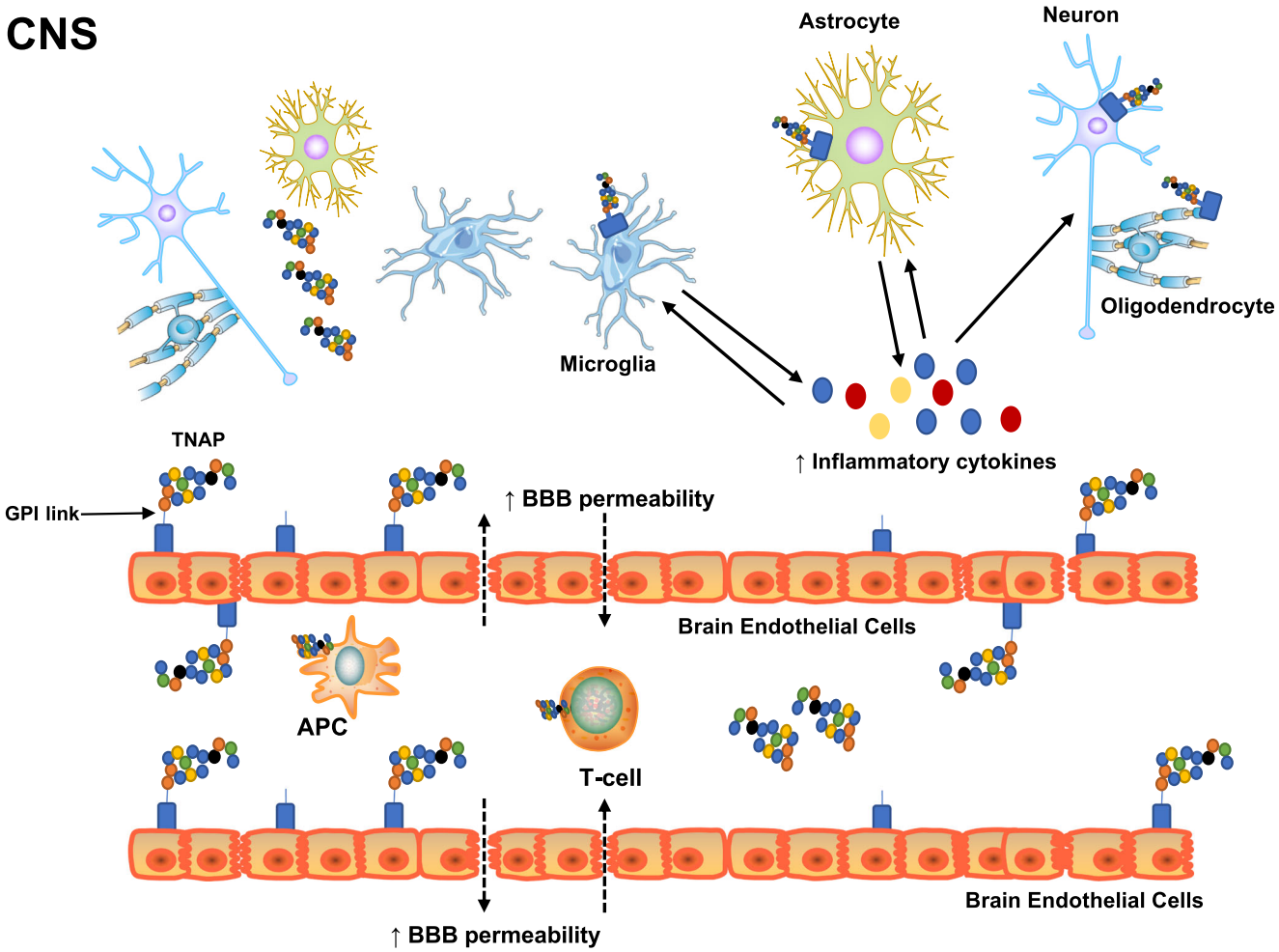

Fig. 2 Role of tissue nonspecific alkaline phosphatase (TNAP) in the central nervous system: TNAP is expressed in neurons, microglia, astrocytes, oligodendrocytes, and is highly expressed in brain endothelial cells. TNAP is localized in the lipid rafts of the plasma membrane outer leaflet via its C-terminus to the GPI. It can also be found as a soluble protein in the serum or as a vesicle-associated protein in the extracellular space. TNAP may have a role in blood-brain barrier (BBB) breakdown, neuroinflammation, and vascular dysfunction in stroke and other neurological disorders. Inflammatory mediators such as reactive oxygen species (ROS), proteases, and inflammatory cytokines, promote the breakdown of junctional proteins at the BBB. The loss of junctional proteins weakens the BBB and allows activated T cells, antigen-presenting cells (APC), other leukocytes, and pro-inflammatory mediators to traverse the BBB, with bidirectional movement between the brain parenchyma and cerebral circulation. These mechanisms play an important role in the pathophysiology of ischemic stroke and other neuroinflammatory disorders

due to hepatic obstruction, hepatitis, and other liver diseases (Schlaeger 1975; Paritpokee et al. 1999). During certain conditions, AP levels can increase greater than 3-fold and are measured at 10–12 times the upper limit of normal, particularly in bone disorders (Mayo Clinic 2017; Moss 1982; Jassam et al. 2009; Teitelbaum et al. 2011). Interestingly, AP levels are generally normal during osteoporosis (Kelly et al. 1967). Although less clinically explored, observations of abnormal AP serum levels have also been associated with neurological disorders such as AD (Kellett et al. 2011; Vardy et al. 2012).

The standard clinical chemistry AP tests used in laboratory medicine report total AP enzyme activity rather than the amount of total AP protein. For simplicity, this review will use AP levels to refer to AP activity, as is commonly done in clinical practice. Thus, when used as part of a typical comprehensive metabolic panel, this test represents the sum of all soluble AP isoenzyme activity in serum or plasma. Clinicians often interpret elevated levels of AP with pathological conditions related to bone and liver disorders because the majority of AP detected in the blood comes from the liver and bone; however, this test can also indicate intestinal or parathyroid disease (Mayo Clinic 2017; Posen et al. 1967; Yoneda et al. 1988; Tuin et al. 2009). Additional testing can also be performed to determine the source of possible dysregulation, including liver (L1 and L2), bone (B1, B2, B/I, and B1x), intestinal, and placental tissues. Normal AP ranges for these various isoenzymes also differ. Clinicians can continue to monitor elevated AP levels as the patient undergoes treatment to indicate that a treatment may or may not be working (Wolf 1978; Van Hoof and De Broe 1994).

Alkaline phosphatase as a putative biomarker for neurological injury

Researchers have used AP activity as a brain microvessel marker in primates for decades, and its presence has been described in the cerebral parenchyma of both young and old monkeys (Friede 1966; Bell and Ball 1985; Anstrom et al. 2002; Fonta and Imbert 2002; Fonta 2004; Fonta et al. 2005). Primate, mouse, rat, and human brains have been used to demonstrate that expression of TNAP activity can be found in brain endothelial cells and neurons (Charegaonkar and Rindani 1961; Meyer 1963; Friede 1966; Narisawa et al. 1994; Nishihara et al. 1994; Fonta 2004; Ermonval et al. 2009; Brun-Heath et al. 2011). Numerous studies indicate that AP RNA expression, protein levels, or enzyme activity may vary significantly between primates and rodents. In primate brains, AP activity can be detected in one or a few cortical layers, but not in all areas, while in rodent brains, AP activity is more scattered with variable levels of intensity (Brun-Heath et al. 2011).

Several studies have demonstrated that TNAP is elevated in many neurological disorders, including some types of brain injury (Yamashita et al. 1989) and AD (Gong et al. 1993; Kellett et al. 2011; Vardy et al. 2012). TNAP has been shown to play a role in tau phosphorylation. Vardy et al. showed that TNAP is increased in both human brain tissue and plasma from patients with familial and sporadic AD (Vardy et al. 2012). Also, in patients with various brain injuries, the concentration of serum AP correlated with functional outcome and increased TNAP had an inverse correlation with cognitive function (Yamashita et al. 1989; Kellett et al. 2011; Vardy et al. 2012). Among patients with brain tumors, those that also had pulmonary carcinomatous meningitis were found to have elevated AP levels in their cerebrospinal fluid (CSF), while AP concentrations in control patients with epilepsy and stroke were decreased in comparison to the brain tumor group (Lampl et al. 1990). Increased liver AP levels were described in patients with nontraumatic intracranial hemorrhages (Meythaler et al. 1998).

Elevated serum AP levels may also underscore brain-peripheral immune interactions during stroke, as Muscari et al. found evidence that the liver participates in the response to acute ischemic stroke by releasing enzymes (Muscari et al. 2014). AP levels have been shown to increase in relation to large-volume cerebral white matter hyperintensities and may be associated with multi-cerebral microbleeds in ischemic stroke patients (Ryu et al. 2014; Lee et al. 2015; Liu et al. 2016). While Lee et al. suggest that increased serum AP may be a marker for impaired cerebral microcirculation, Liu et al. were unable to replicate these results in their study (Lee et al. 2015; Liu et al. 2016). The authors state these differences may be due to the small number and clinical characteristics of their subjects, as well as the statistical methods used in both studies (Liu et al. 2016). In contrast, a smaller number of studies have reported a decrease in serum TNAP in other neurological disorders. For example, TNAP levels were found to be significantly decreased in traumatic brain injury (Arun et al. 2015). Additionally, AP activity was found to be neither significantly elevated nor reduced in aging patients alone (Vardy et al. 2012) or in patients with multiple sclerosis (Hanna et al. 1997; Tremlett et al. 2006). These findings underscore the importance of continued research to elucidate the mechanisms under which AP or TNAP levels are elevated or reduced in neurological disorders.

Alkaline phosphatase as a diagnostic and prognostic stroke biomarker

Prior clinical studies have explored AP as a diagnostic and prognostic marker to assess stroke risk by correlating indices of AP activity such as: dysfunctional bone metabolism (Barnadas et al. 2014; Namba et al. 2017), cardiovascular disease (Webber et al. 2010; Kim et al. 2017; Makil et al. 2017), cancer (Giessen et al. 2014; Barnadas et al. 2014; Hammerich et al. 2017) and periodontitis (Kunjappu et al. 2012). More importantly, elevated AP levels in stroke patients have been correlated with stroke severity and hypertension (Pratibha et al. 2014; Tan et al. 2017). While the underlying molecular mechanisms to support this association are unclear, other studies have provided additional support for this observation. In patients with coronary artery disease who underwent percutaneous coronary intervention, those with the highest AP levels had the greatest risk of 3-year mortality or secondary outcomes (cardiac mortality, nonfatal myocardial infarction, stent thrombosis or stroke) (Ndrepepa et al. 2017). A study using a cohort of patients with preserved kidney function reported AP as an independently useful tool for predicting mortality and stroke recurrence (Zong et al. 2018). Another study of acute ischemic stroke patients revealed that patients within the highest serum AP quartile had the highest incidence of early mortality (Zhong et al. 2018). Lastly, another cohort of patients who experienced a transient ischemic attack showed that those with increased serum AP levels on admission were more likely to have subsequent ischemic stroke events (Uehara et al. 2018). A smaller minority of studies do not support any associations between AP serum and stroke. For example, AP levels did not correlate with extracranial or intracranial arterial stenosis patients with ischemic stroke (Kim et al. 2013). Overall, evidence from most reported studies suggests a significant association between AP and various stroke outcomes. Table 2 describes the major direct and indirect mechanisms that support a role for elevated AP levels in the pathophysiology of stroke.

The majority of AP biomarker studies have explored the use of AP as a prognostic tool. Nearly 30 years ago, Yamashita et al. suggested AP may be useful in predicting prognosis of brain damage in patients with postresuscitation encephalopathy, ruptured cerebral aneurysms, acute subdural hematoma

Table 2 Direct and indirect effects of stroke on alkaline phosphatase levels

Condition	Mechanism Related to Stroke	Reference
Ischemia/hypoxia	↑ cellular stress ➔ ↑ ATP release ➔ ↑ tissue damage	(Beghetti et al. 2003; Kunutsor et al. 2014; Peters et al. 2014; Khoshnam et al. 2017)
Inflammation	↑ cellular stress ➔ ↑ ATP release ➔ ↑ tissue damage	(Kunutsor et al. 2014; Peters et al. 2014; Khoshnam et al. 2017)
	↑ inflammatory cytokines ➔ ↑ tissue damage	(Beghetti et al. 2003; Kunutsor et al. 2014; Peters et al. 2014; Bonaventura et al. 2016; Khoshnam et al. 2017)
	↑ NO levels ➔ ↑ tissue damage	(Kunutsor et al. 2014; Peters et al. 2014; Bonaventura et al. 2016; Khoshnam et al. 2017)
Liver damage	↑ enzyme release	(Muscari et al. 2014)

and contusion, and non-traumatic intracerebral hemorrhage (Yamashita et al. 1989). A large retrospective study assessing serum AP levels in primary sclerosing cholangitis patients at the time of diagnosis and 1 year after diagnosis demonstrated that AP may hold prognostic value in prediction of endpoint-free survival (de Vries et al. 2016). Clinical studies have shown that increased AP is associated with risk of cardiovascular disease, one of the many risk factors for stroke (Tonelli et al. 2009; Park et al. 2013; Wannamethee et al. 2013; Kunutsor et al. 2014). Elevated AP levels are correlated with more vascular deaths and recurrent vascular events, suggesting that AP may be a predictor for mortality in stroke patients (Pratibha et al. 2014; Tan et al. 2017). Abnormal AP has been associated with many of the risk factors leading to stroke, including heavy drinking (Ebuehi and Asonye 2007; Shimizu et al. 2013a), obesity (Menahan et al. 1985; Golik et al. 1991), and hypertension (Shimizu et al. 2013b). Elevated AP has been shown to correlate with poor functional outcome and mortality in cardiovascular disease (Park et al. 2013; Wannamethee et al. 2013; Karabulut et al. 2014; Kunutsor et al. 2014) and in stroke patients (Ryu et al. 2010; Kim et al. 2013; Tan et al. 2016). Investigators theorize that the negative association between AP levels and stroke outcome may be linked to the fact that increased AP levels are associated with increased inflammation and enhanced vascular calcification leading to atherosclerosis (Tonelli et al. 2009; Kim et al. 2013; Ryu et al. 2014). Preclinical and clinical studies can be designed to address this question.

Alkaline phosphatase-based therapeutics in stroke

Therapeutic administration of alkaline phosphatase

Exogenous administration of AP has been shown to have beneficial effects on the outcome of numerous inflammatory disorders in humans and animal models of the associated diseases, including sepsis (Ebrahimi et al. 2011; Heemskerk et al. 2009; Verweij et al. 2004; Pickkers et al. 2009), ulcerative colitis (Lukas et al. 2010; Tuin et al. 2009), necrotizing enterocolitis (Whitehouse et al. 2010), and multiple sclerosis (Huizinga et al. 2012). These studies and a number of others which have shown positive disease outcomes using AP therapeutics are described in Table 3. For example, pre-symptomatic AP administration reduced signs of neurological distress in experimental autoimmune encephalomyelitis (EAE) mice (Huizinga et al. 2012). Systemic inflammation is also common after surgery and often complicates surgical outcomes. In some cases, exogenous administration of AP may be useful to reduce post-operative care requirements. Davidson et al. showed that AP's ability to neutralize inflammatory substrates illustrates that it may be protective against systemic inflammation in post-operative patients (Davidson et al. 2012). Oral administration of AP to ulcerative colitis patients for 1 week also improved clinical response scores and decreased CRP levels (Lukas et al. 2010). Alternatively, intravenous administration of AP decreased plasma creatinine levels in patients with renal complications from severe sepsis or septic shock (Heemskerk et al. 2009; Pickkers et al. 2012). Phase II clinical trials have already shown the benefits of using bovine-derived intestinal AP in a subset of critically ill patients (Heemskerk et al. 2009). Administration of a human recombinant AP (recAP) consisting of a placental/intestinal AP hybrid resulted in positive phase I clinical trial outcome in a subset of septic patients (Kiffer-Moreira et al. 2014; Peters et al. 2016b), that is supported by effective recAP therapeutic efficacy from preclinical models (Peters et al. 2016a, 2017). Thus, the use of TNAP or recombinant AP molecules may provide a viable therapeutic option for patients as well as provide insights on AP's mechanism(s) of action in cerebrovascular disease.

AP therapeutic inhibition of alkaline phosphatase

In contrast, a smaller set of studies have proposed a therapeutic approach that inhibits TNAP. An emerging concept which

Table 3 Positive Therapeutic Outcomes in Preclinical and Clinical AP Studies

Type of AP Therapy	Study Population	Injury or Disease Model	Outcome	Ref.
AP Administration				
PLAP	Mouse	LPS	PLAP administration improved sepsis survival, possibly by halting its' development	(Bentala et al. 2002)
PLAP	Mouse	LPS	PLAP treatment improved survival and lowered NO levels in septic mice	(Verweij et al. 2004)
IAP	Mouse & pig	LPS	IAP administration attenuates LPS toxicity up to 80%, resulting in increased survival and inhibits differentiation of white blood cell and thrombocyte counts	(Beumer 2003)
IAP	Mouse	Sepsis	IAP treatment reduced local and systemic inflammatory responses, as well as distant damage in the liver and lungs	(van Veen et al. 2005)
IAP	Sheep	Sepsis	Administration of IAP in fecal peritonitis-induced septic shock improved gas exchange, decreased blood IL-6 levels, and increased survival time	(Su et al. 2006)
IAP	Phase IIa clinical trial	Sepsis	Infusion of IAP in severe sepsis and septic shock patients inhibits the upregulation of renal iNOS, leading to reduction of NO metabolite production and attenuated tubular enzymuria, resulting in overall improved renal function	(Heemskerk et al. 2009)
IAP	Randomized, double-blind, placebo-controlled clinical study	Sepsis	IAP administration significantly improved renal function in septic patients	(Pickkers et al. 2009)
IAP	Rat	Inflammatory bowel disease	IAP treatment alleviates epithelial layer damage associated with DSS in rat intestines	(Tuin et al. 2009)
IAP	Open-label, first-in-patient exploratory trial	Ulcerative colitis	IAP administration was associated with short-term improvement in UC disease activity	(Lukas et al. 2010)
IAP	Rat	NEC	Supplemental IAP has a protective role in experimental NEC	(Whitehouse et al. 2010)
IAP	Mouse	Antibiotic treatment	IAP supplementation increased growth of commensal bacteria leading to restored gut microbiota lost to antibiotic treatment	(Malo et al. 2010)
IAP	Mouse	Sepsis	IAP treatment enhanced survival and reduced organ damage in septic mice	(Ebrahimi et al. 2011)
IAP	Phase IIa prospective randomized, double-blind, placebo-controlled clinical trial	Sepsis and AKI	Overall, IAP treatment improves renal function in patients with severe sepsis or sepsis shock with AKI	(Pickkers et al. 2012)
IAP	Rat	Inflammatory bowel disease	Intrarectally administered IAP in models of rats colitis resulted in a lower colonic weight and tissue damage score; normalized expression of neutrophil markers and IL-1β; and counteracted bacterial translocation	(Martínez-Moya et al. 2012)
IAP	Mouse	Multiple Sclerosis	Pre-symptomatic treatment of EAE with IAP reduces neurological symptoms	(Huizinga et al. 2012)
IAP	Rat	NEC	IAP supplementation decreased histologic injury scores and barrier permeability in the ileum of rat pups with NEC	(Rentea et al. 2012)
IAP	Mouse	Metabolic syndrome	IAP supplementation inhibited absorption of endotoxins and improved the lipid profile in mice, resulting in prevention or reversal of metabolic syndrome	(Kaliannan et al. 2013)
IAP	Rat	NEC	IAP treatment decreased iNOS and TNF-α expression, and decreased LPS translocation into the serum of infant rats	(Rentea et al. 2013)
IAP	Rat	NEC	IAP supplementation decreased intestinal injury and inflammation, including TNF-α, IL-6 and iNOS by LPS in preterm rat intestine	(Heinzerling et al. 2014)
IAP	Mouse	Antibiotic-associated infections	Antibiotics+IAP oral supplementation resulted in weight maintenance, reduced clinical severity, reduced gut inflammation, and improved survival following infection	(Alam et al. 2014)
recAP	Rat	LPS	recAP treatment has renal protective effects from LPS-induced damage	(Peters et al. 2015)

Table 3 (continued)

Type of AP Therapy	Study Population	Injury or Disease Model	Outcome	Ref.
recAP	Rat	Renal ischemia and reperfusion; LPS	recAP exerted a clear renal protective anti-inflammatory effect	(Peters et al. 2016a)
AP Inhibition				
Levamisole	Prospective clinical trial	Colon cancer	The addition of levamisole to 5FU-adjuvant therapy improved survival in stage II and III colon cancer patients	(Taal et al. 2001)
L-Phen	Rat	LPS	Suggest that IAPs in the gastrointestinal tract reduce LPS content in serum	(Koyama et al. 2002)
SBI-425	Mouse	Medial vascular calcification	TNAP inhibition significantly reduced aortic calcification and cardiac hypertrophy, and extended lifespan over vehicle-treated controls	(Sheen et al. 2015)
SBI-425	Mouse	Hypophosphatasia	TNAP inhibition reduces calcium and lipid levels to improve the course of coronary atherosclerosis	(Romanelli et al. 2017)
SBI-425	Mouse	Pseudoxanthoma elasticum (PXE)	TNAP inhibition attenuated calcification, altering disease development and progression in vivo	(Ziegler et al. 2017)

PLAP: placental alkaline phosphatase; IAP: intestinal alkaline phosphatase; LPS: lipopolysaccharide; NO: nitric oxide; iNOS: inducible nitric oxide synthase; DSS: dextran sodium sulfate; NEC: Necrotizing enterocolitis; AKI: acute kidney injury; EAE: experimental autoimmune encephalomyelitis; recAP: human recombinant alkaline phosphatase; L-Phen: L-phenylalanine

supports a role for AP in vascular disease is that elevated serum AP, most likely due to elevated TNAP activity, promotes vascular calcification and leads to increased risk of cardiovascular disease and stroke. To prevent these outcomes, administration of an AP inhibitor has been suggested as one potential therapeutic option. Research from Pratibha and colleagues suggests that administration of AP inhibitors could be used to prevent cerebral ischemia in high-risk populations (Pratibha et al. 2014). A study in stroke-prone rats found beneficial effects against cardiovascular disease complications using a traditional fungal medicine and found that the number of capillaries that expressed AP in the heart was significantly decreased compared to untreated rats. Typically, TNAP is minimally localized to cardiac microvessels in comparison to its levels in cerebral microvessels (Koyama et al. 2006). Some of the better-known AP inhibitors, including tetramisole and levamisole, are no longer used in the clinic due to lack of AP isoenzyme specificity and serious neurological side effects associated with chronic treatment (Nowak et al. 2015). Sheen et al. have made efforts towards screening for promising TNAP inhibitors. One of their more-promising candidates, SBI-425, has been shown to reduce aortic calcification and prolong life in TNAP-overexpressing mice (Sheen et al. 2015). Overall, AP inhibitors have proven to be useful for reducing vascular calcification, an important risk factor for the development of stroke. Thus, it is imperative that we identify the circumstances when AP, and more specifically TNAP, is beneficial and when it is harmful. The identification of these mechanisms will prove crucial in the development of AP-based therapeutics to prevent or to treat cerebrovascular disorders such as stroke.

Potential mechanistic targets for alkaline phosphatase in stroke

The proposed mechanism of action for AP's therapeutic utility in stroke include enhancement of BBB integrity, relief of inflammation, and promotion of vascular homeostasis, as shown in Figure 3. ATP release is an important consequence of stroke-associated inflammation, induced by multiple brain cell types, especially blood-brain barrier (BBB) endothelial cells. AP enhancement with exogenous PLAP, IAP, or recombinant alkaline phosphatase (recAP) may help to decrease inflammation by catalyzing the reaction of pro-inflammatory, toxic ATP to anti-inflammatory, nontoxic adenosine. This in turn activates neuroprotective signaling cascades which limit inflammation, enhance BBB integrity, and promote vascular homeostasis.

Blood-brain barrier permeability

Increased BBB permeability is likely to have a role in the putative association between AP and stroke. TNAP is expressed in brain endothelial cells and may play an important role in BBB maintenance and integrity (El Hafny et al. 1996; Deracinois et al. 2012), as well as transportation of proteins, including insulin, across the barrier (Calhau et al. 2002). The cerebral microvasculature is protected by astrocytes, pericytes, and the extracellular matrix that surrounds the vessels (Iadecola and Nedergaard 2007). The primary proteins involved in keeping the cerebral environment separate from the rest of the body are tight junctions, and the dysfunction of these proteins leads to BBB breakdown and neuronal cell death. Following stroke, toxic proteases, cytokines, and free

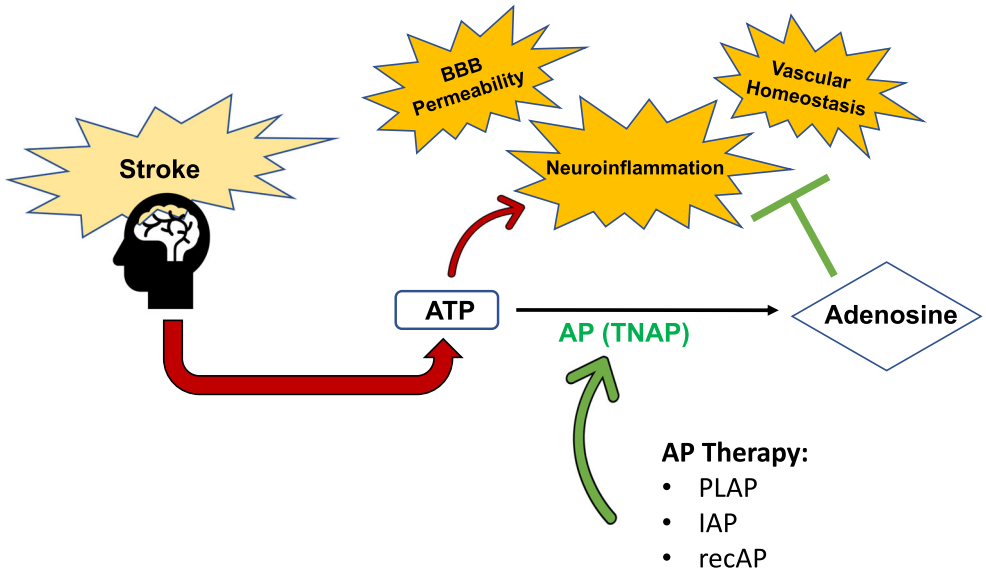

Fig. 3 Proposed mechanism of action for implementation of alkaline phosphatase-based therapeutics in stroke: An important consequence that results from the induction of stroke-associated inflammatory pathways is increased ATP release in multiple brain cell types, particularly in BBB endothelial cells. AP administration, via placental alkaline phosphatase (PLAP), intestinal alkaline phosphatase (IAP), or recombinant alkaline phosphatase (recAP) may help to decrease inflammation by facilitating the hydrolysis of pro-inflammatory, toxic ATP to anti-inflammatory, nontoxic adenosine. Binding of adenosine to its receptors has been shown to activate neuroprotective signaling cascades which limit inflammation, enhance BBB integrity, and promote vascular homeostasis

radicals form to aid in the removal of dead cells, however these molecules also cause tissue damage and participate in BBB disruption (Yang and Rosenberg 2011; Jiang et al. 2018). Rabbits with diabetic ketoacidosis exhibited increased inducible nitric oxide synthase (NOS) activity and decreased AP activity levels in brain endothelium (Zhu et al. 2004). One emerging concept suggests that TNAP may be released into the circulation to neutralize inflammation produced in response to damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs). The release of membrane-bound TNAP as soluble TNAP into the circulation may result in a compromised BBB (Pike et al. 2015). In vitro evidence for a direct role for TNAP in the regulation of BBB integrity was demonstrated by Deracinois and colleagues (Deracinois et al. 2012, 2015). Treatment of cultured brain capillary endothelial cells with the nonspecific AP inhibitor, levamisole, increased permeability to a fluorescent tracer and reorganized the actin cytoskeleton; removal of levamisole reversed the increase in permeability and cytoskeletal disruption (Deracinois et al. 2015). These results support a critical role for TNAP in the integrity of the cerebral microvasculature. TNAP's mechanism(s) of action at the BBB are also summarized in Fig. 2.

Neuroinflammation

Elevated serum AP is a highly characteristic part of the inflammatory response in multiple disorders. Prior studies have suggested that abnormal AP levels contribute to the development of cerebral small vessel disease and cardiovascular disease (Tonelli et al. 2009; Park et al. 2013; Wannamethee et al. 2013; Kunutsor et al. 2014; Lee et al. 2015). Huizinga et al. proposed that AP has a role in limiting neuroinflammation by interfering with immune activation through neutralization of LPS and endogenous substrates such as ATP. They found that AP administration during the priming phases of EAE reduced neurological signs of multiple sclerosis (MS) (Huizinga et al. 2012). Post-stroke infections are very common in stroke patients, particularly respiratory and urinary tract infections (Langhorne et al. 2000; Vernino et al. 2003). Thus, it is likely that mechanisms related to infection-induced inflammation are also involved in the initiation of AP upregulation in stroke patients. Increasing evidence suggests that infection often precedes or triggers chronic neurological diseases such as MS (Buljevac et al. 2002). AP's natural ability to neutralize inflammatory substrates may prove that it has a beneficial role in slowing neuroinflammation. Recent studies have shown the importance of the gut-brain axis in MS, and demonstrate that microbial infection can activate myelin-reactive T cells in the CNS (Nogai et al. 2005; Berer et al. 2011). ATP, an endogenous DAMP signal, is upregulated by multiple cells in response to stress, and has been shown to activate microglia in response to brain injury (Davalos et al. 2005), and can also trigger oligodendrocyte excitotoxicity (Matute et al. 2007). In contrast, chronic liver disease also increased AP activity in rat brains (Dhanda et al. 2018). Elevated brain AP levels found in both CNS and systemic examples of infection-induced inflammation strongly suggests that similar neuroinflammatory mechanisms are also present in the pathophysiology of stroke.

Altered vascular homeostasis

The disruption of cerebral microvascular homeostasis is another common feature of stroke. In contrast to other studies which suggest that serum AP levels are elevated post-stroke, Shimizu et al. speculated that altered vascular homeostasis plays a role in the association between lower AP levels and increased risk of stroke (Shimizu et al. 2013a). Endothelial progenitor cells (EPCs) have been shown to circulate in peripheral blood and contribute to maintenance of the vasculature (Asahara et al. 1997). Previous research has shown that reduced levels of EPCs predict atherosclerotic disease progression (Schmidt-Lucke et al. 2005). Another study showed an association between reduced EPCs and an increased number of infarctions, but no significant correlation with atherosclerosis; this finding is likely due to the multiple risk factors and cell types that contribute to vascular dysfunction (Taguchi et al. 2004). Since EPCs also contribute to vascular repair, it is likely that a reduction in these cells may lead to increased risk of stroke (Shimizu et al. 2013a). Thickening of the cerebral vessel walls via increased collagen represents a normal feature of aging. In leukoaraiosis, which is caused by chronic ischemia, venous collagenosis is further increased and may be due, in part, to altered TNAP activity in cerebral microvessels (Brown et al. 2002). Lee et al. also speculate that the association between AP and indicators of cerebral small vessel disease includes issues with vascular calcification and microcirculation impairment (Lee et al. 2015). It is hypothesized that vascular calcification leads to stiff vessel walls and the resultant microcirculatory dysfunction may lead to myocardial ischemia, and by extension, cerebrovascular dysfunction and the onset of cerebral ischemia (Sigrist and McIntyre 2008). Alternatively, other studies have suggested that elevated bone AP levels may accelerate the development of cardiovascular disease through vascular calcification, presumably due to impaired vascular homeostasis (Shioi et al. 2002; Shimizu et al. 2013a). Thus, there are multiple putative mechanisms through which altered TNAP activity in endothelial cells and EPCs could impact cerebrovascular homeostasis to increase stroke risk or negatively impact post-stroke outcomes.

Conclusion

Although AP is a ubiquitous enzyme expressed in numerous tissues, a comprehensive understanding of its molecular and cellular mechanisms of action remains elusive. Emerging clinical evidence supports the potential utility of AP as a rapid, cost-effective blood biomarker to be used singly or as part of a biomarker panel in stroke patients. In light of the proposed mechanism in Fig. 3, the complex cell biology of AP represents is an important consideration for the development of targeted AP-based biomarkers and therapeutics for stroke. It will be critically important to understand the circumstances under which AP administration or AP inhibition are beneficial as well as detrimental. Harnessing this knowledge may represent an important milestone in the development of novel therapeutic agents for stroke.

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