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*From Cell Biology to Tissue Engineering*

## *Review*

# Platelet-generated amyloid beta peptides in Alzheimer's disease and glaucoma

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**Summary.** Amyloid beta (Aβ) peptides have been implicated in both Alzheimer's disease (AD) and glaucoma and have been shown to be the key etiological factor in these dangerous health complications. On the other hand, it is well known that Aβ peptide can be generated from its precursor protein and massively released from the blood to nearby tissue upon the activation of platelets due to their involvement in innate immunity and inflammation processes. Here we review evidence about the development of AD and glaucoma neuronal damage showing their dependence on platelet count and activation. The correlation between the effect on platelet count and the effectiveness of anti-AD and anti-glaucoma therapies suggest that platelets may be an important player in these diseases.

**Key words:** Beta-amyloid peptide, Alzheimer's, Glaucoma, Platelets

## Introduction

Amyloid beta (Aβ) peptides are 36-43 amino acids in length, have a specific sequence that is slightly different between mammalian species (GenScript database), and are produced in many cell types by cleavage of the longer amyloid precursor protein (APP). Due to hydrogen bonding between the peptide bonds of parallel monomers, Aβ forms dimeric or tetrameric oligomers, even at very low concentrations, while in higher concentrations it associates into β-pleated sheets, tending to join in misfolded aggregations known as amyloid plaques (Lomakin et al., 1997; Tjernberg et al., 1999). Mutations within Aβ and its precursor affect this aggregation, which is the basis of familial early-onset diseases (reviewed and studied in Hatami et al., 2017). A common factor in a number of health problems is the accumulation of Aβ in tissues, including different cancerous tissues (Hansel et al., 2003; Jin et al., 2017), the zone of traumatic brain injury (Johnson et al., 2010), skeletal muscles in special cases of myositis (Askanas et al, 1992), myocardium with diastolic dysfunction (Gianni et al., 2010), and the placenta during pre-eclampsia (Buhimschi et al., 2014). Aβ peptides also accumulate and are thought to be important players in two other well-known health problems, Alzheimer's disease (AD) and glaucoma. Both of these diseases have hereditary forms, usually developing as an early onset, and sporadic forms, usually affecting elderly subjects. In this review, we concentrate on these two sporadic diseases and the evidence for a common systemic source of Aβ, which accumulates in and damages tissues during the course of these diseases, and its relation to platelets.

### *Alzheimer's disease (AD)*

This disease is a slowly developing progressive dementia, with extensive damage to neurons in the brain and their connections (reviewed in: Zott et al., 2018) that

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is accompanied by reactive astrogliosis and even astroglial atrophy (Verkhratsky and Rodríguez, 2018). It has been shown that the first signs of change in the AD brain are in the olfactory bulb, suggesting that the olfactory tracts provide a portal of entry to the brain for any pathogenic agent(s) that might be responsible for induction of the disease (Ohm and Braak, 1987; Mann et al., 1988). Next, damage to the entorhinal cortex follows, which is known to convey olfactory information and is a major input and output structure of the hippocampus. The hippocampus, in turn, is affected in the next stage of the disease, which is characterized by disorientation in space and memory problems. Damage then spreads to other cortical parts, leading to destruction of virtually all isocortical association areas and severe cognitive impairment (Braak and Braak, 1991). Microscopically, the AD-affected brain is characterized by extracellular amyloid-like senile plaques and intracellular neurofibrillary tangles. Since the time that beta-amyloid (Aβ) peptides were found to be the major constituent of amyloid cerebrovascular senile plaques described by Dr. Alois Alzheimer in the brain of dementia patients, these peptides became associated with the development of AD (Glenner and Wong, 1984). The Aβ hypothesis was formulated, suggesting that an imbalance between production and clearance of Aβ (Aβ dyshomeostasis) is an early, often initiating factor in AD (Selkoe and Hardy, 2016). However, it was discovered that Aβ plaques were sometimes present in cognitively normal individuals, while neuronal death also occurred in brain regions devoid of plaques (Sloane et al., 1997). It then became clear that only oligomers of Aβ peptides are toxic to brain cells and that there is no direct correlation between the manifestation of the disease and plaque burden (reviewed in: Sengupta et al., 2016). The most common view is that increased concentrations of Aβ oligomers trigger neuronal dysfunction and network alterations, with secondary damage produced by hyperphosphorylated tau protein aggregated in tangles (reviewed in: Jeong, 2017; Mroczko et al., 2018).

### *Glaucoma*

This disease is a slowly developing, progressive blindness. In many cases glaucoma involves elevated intraocular pressure (IOP) that precedes damage to the optic nerve and vision loss. Disproportionate IOP develops due to a constraint on the outflow of liquid from the eye, in some cases due to vein occlusion (Săninoiu, 1992; Călugăru and Călugăru, 2001). This leads to accumulation of excessive aqueous humor, especially if anatomical problems have complicated the alternative escape (drainage) of the aqueous humor through the trabecular meshwork. Due to disrupted hemodynamics there are also clearly visible anatomical changes in the eye, termed cupping, in the zone of the entrance of blood vessels and the optic nerve to the retina, and the level of damage in this zone is the hallmark of glaucoma. The common view is that IOP at first harms the optic nerve vasculature, leading to optic nerve damage, or that it directly causes damage to the optic nerve, which consists of the axons of retinal ganglion cells (RGC), affecting also the soma of these cells, and finally leads to blindness (Mann et al., 2019). It is also known that many glaucoma cases exhibit only moderate or even normal intraocular pressure.

It is still a matter of debate which factors in glaucoma induce damage to retinal cells, but Aβ is evidently involved. It was shown that Aβ accumulates in the retina, with the highest concentration colocalizing with the layer of apoptotic retinal ganglion cells in experimental glaucoma, while application of synthetic Aβ induces significant RGC apoptosis *in vivo* in a dose- and time-dependent manner. Anti-Aβ treatment was effective in prevention of RGC apoptosis in glaucoma patients (Yoneda et al., 2005; Guo et al., 2007; Ning et al., 2008, Ito et al., 2012; see also reviews: Sivak, 2013; Ratnayaka et al., 2015). An increased risk of developing AD was established for persons diagnosed with glaucoma and certain other ophthalmic conditions (Lee et al., 2019). All these results suggest common pathological mechanisms in glaucoma and AD.

## The association of AD and glaucoma with inflammation and infection

Glaucoma is often initiated by inflammation, and there is a 50% coincidence of glaucoma with chronic uveitis, which can be induced by an autoimmune reaction or a reaction caused by infection (Netland and Denton, 2006; also reviewed in: Bodh et al., 2011). The most common eye infections correlated with glaucoma are caused by herpes simplex virus or varicella zoster virus (Miserocchi et al., 2002). In herpetic anterior uveitis 75% of patients develop elevated IOP (Hoeksema et al., 2017). Various periodontal bacteria may also cause the development of glaucoma (Astafurov et al., 2014). The cause of inflammation leading to glaucoma can be chemical- or laser-induced trauma (Ştefan et al., 2016) or simple mechanical trauma (Markovic et al., 2017). Thus, in many cases glaucoma is a response to inflammation with or without infection.

Similarly, AD pathological changes clearly correspond to regions with inflammation (Akiyama et al., 2000). Inflammatory signaling cytokines, especially the expression and signaling of the cytokines interleukin 12 and interleukin 23, can affect the cerebral amyloid load and the development of AD (Vom Berg et al., 2012; Griffin, 2013; Wilcock and Griffin, 2013). Brain inflammation also develops after trauma (Corps et al., 2015). Interestingly, it was shown that temporary Aβ plaques appeared in the brain of an AD mouse model after mild brain trauma and then disappeared after 7 days, which was correlated with the post-traumatic concentration of soluble Aβ oligomers in the brain (Washington et al., 2014). Aβ plaques and oligomers may also be found in the brains of human patients within

hours of traumatic brain injury (TBI) in non-AD patients (Roberts et al., 1991; Ikonomovic et al., 2004; also reviewed in: Johnson et al., 2010). Like in glaucoma, there are significant associations between AD and various pathogens, including Herpes simplex virus type 1 (HSV-1), cytomegalovirus, other Herpesviridae, Chlamydophila pneumoniae, spirochetes, *Helicobacter pylori*, and various periodontal pathogens (Harris and Harris, 2015, 2018; Maheshwari and Eslick, 2015). Recently, the gram-negative periodontal pathogen *Porphyromonas gingivalis*, which causes chronic periodontitis, was also identified in the brain of AD patients (Dominy et al., 2019), while previously this pathogen was found to cause brain inflammation, neurodegeneration, and Aβ production in a wild type mouse model (Ilievski et al., 2018). Genes upregulated in the AD brain match those upregulated by multiple bacteria, viruses, fungi, or protozoa in immunocompetent cells (Carter, 2017). Lyme spirochetes are also suspected of causing AD (Eimer et al., 2018). Recently, the evidence for human transmission of Aβ pathology after the treatment of children with human cadaver-derived growth hormone was reported, and it was suggested that this was an example of the prion-like spread of AD (Jaunmuktane et al., 2015), although it could be the spread of a septic agent provoking AD development. All these results suggest that Aβ pathology in AD is, in many cases, a response to inflammation and is sometimes a result of infection, which raises the question of why the buildup of Aβ in both glaucoma and AD is correlated with these processes.

### Aβ as a defense peptide

It has been shown that Aβ peptide has strong antibiotic activity against both Gram-negative and Gram-positive bacteria as well as fungi and viruses (Lukiw et al., 2010; Soscia et al., 2010; Bourgade et al., 2014; White et al., 2014). Aβ peptide also protects mice against microbial infection in *in vivo* experiments (Kumar et al., 2016). It has been suggested that Aβ is a previously unrecognized antimicrobial agent that may normally function in the innate immune system (Soscia

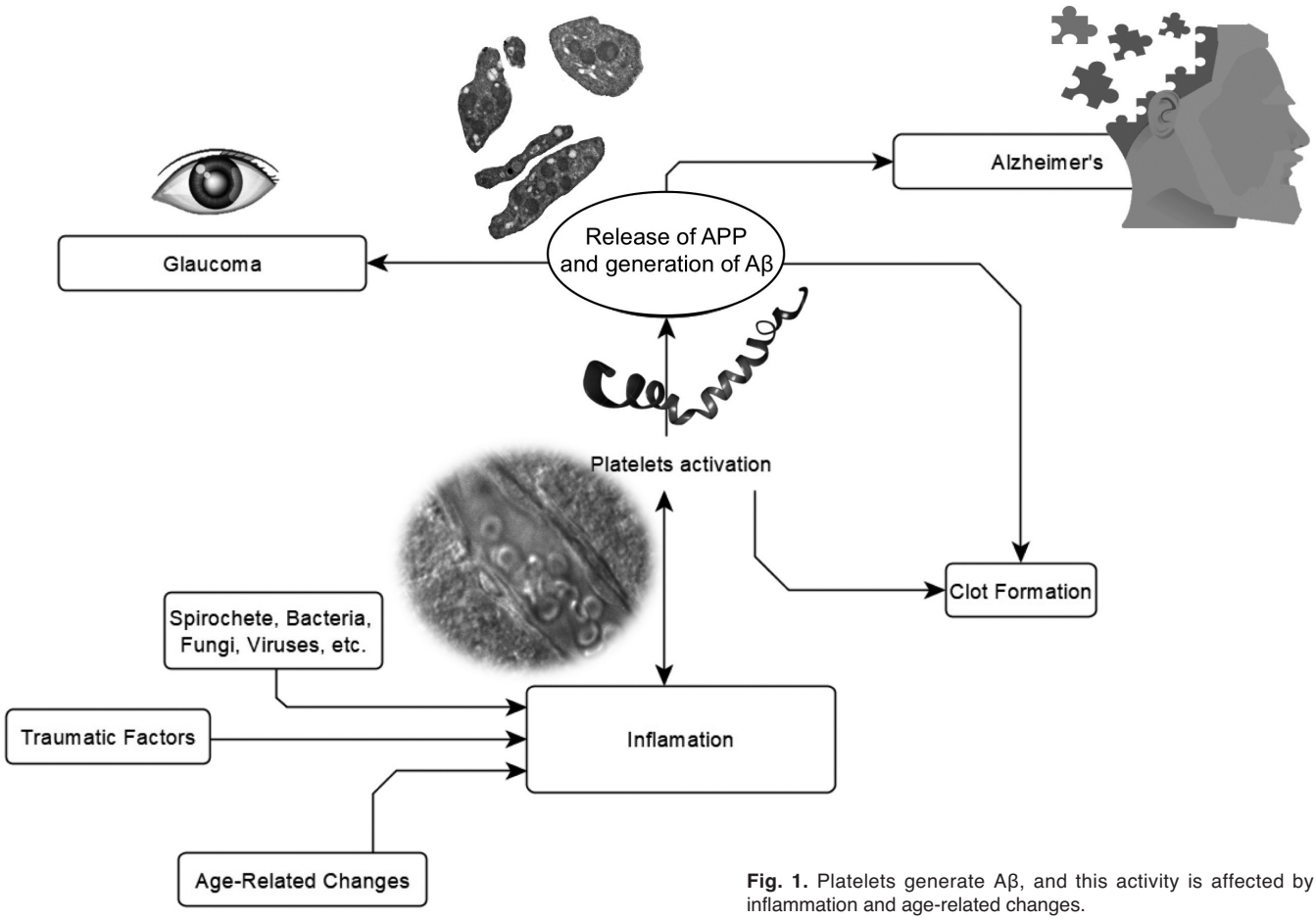


**Fig. 1.** Platelets generate Aβ, and this activity is affected by inflammation and age-related changes.

et al., 2010; Kumar et al., 2016; Kucheryavykh et al., 2017; Inyushin et al., 2017; Gosztyla et al., 2018). We have shown that during thrombosis in skin blood vessels Aβ peptides are generated and released in the nearby skin tissue, functioning as an antibiotic against infection (Kucheryavykh et al., 2018). The appearance of Aβ peptide in the tissues during thrombosis suggests that it has an important function in the platelet defense arsenal. It has been shown that Aβ peptide oligomers aggregated into fibrils entrap microbes (Kumar et al., 2016) or can bind herpesvirus surface glycoproteins, accelerating Aβ deposition and leading to protective viral entrapment (Eimer et al. 2018). Additionally, we suggest that an antimicrobial effect can be achieved by the pore-forming properties of Aβ peptide (Inyushin et al., 2017; Kucheryavykh et al., 2017, 2018). It was shown that soluble Aβ peptide oligomers at low concentrations (number) perforate cell membranes by forming tetrameric channels penetrable by $K^+$ ions and do so at higher concentrations by forming $Ca^{++}$-permeable hexameric pores (Kawahara et al., 1997; Lin et al., 2001; Lal et al., 2007). An excess of $Ca^{++}$ permeability through these pores induces calcium dyshomeostasis and is extremely toxic (Kawahara, 2010; Sepulveda et al, 2010). We have shown that synthetic Aβ peptide perforates the external membrane of yeast (Kucheryavykh et al., 2018), and it is known that natural peptide antibiotics with channel-forming activity kill target cells by this same mechanism (Harder et al., 1997; Hancock and Chapple, 1999). Thus, Aβ may be released as a response to infection (Inyushin et al., 2017; Eimer et al. 2018), and this release is likely triggered by tissue damage and inflammation (Kucheryavykh et al., 2018).

### Platelets are a source of systemic APP and Aβ

Aβ peptides are released by different types of cells. In the brain the most established sources of Aβ are neurons and astrocytes, but there is another important systemic source of these peptides—platelets (reviewed in: Inyushin et al., 2017). Platelets are small anuclear cells derived from the processes of the megakaryocyte precursor cell, and their production is tightly regulated (reviewed in: Kutler, 1996, 2014). They contain diverse types of granules that include alpha granules, dense granules, and lysosomes (Sharda, Flaumenhaft, 2018). Besides coagulation factors, platelet α-granules contain amyloid precursor protein (APP), and full-length APP (containing Aβ peptide) is liberated upon platelet degranulation (Bush et al., 1990; Van Nostrand et al., 1990; Rosenberg et al., 1997; Sevush et al., 1998; Baskin et al., 2000, Padovany et al., 2001). APP represents about half of all proteins secreted from agonist-treated platelets (Van-Nostrand et al., 1990). APP is itself a Kunitz-type protease inhibitor, which effectively inhibits chymotrypsin, trypsin, and other proteolytic enzymes (Van Nostrand et al., 1990; Ledesma et al., 2000) and promotes the activation of coagulation factor XII, affecting the hemostasis and temporal stability of the thrombus (Schmaier, 2016; Zamolodchikov et al., 2016). Brain vessels endothelial cell enzymes can cleave the platelet-released APP, forming Aβ, especially if activated platelets adhere directly to the endothelial cells (Davies et al, 1998). Platelets also generate Aβ peptide itself and are the primary source (~90%) of this peptide in human blood (Chen et al., 1995). The generation of Aβ peptide in platelets involves a regulated secretory vesicle pathway (Hook et al., 2005, 2008).

While in neurons the release of Aβ and cleavage by β-secretase occurs in the soluble intracellular environment (cytoplasm), cleavage by γ-secretase occurs within the transmembrane domain of APP when it is inserted in the membrane (Selkoe, 2004; Haass and Selkoe, 2007). Hook et al. (2008) called this the constructive secretory pathway.

The regulated secretory vesicle pathway (in which APP is present in soluble, non-transmembrane form in intracellular vesicles) releases full-length, soluble APP or Aβ and other fragments. This is known to occur in platelets (Bush et al., 1990, 1993; Van Nostrand et al., 1990) and in chromaffin cells (Tezapsidis et al., 1998). Full-length soluble APP thus has β- and γ-secretease sites accessible for direct proteolytic cleavage in solution (Tezapsidis et al., 1998). The specialized cathepsin B enzyme works as a β-secretase in this pathway. It was suggested that the major portion of secreted, extracellular Aβ peptides is produced by the regulated secretory pathway (Tezapsidis et al., 1998, 2013; Hook et al., 2005, 2009, 2014). Aβ peptides secreted by platelets are similar to those found in the senile plaques of AD patients (Scheuner et al., 1996). Production of shorter Aβ peptides ending at residue 40 (Aβ40) increases if platelets are closely packed in the thrombus, while production of Aβ42 does not depend on platelet density (Casoli et al., 2007).

### Platelets are an important component of the inflammation and immune response

Platelets are best known as cellular mediators of thrombosis, but they are also immune cells that initiate and accelerate many inflammatory conditions. In some contexts these conditions are protective, whereas in others they contribute to adverse inflammatory outcomes (reviewed in: Klinger and Jelkmann, 2002; Morrell et al., 2014, 2019; Manne et al., 2017; Łukasik et al., 2018). Platelets have receptors activated by viral and bacterial antigens and in response release microbicidal peptides (Yount et al., 2004; Trier et al., 2008; Yeaman, 2010; Seyoum et al., 2018). We have shown that during thrombosis after skin injury there is a massive release of Aβ peptide and that this peptide can perforate yeast cell membranes while not affecting somatic cell membranes at the same concentration (Kucheryavykh et al., 2018). However, Aβ peptide is not the only weapon in the platelet arsenal, as other antibacterial peptides were identified long ago (Yeaman et al., 1993, 1997;

Krijgsveld et al., 2000; Kupferwasser et al., 2002; Tang et al., 2002). Like Aβ, one of these antibacterial peptides present in rabbit has a variable length of 72-73 amino acids and is cleaved from a longer precursor (Yount et al., 2004).

Platelets express numerous specialized Toll-like receptors (TLR) that recognize microbe-associated threats. Moreover, they (1) interact with other immune cells using cell-specific adhesion molecules, (2) attach neutrophils and monocytes at the site of lesion and also activate them as well as themselves, (3) release multiple antibacterial factors, and (4) participate in both innate and acquired immune responses (reviewed in: Morell et al., 2014; Łukasik et al., 2018). Stimulation of TLR type 2 (TLR2) amplifies P-selectin expression on the surface of platelets, enhances the pro-inflammatory response of platelets, and increases the formation of platelet-neutrophil aggregations necessary for the innate response (Blair et al., 2009). It was previously shown that the presence of long-chain bacterial polyphosphates or bacteria in the bloodstream promotes platelet activation in a FXII-dependent manner, which may contribute to sepsis-associated thrombotic processes (Zilberman-Rudenko et al., 2018). It is also known that the Aβ peptides that are released by platelets are recognized by TLR2 on the surface of lymphocytes, similarly to other pore-formers, such as nystatin and amphotericin B, inducing a cellular response and leading to the secretion of inflammation factors and tumor necrosis factors (Razonable et al., 2005; Chen et al., 2006; Liu et al., 2012). This additional activation may add positive feedback to the inflammation process.

An important component of innate immunity, FcγRIIB, is the only inhibitory receptor for the fragment crystallizable region (Fc region) of IgM antibodies, which are involved in the complex regulation of acquired defense against infection (Smith and Clatworthy, 2010). On the surface of B lymphocytes this receptor inhibits IgM production until the necessary concentration is achieved. The affinity of FcγRIIB to soluble monomeric IgM is low, and it is activated only when the concentration of IgM is sufficiently high. However, Aβ liberated by platelets can shift this regulation, because FcγRIIb is also a receptor for soluble Aβ oligomers, and it was shown that both cell-derived and synthetic Aβ oligomers bind to the immobilized FcγRIIb ectodomain (Lee et al., 2018). Thus, overproduction of Aβ may lead to overproduction of IgM, provoking pathological inflammation. The overall mechanism of how Aβ affects the regulation of tissue inflammation is unclear. But it is known that FcγRIIB mediates Aβ neurotoxicity and memory impairment in AD, soluble Aβ oligomers interact with FcγRIIb *in vitro* and in AD brains, and inhibition of their interaction blocks synthetic Aβ neurotoxicity (Kam et al., 2013). FcγRIIb is significantly upregulated in the hippocampus of AD brains and neuronal cells exposed to synthetic Aβ (Kam et al., 2013).These results show that Aβ effects on the brain can also be indirect.

**Platelets in AD and glaucoma**

Glaucoma is strongly correlated with coagulation abnormalities. Platelets are hyperactivated in patients with different types of glaucoma and tend to aggregate (Hoyng et al., 1985; Bojić and Skare-Librenjak, 1998-1999; Matsumoto et al., 2001; Kuprys et al., 2014). In primary open angle glaucoma platelet aggregation and the fibrinolytic system may become triggers of vascular damage that can lead to microcirculatory defect at the optic nerve head (Matsumoto et al., 2001). An age-dependent association between spontaneous platelet aggregation and the presence of glaucoma was also observed ($p<0.05$; Hoyng et al., 1985). Anti-platelet effects of anti-glaucomatous eye drops was reported (Moschos et al., 2017), suggesting that glaucoma-related Aβ originates from platelets. A study in human glaucoma patients has shown that the number of platelets (the mean plateletcrit and platelet distribution width) is increased (Li et al., 2016). Aβ co-localizes with apoptotic retinal ganglion cells (RGCs) in experimental glaucoma in rat and induces significant RGC apoptosis *in vivo* in a dose- and time-dependent manner (Guo et al., 2007). Similarly, Aβ appears in the RGC layer in monkey retina after chronic ocular hypertension (Ito et al., 2012). In AD patients, accumulation of Aβ in the eye is more uniform in retina and is spread also to the eye lens, unlike in "pure" glaucoma (van Wijngaarden et al., 2017). Data on Aβ accumulation suggest some similarity in the mechanisms of AD and primary glaucoma, but there is no clear statistical correlation between these diseases (Tsolaki et al., 2011).

Correspondingly, abnormal clotting was found in AD patients and was correlated with cognitive ability, and it was suggested that APP is involved by perturbing clotting parameters (Suidan et al., 2018). Persons with AD dementia have a ~200% higher risk of stroke, according to a study of a large cohort of AD patients in Finland and Taiwan (Tolppanen et al., 2013; Chi et al., 2013). Clots are formed in atherosclerotic lesions (Badimon and Vilahur, 2014), with APP and Aβ peptide present in advanced human atherosclerotic plaques, and these substances originated from platelets (De Meyer et al., 2002). We also reported that Aβ peptide can be detected by immunocytochemistry in and around blood vessels in the brain after experimental thrombosis, and that this peptide is released to the tissue from platelets (Kucheryavikh et al., 2017). During clot formation, the density of platelets in the lumen of the thrombotic vessel is significantly increased (more than 300-500 times), thus allowing a massive release of Aβ peptide (Kucheryavikh et al., 2017). Platelet inclusions in cerebral blood vessels are the first signs of disease in an AD mouse model (Kniewallner et al., 2016). Microinfarcts are closely related to AD pathology (Kövari et al., 2013; Saito and Ihara, 2014, 2016), and there is a correlation with intracranial vessel arteriosclerosis (Dolan et al., 2010; Lathe et al., 2014), in which microclots are chronically formed in brain blood

vessels during arteriosclerosis (Holvoet and Collen, 1998; Badimon and Vilahur, 2014). These findings illustrate the fact that the coagulation system, and platelets in particular, are involved in AD. There are many additional pieces of evidence that AD is a thrombo-hemorrhagic disorder (Schmaier, 2016).

The activated platelets in AD retain greater amounts of APP (Davies et al., 1997) while showing increased platelet adhesion and thrombus formation (Canobbio et al., 2016). In a transgenic mouse model of AD, platelets were found to be the major contributors to cerebral amyloid angiopathy (CAA), which then forms a shield of insoluble Aβ around brain blood vessels (Gowert et al., 2014). Recently, using parabiosis between APPswe/PS1dE9 transgenic AD mice and their wild-type littermates, it was demonstrated that human Aβ originating from transgenic AD model mice entered the circulation and accumulated in the brains of wild-type mice and formed cerebral amyloid angiopathy and Aβ plaques after a 12-month period of parabiosis (Bu et al., 2018). These authors did not study the source of blood-derived Aβ but suggested that it may be platelets.

Liberation of α-granule content is mediated by specific receptors on the platelet. Some of the most important platelet membrane receptor classes that produce platelet activation and generation of Aβ during traumatic/inflammatory tissue damage were previously reviewed (Inyushin et al., 2017). These include the purinergic receptors P2X and P2Y, which are activated by ADP released from damaged tissues, and the thromboxane receptors (TxA2); both these types signal via the specific G protein Gq. It was found that RxR retinoid receptor ligands strongly inhibit Gq, thus impeding both purinergic and thromboxane receptors on the surface of platelets and drastically reducing platelet activation/agregation (Moraes et al., 2007). Interestingly, the RXR ligand bexarotene induces miraculously rapid clearance of soluble Aβ, thereby reducing plaque burden and improving cognition in a mouse model of AD (Cramer et al., 2012; Mariani et al., 2017). Moreover, bexarotene rescues glaucoma phenotypes in mice (Dheer et al., 2019). While the authors of these studies on bexarotene effects proposed alternative explanations for their results, we suggest that platelet deactivation may also be involved. Another antiplatelet drug, cilostazol, inhibits the activation-dependent membrane surface glycoprotein GPIIb/IIIa on the surface of platelets, preventing their activation (Inoue et al., 1999). Cilostazol may reduce the decline of cognitive function in AD patients and patients with mild cognitive impairment (Taguchi et al., 2013; Tai et al., 2017) as well as glaucoma (Okamoto et al., 2010). Similarly, blocking only purinergic receptors on the surface of platelets by antiplatelet drugs, such as clopidogrel, decreased plaque burden in AD model mice (Donner et al., 2016), while the effects of this drug on glaucoma are unknown. These investigators showed that Aβ stimulates the integrin receptor in platelets, leading to the release of ADP and the protein clusterin, and that this protein promoted β-sheet folding and the formation of fibrillar Aβ aggregates (Gowert et al., 2014; Donner et al., 2016). The authors did not discuss the source of Aβ but did confirm the existence of specific mechanisms involving platelets in the process of Aβ aggregation and showed the importance of platelets in AD development.

On the other hand, thrombocytopenia (a low platelet count) is extremely rare in AD patient cohorts. Out of 20,591 FDA reports on cases of AD-type dementia, only 0.4% developed thrombocytopenia, appearing in the advanced stages of the disease after long use of certain anti-AD medicines (eHealthMe, 2018). It has been reported that, while AD patients have similar platelet counts as age-matched controls, their platelets are in a more activated state (Sevush et al., 1998). Twenty years ago these authors (Sevush et al., 1998) concluded that, in light of evidence that platelets are the principal source of both APP and Aβ peptide in human blood, it is possible that AD platelet activation reflects, or even contributes to, the pathogenesis of AD. Unfortunately, this idea has never been tested directly.

Recently, we have shown that thrombocytopenic animals produce lower levels of Aβ peptide during clotting (Kucheryavykh et al., 2017). Therefore, induction of mild thrombocytopenia may be a novel approach to reducing the damaging effects of overproduction of systemic Aβ.

### X-ray treatment of glaucoma and AD

Exposure to X-rays directly affects blood platelet count. For glaucoma it was shown that a mild X-ray dose rapidly ameliorates retinal damage (Anderson et al., 2005; Bosco et al., 2012; Howell et al., 2012). This effect was first shown for whole-body irradiation. Destroying the bone marrow and replacing it with donor bone marrow in a genetic model of mouse glaucoma (DBA/2J mice) reduced glaucoma retinal damage after whole-body irradiation (Anderson et al., 2005). Later, the same group reported that only a single local X-ray treatment (7.5 Gy) of an individual eye in young mice provided the eye with long-term protection from glaucoma. They claim that it had no effect on the contralateral eye (Howell et al., 2012). This X-ray effect was challenged, however, by the research showing that there was no protective outcome if the X-ray irradiation was applied locally (Johnson et al, 2014). Neither of these studies investigated the effects on platelets.

Similar effects for whole-body irradiation and head-only irradiation were reported for AD (Simard et al., 2006; Mildner et al., 2011). The whole-body irradiation (10 Gy) was used first in experiments with a transgenic mouse strain (APPSwe/PS1), genetically modified to develop Aβ plaques, and it was shown that the amount of these plaques after X-ray irradiation was reduced by more than 50% (Simard et al., 2006). Later, whole-body and partial-body (lower part of the body only) irradiation was used in mouse models of AD (APPswe/PS1, APPswe, and APP23 mice) (Mildner et al., 2011). At the

dosage used in these experiments, the bone marrow and its entire hematopoietic lineage became ablated, and the work of both Simard and coworkers as well as that of Mildner, used the repopulation of animals with donor bone marrow to study the effects of newly generated monocytes. After whole-body irradiation senile plaque formation ceased, and the authors concluded that monocytes/microglia were responsible, although thrombocytopenia was not assessed in these experiments. After irradiation of the lower part of the body the effect on plaque formation in brain parenchyma was insignificant (Mildner et al., 2011).

Following the success in treatment of tracheo-bronchial amyloidosis (TBA) with irradiation (20 Gy, administered as 10×2Gyover two weeks), it was proposed to use mild levels of radiation to treat AD (Bistolfi, 2008). Indeed, the other research group used direct irradiation of the cranium to show that radiation causes plaques to became wiped out in the hippocampus and cortex. In AD transgenic mice, high doses of X-rays produced a very clear (>50%) reduction in amyloid deposition, and the authors attributed this to yet undetermined immune mechanisms (Marples et al., 2012; also see WO2012034019A1 Patent Application, 2010). Later, the same group, using different regimes of X-ray irradiation of the cranium, assessed not only Aβ plaque accumulation but also other AD parameters (Marples et al., 2016; Wilson and Marples, 2016). In this work only one side of the brain was irradiated, and a lead irradiation jig was used to shield the other side of the brain and all other tissues from the treatment field. The number of Aβ plaques in the irradiated side of the brain was then compared with the number of plaques in the shielded non-irradiated side. The authors found a clear difference between treated and untreated hemispheres. Anyway, one can see that at higher multiple doses, both shielded and irradiated hemispheres showed fewer plaques, suggesting that the effect of X-ray irradiation is not entirely local (Marples et al., 2016). Similarly, a visible difference can be observed between sham-irradiated and irradiated brains, suggesting that the nonlocal effects of irradiation were much more pronounced (Marples et al., 2016). How effective was the shielding of, for example, lungs, is difficult to determine from the description of the author's work.

It is known that X-ray irradiation of the upper chest, even at low doses (150 mGy), can produce thrombocytopenia. It was shown also that endothelial cell irradiation lowered their ability to attract migrating megakaryocytes (MKs). Moreover, the adhesion of MKs to human vascular endothelial cells (HUVECs) was markedly reduced when these cells were exposed to radiation, which was accompanied by a decreased production of platelets by MKs (Chen et al., 2017). While there is evidence of platelet production in bone marrow/spleen (Davis et al., 1997), it was found recently that the majority of platelet production from the pro-platelet processes of megakaryocyte-type extravascular progenitors is mainly concentrated in the pulmonary capillary bed of the lungs (Howell and Donahue, 1937; Zucker-Franklin and Philipp, 2000; Lefrançais et al., 2017). Thus, special shielding of the lower chest is needed to exclude the effects of a reduction of platelet count on plaque formation.

Additionally, a case report was published in which a low dose of X-rays generated by a CT scan (5x 50 mGy=250 mGy) produced miraculous, but transient, recovery of a patient with terminal AD after cranium imaging studies (Cuttler et al., 2016). CT scanning is performed by a 3D X-ray instrument, which to some extent also applies X-ray irradiation along the Z-axis to the lung during cranial imaging. It must be mentioned that the thrombocytopenia after the low doses of radiation is usually temporary and reverses in a few weeks due to compensatory effects (Ebbe et al., 1986).

The overall results on X-ray effects are interesting and can be interpreted from different points of view. While we suggest that reduction of the platelet count can explain the reported effects of ionizing radiation on both AD and glaucoma, this subject surely needs further in-depth exploration.

### Blood transfusion in glaucoma and AD treatment

Blood transfusion unquestionably affects platelet count and activation. Unfortunately, there are no recent studies devoted to the effects of blood transfusion on glaucoma. We have found only old review of effects in human patients and it was found that blood transfusion can dramatically reduce glaucoma retinal damage. The suggested explanation was that it helps to restore eye hemodynamics and reduce hypoxia, especially if patients previously have some general impairment of the cardiovascular system (reviewed in: Iusupov and Medvedev, 1965).

Blood transfusion has been shown to have profound effects on AD development. Bu and coworkers (Bu et al., 2018) showed that the blood from transgenic AD mice, which usually develop Aβ plaques and neuronal brain damage by 6-7 months of age, can induce similar plaques and damage in normal wild type animal brain after constant transfusion. Constant exchange of blood was achieved by parabiosis, in which the vascular system of one animal is surgically united with the vascular system of another so that they shared a common reservoir of blood. These authors used APPswe/PS1dE9 transgenic AD mice, producing human Aβ, which can be easily distinguished from intrinsic mouse Aβ. Parabiosis between these AD mice and their wild-type littermates has shown that human Aβ originating from transgenic AD model mice enters the circulation and accumulates in the brains of wild-type mice and forms cerebral amyloid angiopathy and Aβ plaques after a 12-month period (Bu et al., 2018). While the source of blood-derived Aβ was not specifically studied, it was suggested that it might be platelets (Bu et al., 2018).

Vice versa, the transfusion of blood from healthy subjects can reduce plaque formation in AD. It was

previously shown that parabiosis between young animals and aged mice mitigates age-related impairment of cognitive function, memory, and vascular function, but exclusively neuronal mechanisms were suggested (Katsimpardi et al., 2014; Villeda et al., 2014). This was followed by a preclinical study with mice (Middeldorp et al., 2016) and clinical trials in which blood from young persons was transfused into AD patients (PLASMA study NCT02256306). Because the study was not specifically focused on platelets, the preclinical animal trial did not investigate if a simple blood dilution (reducing the platelet count) by physiological solution will produce a similar effect. In the clinical trial there is still no published data on whether the effect of saline is any different from plasma transfusion and whether both are positive. If the platelet count is involved in the effect, it is possible that simple plasma dilution (platelet count lowering with saline) will have positive effects.

The overall results concerning the effects of blood transfusion are very interesting and can be interpreted from different points of view. While we suggest that reducing the platelet count can explain the reported effects on both AD and glaucoma, this subject surely needs further in-depth exploration.

### Why older age is a factor in sporadic glaucoma and AD

The greatest known risk factor for AD is increasing age, and the majority of people with AD are 65 and older, similarly people have six times more risk to get glaucoma if they are over 65 years old. Correspondingly, there are clear age-related changes in platelet count, function, and reactivity, driven by changes in hematopoietic tissue, the composition of the blood, and vascular health. These age-related changes are particularly pertinent given that thrombotic disease is much more prevalent in the elderly population (Jones, 2016). As an example, acute coronary syndromes and atrial fibrillation -the most frequent indications for platelet inhibition or anticoagulation- occur mostly in older patients, as does stroke, transient ischemic attack, myocardial infarction, systemic embolism, deep vein thrombosis, and pulmonary embolism (Andreotti et al., 2015). It is known that infarcts are closely related to AD pathology (Kövari et al, 2013; Saito and Ihara, 2014, 2016), as well as the intracranial vessel arteriosclerosis in which microclots are chronically being formed in brain blood vessels (Holvoet and Collen, 1997; Dolan et al., 2010; Lathe et al., 2014; Badimon and Vilahur, 2014). Platelets are responsible for APP and Aβ peptide present in advanced human atherosclerotic plaques (De Meyer et al., 2002).Thus stroke is associated with AD among elderly individuals (Honig et al., 2003).

Similarly, a10 year follow up study within the population of Taiwan have shown that glaucoma is strongly correlated to stroke (Lee et al., 2017). The similar strong correlation was found for myocardial infarction and glaucoma in large India and Taiwan studies (Mondal et al., 2013; Chen et al., 2016).

Platelet count is stable up to about 60 years old in humans, and then falls about 8% (reviewed in Jones, 2016) in the general population, this may be as a compensation for the increased platelet reactivity which is augmented with age in an almost linear fashion. Similar changes occur in other mammalian species with aging (Balduini and Noris, 2014; Jones, 2016). Platelets are hyper-activated in AD (Jarre et al, 2014) and glaucoma (Kuprys et al., 2014), and these hyper-activated platelets more aggressively damage healthy vessels (Kniewallner et al., 2018).

Therefore, regulation of platelet count and activation, especially in old age, may be a novel approach to reducing the damaging effects of platelet-generated systemic Aβ in AD and glaucoma.

### Conclusions

- Aβ peptide is implicated in both AD and glaucoma and has been shown to be the important etiological factor for these dangerous health complications.
- Aβ has many functions, but is well established as an antimicrobial/antibiotic peptide.
- It is known that Aβ peptide is generated from its precursor protein and massively released to the blood upon the activation/aggregation of platelets, and is thereby accumulated locally from a systemic source.
- Platelets are an important part of the inflammation and immune response, and both glaucoma and AD correlate with significant local inflammation.
- Platelets are the main source of systemic APP and Aβ.
- Platelet hyper-activation has been conclusively shown to be an aspect of both AD and glaucoma.
- Induction of mild thrombocytopenia and/or the reduction of platelet activation may be an effective approach to reduce the damaging effects of systemic Aβ.

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