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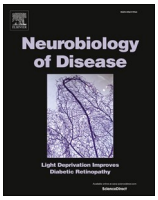

Review

Alternative platelet activation pathways and their role in neurodegenerative diseases

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ABSTRACT

Purpose of the review: The study of platelets in the context of neurodegenerative diseases is intensifying, and increasing evidence suggests that platelets may play an important role in the pathogenesis of neurodegenerative disorders. Therefore, we aim to provide a comprehensive overview of the role of platelets and their diverse activation pathways in the development of these diseases.
Recent findings: Platelets participate in synaptic plasticity, learning, memory, and platelets activated by exercise promote neuronal differentiation in several brain regions. Platelets also contribute to the immune response by modulating their surface protein profile and releasing pro- and anti-inflammatory mediators. In Alzheimer's disease, increased levels of platelet amyloid precursor protein raise the production of amyloid-beta peptides promoting platelet activation, triggering at the same time amyloid-beta fibrillation. In Parkinson's disease, increased platelet α-synuclein is associated with elevated ROS production and mitochondrial dysfunction.
Summary: In this review, we revise different platelet activation pathways, those classically involved in hemostasis and wound healing, and alternative activation pathways recently described in the context of neurodegenerative diseases, especially in Alzheimer's disease.

1. Introduction

Platelets are small anucleated blood cells originally described as main actors in wound healing through different activation mechanisms. However, over the past years, numerous additional physiological and pathological functions, including the mediation of synaptic plasticity and function, have been reported. Platelets are able to sense, adapt and respond, and, accordingly, their molecular composition varies depending on different environmental stimuli (Leiter and Walker, 2019). Therefore, platelets are attracting the interest of their study in the context of different disorders. In both ageing and neurodegenerative diseases, reduced brain plasticity, as well as altered blood composition, have been found; thus platelet dysfunction could be implicated in several neurodegenerative diseases and inflammatory CNS disorders (Behari and Shrivastava, 2013). Platelets show an enzymatic pathway similar to dopaminergic neurons, and can store and release neurotransmitters, such as serotonin, glutamate and dopamine. Oxidative stress induces mitochondrial dysfunction and cell death in both platelets and neurons. Because of this accumulating evidence, it has been recently proposed that platelets might provide a link between environmental factors and brain homeostasis (Leiter and Walker, 2019). Taking into account these considerations, the present review aims to provide a comprehensive overview of the current knowledge on platelet activation mechanisms, their role in the pathogenesis of neurodegenerative disorders and the contribution of APP/amyloid-beta and α-synuclein to disease-associated platelet dysfunction.

2. Platelets and platelet activation

Platelets have a biconvex discoid structure, a diameter of 2–3 μm and are formed by megakaryocytes in the bone marrow. After their release into the blood stream, the normal count is of 150.000–350.000 platelets per μl, and their half-life ranges between 7 and 10 days (Paulus, 1975). After sensing a stimulus, platelet reaction initiates and consequently the activation process starts (Rendu and Brohard-Bohn, 2001).

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2.1. Platelet activation pathways and aggregation

In a situation of vessel wall injury and endothelial damage, platelet activation is directed to blood clot formation (Michelson, 2013). As reviewed in detail by Rivera and colleagues (Rivera et al., 2009), the process comprises the initiation phase, extension or amplification phase, which negative regulation prevents uncontrolled thrombus gout (Kauskot and Hoylaerts, 2012), and the stabilization phase. In brief, in the initiation phase several adhesion receptors on the platelet membrane surface interact directly or indirectly with collagen fibers (Knight et al., 1999). At high shear rates, the binding of the Glycoprotein Ib-IX-V complex to von Willebrand factor (VWF) is required (Nieuwenhuis et al., 1986; Savage et al., 1998), permitting subsequent interaction between glycoprotein VI receptor (GPVI) and integrin α2β1receptor (GPIa-IIa) to collagen (Savage et al., 1999). Simultaneously, several integrins also bind to collagen, laminin, fibronectin, vironectin and/or vWF (Kauskot and Hoylaerts, 2012). These processes initiate kinase activation and morphological platelet changes, leading to the extension phase (Michelson, 2013; Rendu and Brohard-Bohn, 2001). Adherent platelets then release the content of their granules: α-granules (AGs), δ-granules (DGs) and lysosomes (George, 2000).

The three main platelet activation pathways, summarized in Fig. 1, are mediated by: (1) ADP released from DGs, binding to P2Y1 and P2Y12 (Murugappan and Kunapuli, 2006); (2) binding of TxA2, after conversion from arachidonic acid, to its receptor TP (Offermanns et al., 1994); (3) thrombin synthesis after exposure to tissue factor, and binding to PARS (for more detail see Kauskot and Hoylaerts, 2012). Platelet response to low concentrations of thrombin and TxA2 is reduced in the absence of ADP, highlighting the key role of ADP as a positive feedback mediator and preserving platelet activation (Vaduganathan and Bhatt, 2016).

The final event of the cascade is the activation of the integrin glycoprotein αIIbβ3 from a low affinity resting state through a conformational change to a high-affinity activated state (Coller, 1995). Consequently, the platelet receptor binds to extracellular soluble ligands such as divalent plasma fibrinogen and monovalent vWF (De Marco et al., 1985; Nieuwenhuis et al., 1986), acting as a bridge between platelets, creating the physical barrier stopping the blood loss. Platelets forming the plug have a very close contact, which decreases the diffusion of more platelet agonists consolidating the stability of the thrombus growth.

However, platelet activation can also be triggered by other molecules (Tomaiuolo et al., 2017), such as serotonin, released from DGs (Coller, 1995; De Marco et al., 1985), collagen or epinephrine (Gremmel et al., 2016). Additional components are essential during later stages (for more detail see Estevez and Du, 2017), including aggregation (fibrinogen and vWF), perpetuation of the aggregation (receptors JAMA, JAMC, growth arrest gene 6 and ephrin) and platelet-monocyte adhesion (e.g. P-selectin) (Denis et al., 2005). Besides, these activation and aggregation processes can be modulated by platelet antagonists, such as nitric oxide, prostacyclin and ADPase, produced by the vascular endothelium (Denis et al., 2005; Offermanns et al., 1994).

Upon activation and response to different stimuli, platelets also secrete two different microparticle populations (PMPs): (1) membrane budding microvesicles with similar content to the platelet plasma membrane and inflammatory functions; (2) exosomes of endosomal origin, derived from AGs and multivesicular bodies (MVBs) with numerous different functions (Coughlin, 2000; Offermanns et al., 1994).

2.2. RNAs in platelets

The above-discussed physiological changes during platelet activation are mediated by molecular pathways, which evolve rapidly, suggesting that platelets are able to sustain de novo translation and post-transcriptional gene regulation (Gremmel et al., 2016). Although platelets are anucleate lacking genomic DNA, they host diverse types of RNA. Evidence shows that platelet RNA is inherited from their parent megakaryocytes (Denis et al., 2005), and a clear relationship between the platelet transcriptome and proteome (McRedmond et al., 2004) underlies the ability of platelets to perform translational processes (Booyse and Rafelson, 1967). Since the composition of platelet granules varies depending on different environmental influences and factors, platelets are thought to collect mRNA also via endocytosis from the plasma (Coppinger et al., 2007; Italiano et al., 2008).

In addition to precursor and mature RNA (pre-mRNA and mRNA) involved in protein synthesis, other RNA families have been identified in platelets. These include transfer and ribosomal RNA, and regulatory RNAs as antisense and microRNA (miRNA) (Booyse and Rafelson, 1967;

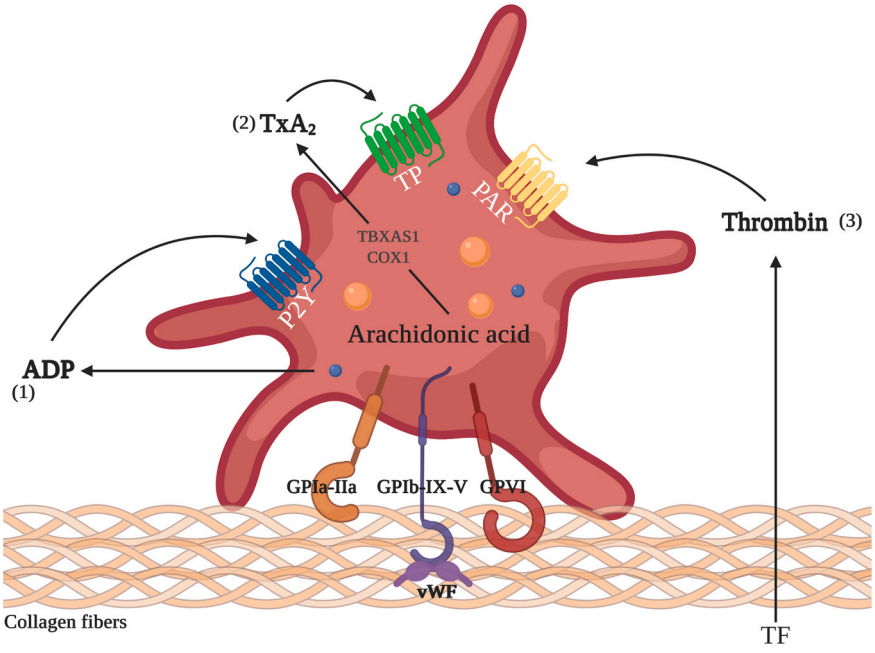

Fig. 1. Platelet adhesion and activation. Adherent platelets release the content of their granules. Three main platelet activation pathways have been characterized, and these are induced by ADP, TxA_2 and thrombin. Created with biorender.com.

Thon and Devine, 2007). Indeed, platelets contain pre-mRNAs that can be processed into mRNAs through splicing and levels of specific platelet miRNA correlate with platelet reactivity. Over the past decade, the expression of functionally active miRNAs during platelet activation has been described and investigated (Rowley et al., 2011; Schwertz et al., 2006).

MiRNAs and the corresponding functional miRNA pathway are common platelet constituents (Hunter et al., 2008; Landry et al., 2009). miRNAs play an important role during platelet genesis, activation and human hematopoiesis (Hunter et al., 2008; Landry et al., 2009), and play also an important role in the development of common diseases (Dangwal and Thum, 2012; McManus and Freedman, 2015; Liang et al., 2015; Wojtukiewicz et al., 2017). Therefore, platelet miRNAs might represent potential biomarkers to predict disease and disease progression.

3. Platelets and brain homeostasis

3.1. Alternative platelet activation and functions

Their translational machinery allows platelets to respond to a stimulus by modifying their protein profile, experiencing morphological and ultrastructural changes, highlighting their environmental adaptability. Platelets are considered a systemic tool, providing a link between external factors and inner body homeostasis. During the last decades, new platelet mechanisms have been found explaining that platelet concentration required for hemostasis is only 10×10^9 per litre (Duan et al., 2014; Fejes et al., 2017), which represents 2–6% of the total platelet content in healthy individuals. These observations suggest that platelets have alternative functions beyond wound healing and homeostasis of blood flow. Accordingly, alternative platelet activation pathways linking platelets to several biological processes have been described. Eventually, shear and oxidative stress might alter platelet activation (Carnevale et al., 2014; Slichter, 2011), as well as hypertension (Ehrlich et al., 2013; Violi and Pignatelli, 2012), physical activity and the immune response, among others (Fig. 2). A study performed by Imhold and colleagues showed that immune stimulation results in platelet activation with an own proteomic signature, suggesting another type of activation (Imhof et al., 2016). In fact, in an immune response context, platelets increase surface molecules, up-regulating receptors and molecules to interact with other immune cells, as well as releasing pro- and anti-inflammatory mediators (Clelland et al., 2009; Imhof et al., 2016) (Fig. 2). Additionally, platelets express several immune molecules that may modulate brain function such as transforming growth factor-ß, ß-2 microglobulin, and gelsolin.

3.2. Platelets and brain functionality

In 2015, Heber and Volf reviewed the importance of acute exercise and physical activity on platelets, stating that both modulate platelet

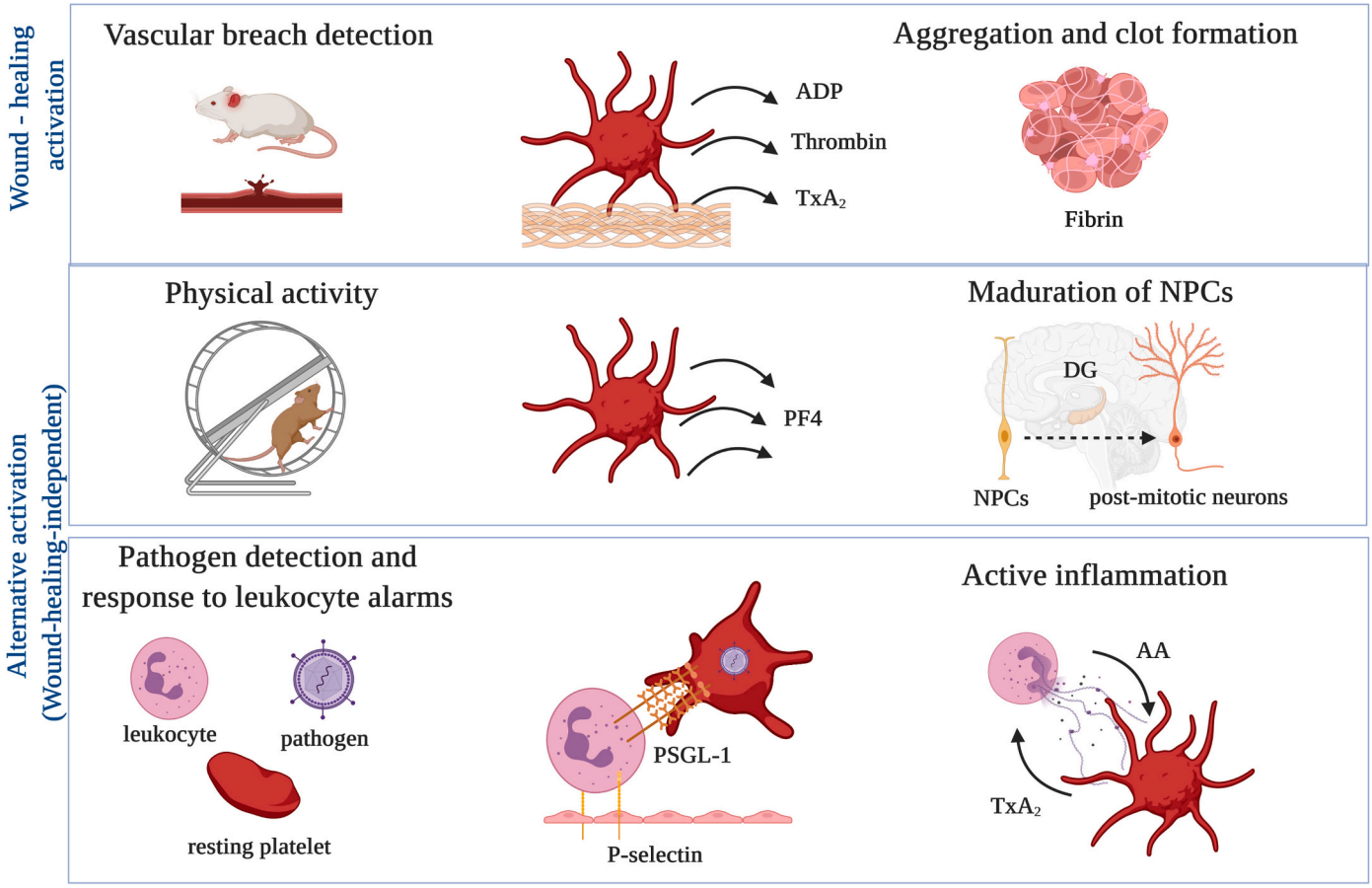

Fig. 2. Platelet activation pathways. *Wound-healing-dependent*: The detection of a vascular breach leads to the release of the three main platelet activation factors: ADP, Thrombin and TxA2, resulting in clot formation. *Wound-healing-independent:* by physical activity – periods of acute physical activity lead to PF4 release and modification of the platelet transcriptome, and subsequently, to increasing proliferation of neural precursor cells (NPC) in the DG (hippocampal dentate gyrus); by immune response – platelets recognize direct immune-related receptors and ligands through conserved pattern recognition receptors or indirectly via leukocyte alarms, such as cytokines and/or neutrophil extracellular traps (NETs). Upon immune activation, platelet interactions with leukocytes are mediated by PSGL-1 and P-selectin, enabling pathogen phagocytosis. Physical interaction between platelets and leukocytes comprises signal exchange including arachidonic acid (AA) to synthesize TxA2, and allowing to generate a fully active inflammatory response. Created with biorender.com.

activation (Heber and Volf, 2015). In a recent study, Leiter and colleagues provided further evidence for the role of exercise on platelet activation, reporting an elevated platelet activation rate in mice after 1 day of acute running (Leiter et al., 2019). Platelets activated via exercise expressed a different protein profile suggesting the stimulation of a different activation pathway. The study also showed that activated platelets promote neuronal differentiation through platelet factor 4 (PF4), resulting in a higher number of proliferating neural precursor cells in the dentate gyrus and thus, contributing to the regulation of adult hippocampal neurogenesis (Fig. 2). Moreover, other studies indicate that platelets also promote neurogenesis in the subventricular zone (SVZ) (Leiter et al., 2019; Preston et al., 2003). Since the hippocampus is the most important region for learning and memory, and impairment in hippocampal neurogenesis results in cognitive decline, platelet activation could be related to neurodegenerative diseases (Hayon et al., 2012; Kazanis et al., 2015). Accordingly, these studies show a potential link between platelet activation and brain homeostasis.

Additionally, during the last decade, the involvement of peripheral immune factors for the maintenance of brain function by different mechanisms has been described. First, immune cells participate in neuronal plasticity during development and adulthood (Morrell et al., 2014; Von Hundelshausen and Weber, 2007). Second, a link between platelets and the complement system has been shown (Morimoto and Nakajima, 2019; Nisticò et al., 2017), third, a recent study highlights the influence of acute peripheral immune activation to glial activation in rat brains (Bruce et al., 2019), and fourth, alterations in the communication between immune and nervous systems result in pathological conditions, including neurodegenerative diseases (Dantzer, 2018).

3.3. Implication of platelets in neurological processes

Platelet counts are stable between the age of 20–60 years, but decrease by approximately 10% in individuals older than 70 years (Montenont et al., 2019). Women have around 15% more platelets than men, and this difference maintains with ageing. Although there is a decrease in the platelet number, the general increase in their reactivity correlating with increased plasma PF4 levels has been described (Montenont et al., 2019). Ageing also correlates with phenotypic and functional changes in monocytes, leading to increased platelet-monocyte interactions resulting in an incremented inflammatory response (Hearps et al., 2012). The binding of activated platelets to monocytes activates a signaling cascade resulting in the synthesis of pro-inflammatory cytokines (Montenont et al., 2019).

Mitochondrial dysfunction is not only found in the CNS but in peripheral tissues such as skeletal muscle, liver and blood, in lymphocytes and platelets (Xu et al., 2007). Under pathological conditions and on physiological stimulation, platelets release reactive oxygen species (ROS), leading to mitochondrial damage (Hearps et al., 2012; Xu et al., 2007), specifically, to mitochondrial membrane depolarization, membrane permeability and alteration of the mitochondrial membrane potential (MMP) (Beal, 1996). In AD and other diseases, oxidative stress induces platelet and neuronal mitochondrial dysfunction and cell death (Barnham et al., 2004; Beal, 1996). Specifically, diminished respiratory parameters were found in platelet mitochondria of AD patients compared with controls (Fišar et al., 2019). Also, the reduction of mitochondrial enzymes, including pyruvate dehydrogenase complex, enzymes of the citric acid cycle and respiratory complex IV was found in mitochondria from AD platelets, and these changes were comparable to those characteristic for mitochondria from AD brain (Swerdlow et al., 2017). In this context it has been proposed that carnosine, a metal chelator with heat-shock protein activation properties, might attenuate ageing-induced ROS production (Banerjee and Poddar, 2020). Platelets also participate in synaptic plasticity, learning, memory and neuronal differentiation (Bazan, 1998), and express an enzymatic pathway similar to dopaminergic neurons, releasing neurotransmitters such as serotonin, glutamate, and dopamine (Banasr et al., 2004; Bazan, 1998; Kasatkina and Borisova, 2013; Swerdlow et al., 2017). Their AGs contain bioactive neurogenesis promoting molecules, such as IGF1 and PF4, among others (Leiter and Walker, 2019), and express several neuronal receptors (Wojsiat et al., 2017). Correspondingly, they seem to play a role in adult neurogenesis in the hippocampus (Leiter et al., 2019).

Finally, changes in platelet activation and aggregation have been documented in Lewy body diseases, amyotrophic lateral sclerosis (ALS) and multiple sclerosis (MS) (Espinosa-Parrilla et al., 2019; Wojsiat et al., 2017). A common feature of these neurological diseases is the progressive loss of selective neuronal cell populations and the formation of aggregates of misfolded proteins. The most common neurodegenerative disorders are amyloidoses, α-synucleinopathies, tauopathies, and TDP-43 proteinopathies, and platelets contain a high percentage of circulating amyloid precursor protein (APP) (Ponomarev, 2018; Rainesalo et al., 2005), and also α-synuclein (Barbour et al., 2008).

4. Platelets in AD

AD is characterized by the presence of neuritic plaques (NPs) and neurofibrillary tangles (NFTs) in the brain. Altered γ-secretase activity leads to increased amyloid-beta (Aβ) peptide production after APP cleavage (Selkoe, 1994; Singh et al., 2016). Especially longer, more hydrophobic peptides accumulate, shift the normal Aβ40/Aβ42 ratio, and enhance the generation of Aβ oligomers. Accumulation of these oligomers gives rise to the formation of NPs, triggering tau hyperphosphorylation and the development of intraneuronal NFTs (Choi et al., 2014).

4.1. Effect of APP and Aβ on platelet activation

Platelets contain about 90% of the circulating APP at their plasma membrane and in AGs (Rendu and Brohard-Bohn, 2001), and host the complete enzymatic machinery to process the protein into Aβ peptides (Ponomarev, 2018; Rainesalo et al., 2005). Indeed, full-length APP, encoded by platelet mRNA, acts as a platelet receptor, which upon activation shows a threefold increase at the platelet surface (Gardella et al., 1990). The effect of altered APP processing on platelets was described for the first time in 1997 (Abubaker et al., 2019), and in several later studies, platelet alterations including increased β-secretase activity and altered APP metabolism have been observed.

Moreover, there is extensive evidence showing that Aβ stimulates platelet reaction (activation, adhesion and aggregation) (Sonkar et al., 2014), inducing changes in platelet structure and morphology, modifications in the membrane fluidity (Grimm et al., 2006), increased release of ROS and altered APP processing (Ehrlich et al., 2013). The result is abnormal platelet activation in a high ROS and neuroinflammatory environment, leading to mitochondrial dysfunction and apoptosis (Shrivastava et al., 2011b; Xu et al., 2007).

In this context, it was first shown that in vitro formed β-amyloid from different proteins induces platelet activation through two pathways, binding to the scavenger receptor CD36 and to GP1bα, and activating p38 MAPK/COX1 pathways. These pathways induce the release of TxA2, triggering platelet activation (Herczenik et al., 2007). Later studies have shown that both Aβ40 and Aβ42 bind GPIIb-IIIa, and initiate platelet adhesion without degranulation, indicating that soluble Aβ peptides are not able to fully activate platelets (Abubaker et al., 2019; Donner et al., 2016).

Additionally, platelets from recently diagnosed AD patients present an increased activation state characterized by increased fibrinogen binding and altered morphology (Wiest et al., 2019). At the same time, diminished aggregation response is characterized by decreased CD62P, and CD63 positivity indicating impaired platelet degranulation (Wiest et al., 2019). However, a recent study in human platelet cultures revealed that platelet activation after stimulation with soluble Aβ40 is similar to activation after stimulation with collagen as measured by the release of ATP (Donner et al., 2020). This activation occurs through

Aβ40 binding and activation of both GPIIb-IIIa and GPVI receptor, leading at the same time to the induction of Aβ fibril formation (Donner et al., 2020). Since the main substrate of platelet GPVI receptor are collagen fibrils, fibrillary forms of Aβ may act as well as a substrate for GPVI (Abubaker et al., 2019), triggering a bi-directional loop with increasing Aβ aggregation which at the same time increases platelet activation (Fig. 3). Finally, recent studies suggested that Aβ42 has an even higher capacity of GPVI receptor binding (Abubaker et al., 2019), and that both fibrillar Aβ40 and Aβ42 stimulate platelet aggregation after activation of GPIb-IX-V and CD36 (Visconte et al., 2020).

4.2. *Relationship between platelet APP and Aβ and the brain*

Several studies have investigated the effect of platelet APP and Aβ-peptides on the brain using different mouse models. One of these studies explored the relationship between Aβ levels in the hippocampus and platelets during normal and accelerated AD-like ageing (Chen et al., 2019). Mice exhibiting fast ageing and accelerated senescence (SAMP8) were compared with similar mice but resistant to senescence (SAMR1). Mice were analyzed at 3, 6 and 9 months, and although Aβ40 and Aβ42 levels increased linearly with age in hippocampi and platelets of both SAMR1 and SAMP8 mice, Aβ levels were significantly higher in SAMP8 mice. Especially in platelets of the oldest SAMP8 age group, both Aβ peptides were drastically increased (Chen et al., 2019). Accordingly, Aβ producing pathways were altered, and in platelets, an age-dependent decrease of α-secretase levels was accompanied by the age-dependent increase of β-secretase levels, mainly in SAMP8 mice.

Another recent study was carried out in 14-months-old APP-PS1 transgenic mice presenting the full pathological spectrum (Kniewallner et al., 2020). The most striking result revealed that 22% of platelets were found in the extraluminal space of APP-PS1 mice brain compared with 6.8% in control mice. About 70% of these were activated in APP-PS1 mice, but only a small percentage was in wild type mice. In contrast, no significant differences regarding the activation status were found in blood (Kniewallner et al., 2020). The question about how platelets may enter the brain was addressed in a very recent study, where platelets obtained from 15-months old APP-PS1 mice were injected into 10-month-old non-transgenic mice (Wu et al., 2021). As a result, not only the deposition of aggregated Aβ accompanied by the activation of microglia was observed in the hippocampus, but increased permeability of the blood-brain barrier (BBB) was also detected using an in vitro BBB model (Wu et al., 2021). Once entered the brain, platelets seem to contribute directly to blood vessel damage and might be able to modulate the function of specific cell types, enhancing disease development (Kniewallner et al., 2020).

In addition to platelet heterogeneity caused by ultrastructural abnormalities, AD platelets also show mitochondrial dysfunction, which might be driven by COX deficiency (Linnebank et al., 2006; Selfridge et al., 2013). Moreover, decreased glutamate uptake and glutamine synthetase dysfunction have also been described in platelets of various

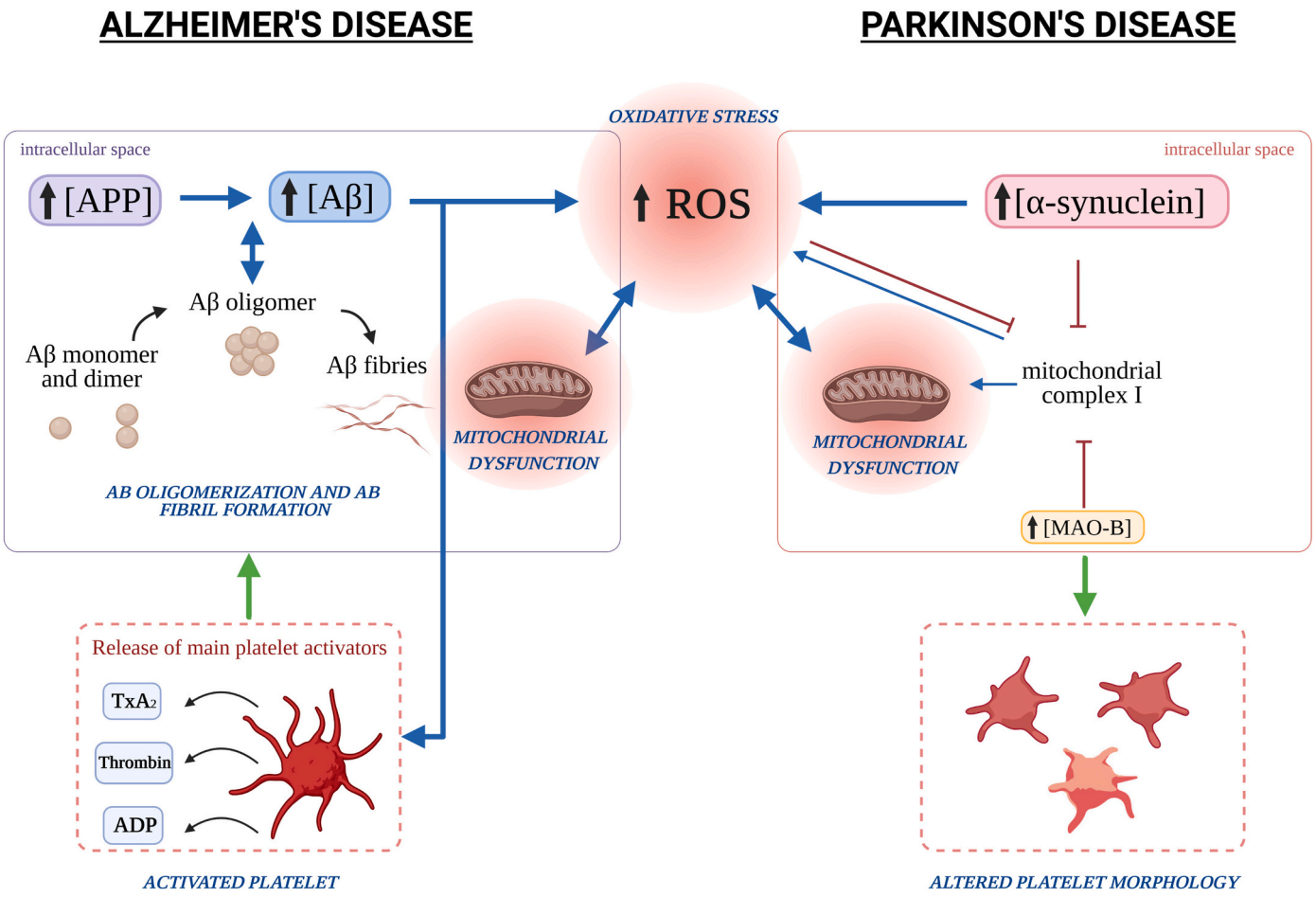

Fig. 3. Effect of APP/Aβ and α-synuclein on platelets in AD and PD. In AD, elevated platelet APP levels increase Aβ production promoting platelet activation, raising reactive oxygen species (ROS) and altering APP processing. Abnormal platelet activation induces Aβ fibril formation and APP production, further enhancing platelet activation pathways. In PD, increased platelet α-synuclein triggers oxidative stress and mitochondrial dysfunction through complex I inhibition leading to increased ROS levels. MAO-B overexpression found in PD platelets causes, together with increased ROS, further inhibition of mitochondrial complex I resulting in mitochondrial dysfunction and altered platelet morphology. Created with biorender.com.

neurodegenerative diseases (Ferrarese et al., 2000).

5. Platelets in synucleinopathies

Synucleinopathies include Lewy body diseases (LDB) and multiple system atrophy (MSA), and are characterized by abnormal α-synuclein aggregation, primarily in the brain. Whereas in MSA α-synuclein aggregates in form of glial cytoplasmic inclusions, in LBD α-synuclein aggregation leads to the formation of intraneuronal Lewy bodies and Lewy neurites. LBD comprise dementia with Lewy bodies (DLB) and Parkinson's disease (PD), and platelets have been studied mainly in the context of the latter.

5.1. Platelets in Parkinson's disease

PD is the second most common neurodegenerative disorder after AD and currently, more than 10 million people are living with PD worldwide (Dorsey et al., 2018). It develops after the loss of dopaminergic neurons in the *substantia nigra*, the ventral part of the *pars compacta* (SNpc), leading to motor symptoms including bradykinesia, tremor and rigidity (Jankovic, 2008). Although the molecular mechanisms underlying the loss of these neurons remain unknown, the presence of Lewy bodies is detected early in the SNpc (Schapira and Jenner, 2011). As most neurodegenerative diseases, PD is a multifactorial disorder, where the interaction of genetic and environmental factors is enhanced by the ageing process (Riess and Krüger, 1999).

In PD, the link between peripheral tissue and CNS has been mainly described by mitochondrial dysfunction, which is one of the most affected pathways (Vos and Klein, 2021). Mitochondrial complex I (NADH CoQ reductase) deficiency can explain neuronal apoptosis in the SNpc accounting for one of the primary sources of ROS in PD. Early studies on mitochondrial function in PD revealed decreased complex I activity in different brain regions, fibroblasts, skeletal muscle, platelets, and complex II/III in lymphocytes and platelets (Blesa et al., 2015). The inhibition of mitochondrial complex I enhances the presence of ROS species, which in turn inhibit complex I activity through negative feedback. Mitochondrial complex I is also inhibited by monoamine oxidase B (MAO-B) (Lim et al., 2009), which is expressed in platelets and significantly increased in PD (Meredith et al., 2009). Thus, the high amount of ROS in PD platelets has been associated with altered platelet activity in PD (Melchinger et al., 2019; Zhou et al., 2001) and points to oxidative stress as a key factor for PD development (Fig. 3) (Lim et al., 2009). However, if mitochondrial dysfunction found in platelets directly enhances dopaminergic neurotoxicity in the SNpc remains to be elucidated.

Moreover, glutamate levels are increased in the SNpc in PD, and impaired platelet glutamate uptake has been described in pathological conditions (Hashimoto et al., 1997; Pei and Maitta, 2019), and also dopamine uptake seems to be increased PD platelets (Roussakis et al., 2016).

About 50% of patients develop PD with dementia (PDD) at later disease stages (Caballol et al., 2007). The brains of these patients are characterized by an elevated burden of AD pathology, including accumulation of Aβ in senile plaques, especially in cortical regions (Irwin et al., 2013; Jellinger, 2018). Since it is known that platelets are the primary source of systemic APP and Aβ, their involvement in PD progression at later disease stages has been suggested (Inyushin et al., 2020). However, so far there are no studies addressing the role of platelet Aβ in the development of dementia in PD.

5.2. The role of platelet α-synuclein in PD

α-synuclein is expressed in platelets, participates in their differentiation and localizes at the plasma membrane, the endoplasmatic reticulum, and the membrane of AGs (Hashimoto et al., 1997; Pei and Maitta, 2019). It participates in the regulation of vesicle transfer and platelet granule release by inhibiting Ca^{++}-induced PF4 release (Park et al., 2002). The overexpression of platelet α-synuclein found in PD seems to be associated with the promotion of oxidative stress leading to mitochondrial deficit (Fig. 3) (Hsu et al., 2000; Pei and Maitta, 2019) and induces changes in platelet morphology (Pei and Maitta, 2019). Accordingly, it has been reported, that platelets obtained from PD patients have an increased volume compared to both AD patients and control individuals (Koçer et al., 2013). Finally, in contrast to Aβ, which has been found in dense platelet microvesicle fractions, α-synuclein has been detected in less dense microvesicles (Pienimaeki-Roemer et al., 2015), underlining the involvement of both in different functions.

6. Platelets in other neurodegenerative diseases

6.1. Platelets in amyotrophic lateral sclerosis

ALS is a progressive neurodegenerative disorder that affects nerve cells in the brain and the spinal cord. It presents a progressive decline of motor neuron functionality and subsequent respiratory failure and death. This neuromuscular paralytic disorder has an incidence ranging between 0.6 and 3.8/100 000 person-years (Longinetti and Fang, 2019), and is highly devastating, with 50% of the cases dying in the first three years of onset (Rowland and Shneider, 2001). Although ALS is still very poorly understood, it is known that in addition to the CSN, also peripheral tissue is affected, playing a key role in ALS development (Bos et al., 2006; Kiernan et al., 2011).

However, during the last decades, several studies have reported abnormal properties of ALS platelets. Glutamate excitotoxicity is an important characteristic in ALS pathogenesis and could be explained by an atypical glutamine synthetase increase in platelets (Rao et al., 1992; Smirnova and Festoff, 1994). The resulting decrease in glutamate uptake has also been reported for AD, PD and MS. Moreover, the increase of thrombospondin, a glycoprotein stored in AGs, is accompanied by serotonin decrease in ALS platelets (Dupuis et al., 2010; Shrivastava et al., 2011a). These changes can be related to uncontrolled neuron excitability. However, mitochondrial abnormalities and dysfunction are the most important changes found in ALS platelets. In this context, Shrivastava and colleagues identified changes in the permeability and potential of the mitochondrial membrane, and ultrastructural platelet modifications in ALS cases (Briones et al., 2018; Dantzer, 2018). According to these results, Ehinger and colleagues demonstrated later that reduced complex IV activity was accompanied by an increase of mitochondria in ALS blood cells (Ehinger et al., 2015). Recently, Marcelo et al. highlighted the importance of platelet–activating factor (PAF) as a major mediator of neuroinflammation in platelets of a mice model for ALS, proposing a potential novel therapy by using PAF-receptor specific inhibitors (Briones et al., 2018).

6.2. Platelets in multiple sclerosis

MS is a neurological disease that affects the CNS, including both the brain and spinal cord, and the peripheral nervous system. It is an immune-mediated demyelinating disorder in which the protective axon- and nerve-covering myelin sheath is damaged, leading to progressive sensation and motor deficits (Magyari and Sorensen, 2019; Spanevello et al., 2009). MS is considered the most common chronic inflammatory disease of the CNS, with a prevalence of more than 2.3 million people worldwide (Magyari and Sorensen, 2019).

Similar to the other neurodegenerative diseases, platelets in MS present abnormal activation, which seems to be associated with neuronal dysfunction. The myelin and axonal damage in MS is related to oxidative stress (Ohl et al., 2016; Spanevello et al., 2009), and platelets produce ROS affecting primarily glial cells, which change from resting to reactive state. Consequently, macrophages are activated and promote an excessive attack on the myelin sheath, resulting in neuronal demyelination and tissue damage. Specifically, in MS, different cells have been

found in the brain corresponding to a previous infiltration through the BBB (Balashov et al., 1999). BBB damage is caused by activated platelets which release mediators, increasing BBB permeability after being adhered to the endothelium (Imhof et al., 2016). The result is an increase in neurovascular inflammation (Dutta et al., 2006; Imhof et al., 2016).

Also, mitochondrial dysfunction has been found in this pathology (Werner et al., 2000), and similar to ALS, the abnormal increase of glutamine synthetase leads to less glutamate uptake, glutamate excitotoxicity (Dutta et al., 2006), increased thrombospondin levels (Dutta et al., 2006), and the reduction of platelet serotonine (Hesse et al., 2014). Altogether, these changes have been associated with neuronal changes.

7. Conclusions and future directions

The aspects reviewed here show the complex mechanisms that underlie platelet function. Several studies have demonstrated that platelet function goes beyond hemostasis, thrombosis, and wound healing, and their role in numerous other biological mechanisms, including inflammation, innate immunity and neurological processes has been described. Platelets regulate neural cells, contribute to brain plasticity and carry pro-neurogenic factors, and multiple mechanisms are involved platelet-neural cell communication. In this review, we discuss findings that link platelets to neurodegenerative diseases such as AD, PD, MS, and ALS.

Neurodegenerative disorders are complex and heterogeneous, and the age-related development of overlapping brain pathologies difficults their clinical diagnosis. With the increasing age of the world population, the incidence of neurodegenerative diseases rises. On one hand, there is an urgent need to identify diagnostic and prognostic biomarkers to improve the clinical management of these patients, and on the other, therapeutic options are reduced and primarily comprise symptomatic treatment. Accordingly, for AD, a disease affecting around 50 million people worldwide, the success rate of clinical trials is still below 1% (Cummings et al., 2014). This fact underlines the complexity of the development of assays for AD diagnosis and prognosis, and of effective therapies.

Since the definitive diagnosis of most neurodegenerative diseases can only be achieved post-mortem, the use of peripheral biomarkers is mandatory. These can provide reliable, quick and safe data to be used for differential diagnosis. Currently, cerebrospinal fluid AD biomarkers are available, but their obtaining through invasive interventions is a significant disadvantage (Blennow et al., 2010).Therefore, blood components are being studied, and platelets were considered a systemic tool for investigating neurological disorders as early as the 1970s (Stahl, 1977). Indeed, they are abundant in a small blood volume, easy to collect, and are able to change rapidly both their transcriptome and proteome in response to different stimuli. We have discussed above that disease-specific conditions may modulate platelet activation, indicating that platelets may be present in a disease-specific state. Accordingly, corresponding RNA or protein profiles might be enriched in platelets of diseased individuals, and their determination and characterization could lead to the discovery of diagnostic biomarkers for different neurodegenerative disorders. If these profiles were associated with the very first pathological changes in the brain, their determination could serve as early disease biomarkers.

In AD, increased platelet APP levels increase the production of Aβ peptides promoting platelet activation, which at the same time triggers Aβ fibrillation. Also, exercise promotes platelet activation, however, through a pathway that induces neurogenesis in the brain. Although far less studied, in PD, increased platelet α-synuclein levels are associated with mitochondrial dysfunction.

These observations raise several questions: can exercise-induced platelet activation counteract increased platelet-associated Aβ production in AD and prevent mitochondrial damage in PD? Does fibrillated Aβ enter the brain through damaged BBB and contribute directly to the development of AD-related pathology?

If, in fact, platelets directly contribute to disease development, intervening in their activation triggering specific pathways might represent a novel therapeutic strategy for these diseases.

In summary, this review highlights the potential clinical significance of platelets as peripheral diagnostic and prognostic biomarkers for neurodegenerative diseases on the one hand, and as therapeutic targets, on the other. Thus, as new potential biomarkers and technologies emerge, promising platelet-based testing and therapies might represent a possible future direction for diagnosis and treatment of neurological disorders.

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Declaration of Competing Interest

Paula Ferrer-Raventós y Katrin Beyer have no conflict of interest.

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