NEUROSCIENCE RESEARCH NOTES

OPEN ACCESS | MINI-REVIEW ISSN: 2576-828X

Platelets as mediators of neuropsychiatric and neurodegenerative diseases

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Received: 11 March 2024; **Accepted:** 21 June 2024; **Published:** 15 September 2024
Edited by: Pike See Cheah (Universiti Putra Malaysia, Malaysia)
Reviewed by: Konstantina Tsioni (Ippokrateio General Hospital, Greece);
Eleni Vagdatli (Hippokrateion General Hospital, Greece)
https://doi.org/10.31117/neuroscirn.v7i3.349

ABSTRACT: Numerous studies showing platelets' role in mechanisms beyond hemostasis have sparked interest in investigating all the pathways in which they may be involved. A growing body of evidence indicates that platelets play a key role in immune response. Platelets carry various membrane receptors and release many bioactive molecules that recruit and activate immune cells. Consequently, platelets have a significant immunoregulatory role in infectious, inflammatory, and degenerative diseases. Moreover, immune cells contribute to neuronal development, neural plasticity, and neuroglial activation. The interaction between platelets and immune cells reveals an additional regulatory mechanism of brain function. This review explores the relationship between platelets and the central nervous system (CNS). It highlights the role of platelets in the development of severe neurodegenerative and neuropsychiatric diseases, such as Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS) and depression.

Keywords: Platelets; Neuroinflammation; Neurodegenerative diseases; Neuropsychiatric disorders

1.0 INTRODUCTION

For many years, it was believed that hemostasis, thrombosis, and coagulation were the only processes platelets could promote. Recent research indicates that platelets play a key role in immune response and the pathogenesis of numerous diseases, revealing their new functions (Ferrer-Raventos & Beyer, 2021). Due to their strong immunomodulatory functions and ability to interact with distant cells and tissues, recent research focuses on the possible role of platelets in the perturbation of cerebral balance (Chaudhary et al., 2022).

Platelets are characterized as the "motile form of neurons" because of their numerous structural and functional similarities to neurons. In particular, serotonin and catecholamines are the most prominent neurotransmitters that platelets can store and secrete, which can trigger processes that worsen neuroinflammation in the brain parenchyma. Therefore, platelet dysfunction can promote nervous system disorders. This review explores platelets' interactions with CNS structures and highlights their role in the pathogenesis of numerous neurodegenerative and neuropsychiatric disorders.

2.0 INTERACTIONS BETWEEN PLATELETS AND IMMUNE CELLS

Platelets contain two main types of secretory organelles, α-granules and dense granules, which carry numerous membrane receptors and soluble molecules (**Table 1**) (Fard et al., 2021). The α-granules store the majority of secreted bioactive molecules as they contain membrane receptors, coagulation factors, coagulation inhibitors, fibrinolytic proteins, cytokines, chemokines, growth factors, angiogenic and anti-angiogenic factors, microbicidal proteins and immune mediators. The dense granules and lysosomes are less expressed but equally significant regarding platelet's function in immune response. Dense granules contain serotonin, ATP, ADP, polyphosphates and cations (Golebiewska & Poole, 2015; Yun et al., 2016; Rawish et al., 2020; Fountain & Lappin, 2022).

Table 1: Platelet receptors

Receptor	Function
Thrombin Receptors	Adhesion, spreading, secretion
ADP Receptors	Aggregation
Chemokine Receptors	Adhesion on endothelium
TXA2	Aggregation
vWF, Receptors (GPIIb/IIIα)	Aggregation
Integrins ($\alpha_{IIb}\beta3$, $\alpha_2\beta_1$, $\alpha_5\beta_1$, $\alpha_6\beta_1$, $\alpha_v\beta_3$)	Adhesion on endothelium. Aggregation,
GPIb-IX-V Complex	Aggregation
Toll like Receptors (TLR)	Inflammatory response
IgSF Group Proteins (GPVI, FcγRIIA)	Aggregation
PSGL1	Interaction between PLT-WBC
CD36, CD63, CD40	Aggregation, stabilization of aggregation, interaction between PLT-WBC, PLT-ECs, Inflammation

ADP, Adenosine diphosphate; TXA2, *Thromboxane A2;* vWF, *Von Willebrand factor;* GP, *glycoprotein;* IgSF, Immunoglobulin superfamily; FcγRIIA, *receptor* for the constant fragment of immunoglobulin G; PSGL1, P-Selectin Glycoprotein Ligand; CD, cluster of differentiation; PLT, Platelet; WBC, White Blood Cells; EC,Endothelial Cells

Therefore, platelets have a distinctive immunoregulatory role in infectious, inflammatory, and degenerative diseases (Ali et al., 2015). The platelet granules mainly support this role, which releases various bioactive molecules that recruit and activate immune cells and interact with platelets (Gremmel et al., 2016). Platelet extracellular vesicles (PEVs), a second class of particles released by active platelets, are frequently found in inflammation (Puhm et al., 2020). PEVs express large amounts of platelet activation markers, such as P–selectin. This indicates that secretion is enhanced in conditions of intense platelet stimulation (Spakova et al., 2021). PEVs primary functions include facilitating intercellular communication and transferring platelet content from blood circulation to distant and inaccessible tissues, such as the blood-brain barrier and lymph (Puhm et al., 2020; Ferrer-Raventos & Beyer, 2021). Studies of human platelets in vitro demonstrated that platelets can activate and recruit all the subpopulations of white blood cells, primarily neutrophils and monocytes. Platelets and leukocyte aggregates (PLAs) are formed when P-selectin and CD40 bind to their ligands, P-selectin Glycoprotein Ligand-1 (PSGL-1) and CD40 ligand (CD40L), respectively, on the surface of leukocytes (Sonmez & Sonmez, 2017; Koupenova et al., 2018; Maouia et al., 2020). This process requires platelet stimulation and accumulation on the endothelium (Rossaint et al., 2018).

Platelet membrane glycoproteins bind to the neutrophil surface integrin alphaMbeta2 (αMβ2). In addition, chemokines, such as platelet factor 4 (PF4) and Regulated on Activation, Normal T cell Expressed and Secreted (RANTES), as well as neurotransmitters, like serotonin, exert chemotactic action on neutrophils, directing them toward sites of inflammation (Rossaint et al., 2018). Platelets facilitate the differentiation of monocytes into macrophages and their recruitment at sites of endothelial damage through secreted factors, such as RANTES, High Mobility Group Box 1 Protein (HMGB1), PF4, Interleukin –1β (IL-1β), and Chemokine (C-C motif) ligand (CCL5), and connections between Glycoprotein IIb/IIIa (GPIIb/IIIa) on platelets and CD11b on monocytes (Dziedzic & Bijak, 2019; Ebermeyer et al., 2021).

The platelet phagocytosis and antigen presentation by dendritic cells to T lymphocytes are triggered by the interaction between platelets and dendritic cells via the Junctional Adhesion Molecule C (JAM-C) and Macrophage 1 antigen (MAC-1) pathways and by the serotonin secreted by platelets (Seyoum et al., 2018). The interaction between innate and adaptive immunity is further assisted by two pathways: (a) the connection of platelet GPIIb/IIIa and CD40 with T cell CD11b molecule to recruit lymphocytes to the inflammation sites and (b) the remarkable ability of platelets to express Major Histocompatibility Complex – 1 (MHC – 1) molecules, which contribute to the direct antigen presentation to T cells by platelets (Ali et al., 2015;

Koupenova et al., 2018; Dziedzic & Bijak, 2019). At the same time, soluble molecules, such as RANTES, PF4, Transforming Growth Factor–β (TGF–β) and serotonin, affect T cell proliferation and differentiation (Ali et al., 2015; Koupenova et al., 2018; Seyoum et al., 2018; Dziedzic & Bijak, 2019). The collaboration of platelets and B lymphocytes is less decisive but significant. Studies show that this interplay requires the initial interaction between platelets and T cells, which activates B cells to change their isotype and eventually produce immunoglobulins (Ali et al., 2015; Seyoum et al., 2018; Maouia et al., 2020; Ebermeyer et al., 2021).

3.0 PLATELETS IN BRAIN HOMEOSTASIS

The translational mechanisms of platelets, which enable them to respond to injuries, change their protein profile, and ultimately become activated, have been recently studied (Dantzer, 2018; Ma et al., 2023). As a result, platelets can maintain homeostasis even in the most remote cavities, such as the brain parenchyma. Molecules secreted by platelets, such as TGF – β and β-microglobulin, significantly impact brain function (Leiter & Walker, 2019; Lv et al., 2024). It has also been established that platelets maintain cerebral equilibrium following prolonged physical activity by regulating the proliferation of precursor neuron cells, which controls neuronal differentiation in the hippocampal region of the brain (Kazanis et al., 2015; Puricelli et al., 2023). Furthermore, immune cells contribute to neuronal development, plasticity, and neuroglial activation (Canobbio, 2019; Kopeikina & Ponomarev, 2021). As mentioned, platelets interact with immune cells, revealing an additional brain function regulatory mechanism. Consequently, platelet dysfunction can promote nervous system disorders (Fisar et al., 2016; Hishizawa et al., 2019).

4.0 PLATELETS IN ALZHEIMER'S DISEASE (AD)

AD was initially described as a peculiar neuron's disease of brain tissue. Neurofibrillary tangles (NFTs) and neuritic plaques (NPs) are now widely recognized as basic characteristics of the disease (Inyushin et al., 2017; Yu et al., 2021). Studies have shown that the two major initiators of their formation are the deposition of amyloid-beta (Aβ) to the brain tissue and vessels (also known as cerebral amyloid angiopathy or CAA) and the formation of Tau protein intercellular aggregations (Rawish et al., 2020).

Aβ, mainly Aβ40 and Aβ42, and the precursor protein for amyloid (APP) is found primarily in platelets (Inyushin et al., 2020). In addition, elevated beta-secretase activity has been detected in the patients' platelets (Burnouf & Walker, 2020). This enzyme catalyzes the cleavage of precursor protein for amyloid into monomers Aβ, which in turn form oligomers. Aβ oligomerics promote the hyperphosphorylation of protein Tau and the formation of interneuronal (NFTs) (Wu et al., 2021; Sarg et al., 2022).

Platelets have been characterized as a circulating form of neurons. They secrete numerous neurotransmitters, including serotonin and dopamine, and contribute to synaptic plasticity and learning, memory and neuronal differentiation processes (Izzi et al., 2020; Wassmer et al., 2021). Consequently, there is a direct correlation between the pathophysiology and progression of AD and the abnormal activation of platelets, which can lead to progressive cognitive decline (Kniewallner et al., 2020). As evidenced by the finding of decreased mitochondrial enzymes, such as pyruvate dehydrogenase complex, the severe neuroinflammation observed in AD causes the release of reactive oxygen species (ROS) and the onset of oxidative stress, which increases platelet and mitochondrial dysfunction (Donner et al., 2021).

4.1 Platelet activation in AD

As previously mentioned, platelets are the primary source of Aβ, which can be greatly reconnected on their surface through two distinct pathways, causing further activation. On one side, Aβ binds to the CD36 and GPIbα receptors, triggering the p38 mitogen-activated protein kinase/ Cyclooxygenase1 (p38MAPK/COX1) pathways and in turn, platelets' production of Thromboxane A2 (TXA2) (Donner et al., 2021). Additionally, Aβ40 and Aβ42 can bind to GPIIb/IIIa and GPVI, which activates the production of Aβ fibrils. In particular, Aβ and GPIIb/IIIa are connected via the RHDS (arginine, histamine, aspartic acid, and serine) sequence of Aβ40, which forms Aβ aggregations, releases them into the extracellular cavity, and eventually forms beta-amyloid plaques (Abubaker et al., 2019; Donner et al., 2020).

Kniewallner and colleagues studied the spatial location and state of platelet activation in the brain of transgenic mice with AD of the APP-PS1 type (mice with severe formation Aβ plaques without CAA. The study demonstrated a mild activation of platelets in the bloodstream, confirming that platelet stimulation starts in the periphery and is completed in the cerebral parenchyma (Kniewallner et al., 2020).

According to the findings of Kniewallner and colleagues (Kniewallner et al., 2016), platelet entry in the brain parenchyma, which is stimulated by matrix

metalloproteinases (MMPs), disrupts the vascular sequence. Studies using animal models with subarachnoid hemorrhage demonstrated that platelets enter the brain parenchyma through platelet-sized-holes in the basement membrane, possibly created by platelet-derived proteases, such as MMP2 and MMP9 (Doczi et al., 1986; Friedrich et al., 2010). These findings and studies on mice with severe formation Aβ plaques without CAA confirmed that platelets can penetrate the blood-brain barrier (BBB) and transfer Aβ into the brain (Leiter & Walker, 2020).

As platelets enter the cerebral parenchyma, they circulate as single cells or aggregates, interacting with cellular structures to regulate their function and contribute to AD's pathogenesis. In particular, releasing mediators such as thromboxane A2, CD40 ligand (CD40L), P-selectin, and IL-1β stimulates the deposition of Aβ peptides to blood vessels, enhancing vascular degeneration and neuroinflammation. Furthermore, platelets bind and stimulate microglia, releasing Tumor Necrosis Factor-a (TNF-α). Meanwhile, platelets and astrocytes may interact, aggravating the inflammation (Kazanis et al., 2015). Strong Glycogen Synthase Kinase-3 beta (GSK-3β) activity on patients' platelets raises Tau protein hyperphosphorylation and NFT formation. Increased stimulation of monoaminoxidase-B (MAO-B) is linked to neuronal apoptosis and mitochondrial damage. Moreover, the generation of bioactive products from lipid peroxidation propagates platelet activation, leading to an excessive accumulation of Aβ and the emergence of common complications in the disease (**Figure 1**) (Selfridge et al., 2013; Visconte et al., 2020; Yu et al., 2021).

5.0 PLATELETS IN PARKINSON'S DISEASE (PD)

A-synuclein complexes are accumulated in the brain parenchyma of patients suffering from synucleinopathies, such as PD (Ransohoff, 2016; Alam et al., 2022). In the early stages of the disease, this accumulation results in the loss of neurons in the substantia nigra. At the same time, Lewy bodies are present in this cavity (Dijkstra et al., 2014). The increased mitochondrial dysfunction observed in the disease supports the link between peripheral blood and the central nervous system. However, the precise molecular mechanisms of the disease are not completely elucidated (Li et al., 2022).

Studies in PD patients showed that inhibiting mitochondrial complex I in brain tissue, fibroblasts, skeletal muscles, and platelets promotes the release of ROS and leads to mitochondrial dysfunction and decreased activity of mitochondrial enzymes (Dias et al., 2013; Bandookwala & Sengupta, 2020). Oxidative stress develops due to abnormal platelet activation caused by the increased ROS production (Melchinger et al., 2019). It has been demonstrated that platelet MAO-B exhibits high activity, amplifying the inhibition of mitochondrial complex I in the substantia nigra, when glutamic acid levels are elevated. Platelets' decreased absorption of glutamic acid, explains its high levels in substantia nigra (Pei & Maitta, 2019).

A-synuclein accumulation in the brain suggests a strong relationship between the disease and platelets since it is present in large amounts in a-granules (Grotemeyer et al., 2022). Studies in PD patients suggest that elevated a-synuclein levels exacerbate pre-existing oxidative stress, mitochondrial dysfunction, and platelet morphological changes (Melchinger et al., 2019; Espinosa-Parrilla et al., 2019). Studies on drug addicts demonstrated that 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine (MPTP) was the main cause of the disease, and it was strongly correlated with mitochondrial dysfunction (Langston et al., 1983). Platelet MAO-B catalyzes the conversion of MPTP to 1-Methyl-4-Phenylpyridinium (MPP+), which migrates to the brain tissue through the BBB. This results in the inhibition of mitochondrial complex I and neurodegeneration (Lim et al., 2009; Li et al., 2022). Significantly elevated levels of neuroinflammatory mediators, including RANTES, macrophage inflammatory protein-1 alpha (MIP-1a), IL-1β, and TNF-α have also been observed in animal models, which undoubtedly explains the high level of platelet activation and hypersecretion of these molecules (Chandra et al., 2017). More research is still needed to fully elucidate platelets' role in PD and the precise molecular mechanisms.

6.0 PLATELETS IN MULTIPLE SCLEROSIS (MS)

Multiple Sclerosis (MS) is a neurodegenerative disease. The main characteristics of the disease are the progressive loss of neuronal structure and function in particular areas of the CNS, along with persistent inflammation (Kaufmann et al., 2022). The development of microglia reactivity and demyelination are further pathophysiological features that follow the initial stage of neuroaxonal degeneration (Baecher-Allan et al., 2018). The BBB is disrupted at the focal sites of demyelination, which results in the breakdown of the CNS immune system and metabolic homeostasis (Schreiner et al., 2022). The pathogenesis of MS is based on the destruction of myelin and the pathological features of oligodendrocytes due to significant

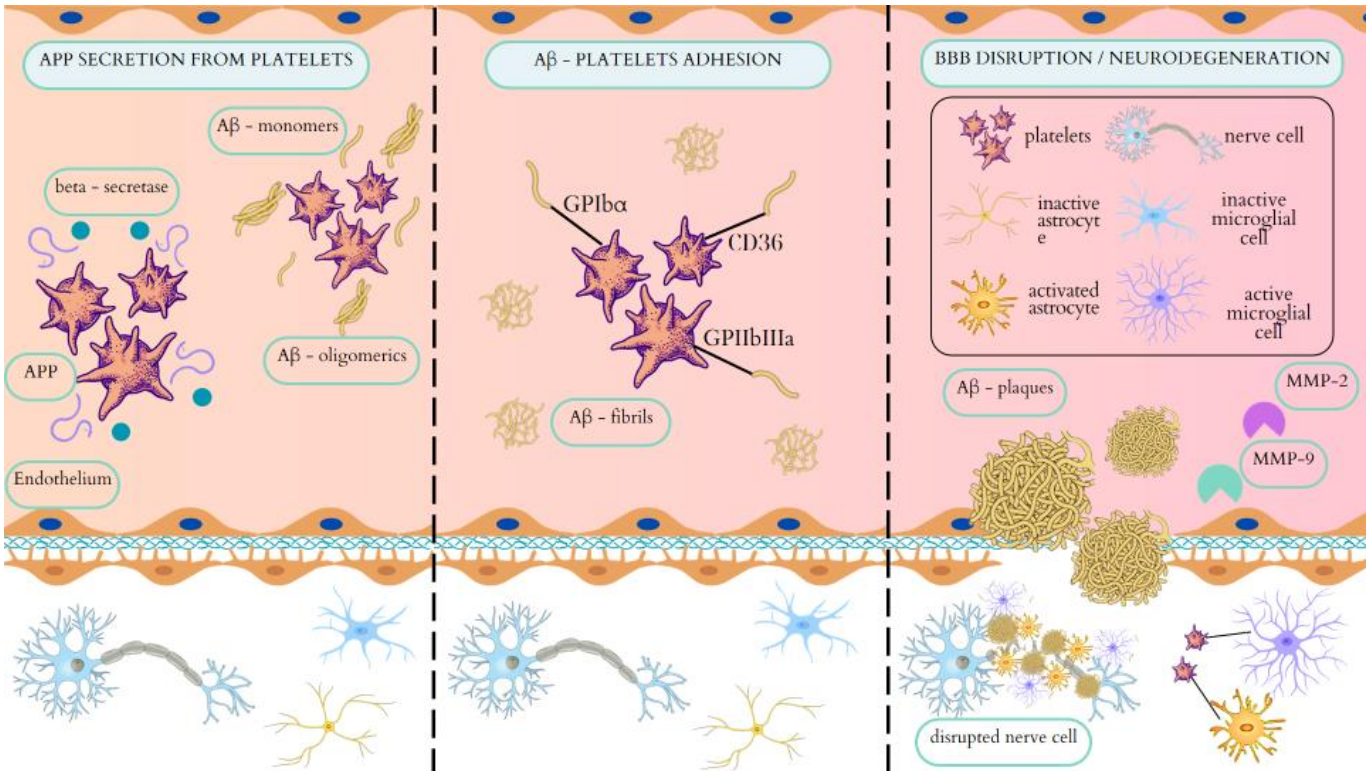

Figure 1. Platelet activation in Alzheimer's Disease. Platelets are the main source of Aβ and its precursor protein APP. The enzyme beta-secretase catalyses the conversion of APP to Aβ–monomers, which form Aβ oligomerics. Aβ – monomers bind on platelets surface via GPIbα, CD36 or GPIIb/IIIa and regulate the formation of Aβ – fibrils and finally Aβ – plaques. The stimulated platelets activate metalloproteinases (MMPs), which create holes on the basement membrane, facilitating the entrance of Aβ – plaques and platelets through BBB. Platelets interact with astrocytes and microglia in the brain parenchyma, enhancing their pathological activation and directing them to the nerve cells. Reactive microglia and astrocytes stimulate the production of Aβ and the formation of NFTs and also accumulate on Aβ – plaques, exacerbating the neuroinflammation and the damage of nerve cells. The figure was originally designed by the authors using Chrome Canvas. BBB: Blood-brain barrier, APP: Amyloid precursor protein, Aβ: Amyloid β protein, GPIbα: Glycoprotein Ib alpha, GpIIbIIIa: Glycoprotein IIb/IIIa, MMP-2: Matrix metalloproteinase 2, MMP-9: Matrix metalloproteinase 9.

lymphocyte infiltration in the brain parenchyma (Correale & Farez, 2015; Orian et al., 2021). In addition, cytokines, ROS and reactive nitrogen species (RNS) are released, which provoke the rupture of the axonal myelin sheath and neuroaxonal degeneration (Lucchinetti et al., 2001; Von Essen et al., 2019). As has been observed in patients with MS, metalloproteinases (MMPs), such as MMP2, MMP7, MMP9 and MMP12, play a significant role in the degradation of the extracellular matrix (ECM) and BBB disruption (Thornton et al., 2010).

Platelet hyperactivation in multiple sclerosis is caused by abnormal immunological background and BBB damage. The BBB disruption is the cause of the circulation's loss of fibrinogen. This phenomenon is evidenced by the expression of Tissue Factor (TF), CRP, thrombin, β-Thromboglobulin (β–TG) and FXII factor, presenting an intense thrombotic predisposition (Sheremata et al., 2008). Increased fibrinogen levels were found in a study involving 50 patients with secondary progressive multiple sclerosis (SPMS) and 50 healthy volunteers. This finding was linked to platelet hyperactivity in MS (Bijak et al., 2019). Besides, the production of IgM immunoglobulins, complement system elements, and ADP, as a consequence of acute immunization, stimulates platelets (Horstman et al., 2010).

Several in vitro studies in human cells demonstrated the platelets' role in MS. By secreting various soluble factors such as IL-1β, Platelet Activating Factor (PAF), PF4, and

5-hydroxytryptamine (5-HT), activated platelets play a significant role in the development of the disease (Chihara et al., 1992). These factors regulate the responses of activated T cells, their production of cytokines, and their differentiation into pathogenic T helper 17 cells (Th17) and interferon γ-producing CD4+ T (IFN-γ/CD4 T) cells, which release IL-17 (Dressman & Elyaman, 2021). Concurrently, IL-1β increases endothelial permeability and promotes white blood cell recruitment and adhesion on endothelium (Chen et al., 2020). A large amount of platelet microparticles is produced as MS progresses. Platelet factor transporters, platelet microparticles, carry P-selectin, which binds leukocyte PSGL-1 and Platelet Endothelial Cell Adhesion Molecules-1 (PECAM-1) to create a connection between white blood cells and endothelium. Additionally, platelet microparticles transfer PAF, which disrupts the endothelial bonds, causing the rupture of BBB (Thomas & Storey, 2015). After interacting with leukocytes, platelets secrete MMPs. This process justifies the high MMP1, MMP2, MMP3, and MMP4 levels in MS (Bar-Or et al., 2003; Seizer & May, 2013).

The accumulation of inflammatory cells and the proinflammatory stimulation of microgliocytes triggers platelet response, activating the characteristic pathways of CD40–CD40L and P–selectin–PSGL-1. As a result, endothelial and immune cells interactions are promoted (Kuenz et al., 2005; Wachowicz et al., 2016). Platelets attach to endothelial cells via the CD40–CD40L pathway, which increases the expression of chemokines (CCL2, CXCL4, CCL5), MMPs (MMP1, MMP2, MMP9), and endothelial adhesion molecules [E–selectin, PECAM-1, Vascular Cell Adhesion Molecules-1 (VCAM-1), Intracellular Adhesion Molecules-1 (ICAM-1)]. This causes neutrophils, monocytes, and lymphocytes to adhere to the inflammatory vascular walls (Rayes et al., 2020).

Furthermore, platelets interact with leukocytes, release RANTES, recruit T cells, differentiate CD4, T regulatory cells (Tregs), T helper 17 cells, produce T helper 1 cells, and change the isotype of B cells from IgM to IgG (Saluk-Bijak et al., 2019). Regarding the axon P-selectin- PSGL-1, platelet-neutrophil interaction causes hypersecretion of ROS, which targets the myelin sheath and amplifies neurodegeneration (Morel et al., 2016; Dziedzic et al., 2020). The pathological form of CD4 T cells, their proliferation, and the expansion of the immune and inflammatory processes are activated by a specific bond between the adhesion molecule CD166 of CD4 T cells and platelet P-selectin (Drolet et al., 2011, Morel et al., 2015). Interactions between platelets and leukocytes in multiple sclerosis are shown in **Figure 2**. It has been recently demonstrated in an experimental study in mice that gangliosides integrate into astroglia and neural lipid structures, specifically gangliosides GT1b and GQ1b, as well as brain-specific glycolipids, by platelets. As a result, gangliosides accumulate in the cerebral parenchyma, eventually triggering immune reactions that aggravate inflammation and accelerate neurodegeneration (Sotnikov et al., 2013).

Several studies use experimental autoimmune encephalomyelitis (EAE), an animal model which mimics the pathological mechanisms of MS, to investigate possible pathogenetic pathways and to develop new therapeutic approaches. Kocovski and colleagues detected high reactivity and accumulation of platelets, which led to intense CD4+ penetration in cerebral parenchyma after 3-6 days. After administering an antiplatelet GPIba receptor injection to mice, researchers noticed a decrease of CD4+ in blood, lymphatic organs and central nervous system (Kocovski et al., 2019). Moreover, Vogelsang and colleagues inhibited the sensitivity of EAE in neuroinflammation by using the antiplatelet factor acetylsalicylic acid. Reduced platelet counts attenuated the degree of demyelination, the disease's severity and the immune cells' concentration in the CNS (Vogelsang et al., 2021).

In MS patients, cardiovascular disease appears to be the primary cause of death, suggesting that platelets may act as mediators in the fatal progression of the disease (Dziedzic et al., 2020). A large Swedish cohort study demonstrated a higher risk of cardiovascular disease in patients with MS. This finding highlights the critical role of hyperactivated platelets (Roshanisefat et al., 2014). Interestingly, MS pathogenetic processes may be related to platelet RNA profiles. Platelets from multiple sclerosis patients had higher specific spliced RNA transcript levels than those from healthy individuals (Sol et al., 2020).

7.0 PLATELETS IN NEUROPSYCHIATRIC DISORDERS

As previously mentioned, platelets mimic the stable synaptic structure of neurons by sharing several characteristics, including the expression of certain receptors and transporters, such as serotoninergic receptors, and secretory vesicles and their contents, which include Reelin, Amyloid Precursor Protein, and Brain-Derived Neurotrophic Factor (BDNF).

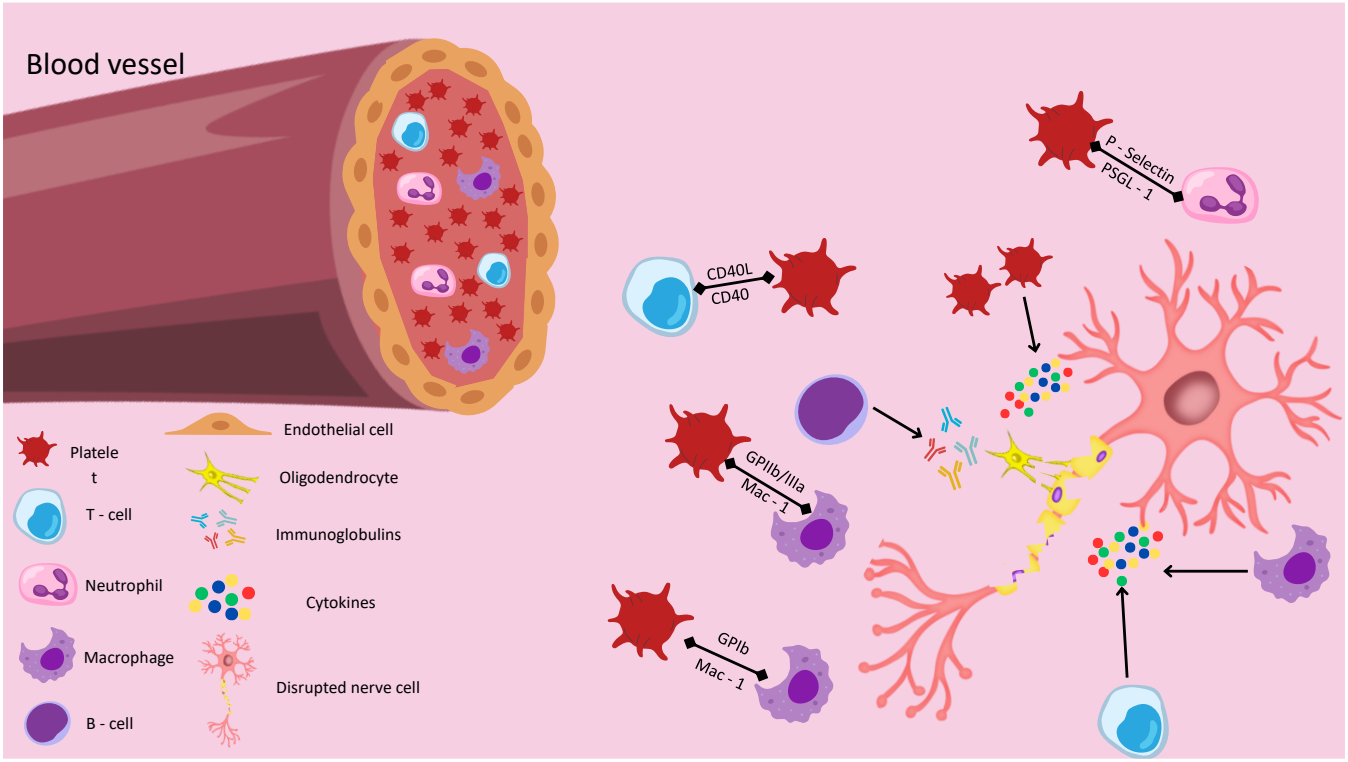

Figure 2. Interactions between platelets and leukocytes in multiple sclerosis (MS). MS is characterized by an intense immune response, which causes extensive loss of myelin. MS primarily targets the myelin of the nerve cell axons in the CNS, which oligodendrocytes produce. Since myelin plays a crucial role in impulses' propagation among the axon, demyelination promotes disease development. The interaction between leukocytes and platelets leads to hyperactivation of platelets and the release of soluble mediators by platelets, macrophages and T-cells. The accumulation of cytokines increases the inflammation in brain parenchyma. The inflammation and the immunoglobulins secreted by abnormally activated B-cells promote the damage of oligodendrocytes, demyelination, and, finally, the degeneration of nerve cells. The figure was originally designed by the authors using Chrome Canvas. CNS: Central nervous system. GPIIbIIIa: Glycoprotein IIb/IIIa, Glycoprotein Ib, Mac-1: Macrophage 1, PSGL-1: P-selectin glycoprotein ligand-1

Furthermore, the same molecular mechanisms regulate the stimulation of the granules in these two cell types, as seen by the fact that they are both activated by calcium to release neuronal neurotransmitters and platelet-derived agonists. These data have led to the theory that platelets are a significant "bridge" between neuropsychiatric diseases, such as depression, and circulation (Tseng et al., 2009; Gresele et al., 2017; Santana & Marzolo, 2017).

7.1 Platelets in depression

Studies in patients with depression have demonstrated significantly increased levels of platelet markers, such as β-thromboglobulin (β-TG), PF4, IL-1β, GPIIb/IIIa, P-selectin and CD40. These findings demonstrate an intense platelet activation and reactivity (Williams, 2012). It is known that patients with major depressive disorder (MDD) have elevated levels of serotonin and other neurotransmitters, such as BDNF and Reelin, in serum and cerebrospinal fluid (Tseng et al., 2009; Serra-Millas et al., 2011).

Serotonin is transported in the bloodstream by the serotonin transporter SERT and is deposited in the dense granules by the vesicular monoamine transporter 2 (VMAT2). Serotonin is released during platelet activation and binds to the platelet surface through specific receptors 5-HT-2A and 5-HT-3A, which induces platelets' further stimulation and accumulation (Izzi et al., 2020). It is difficult to fully understand the correlation between platelets and the pathogenesis of depression because the data linking platelet serotonin to the disorder's progression are contradictory. Most clinical studies indicate a decrease in the binding capacity of serotonin transporter and an increase in the concentration of its receptors in the bloodstream (Owens & Nemeroff, 1998; Stain-Malmgren et al., 2001; Peitl et al., 2020). However, some studies indicate

reduced levels of serotonin and its main metabolite, 5-Hydroxyindoleacetic acid (5-HIAA), in brain tissue necropsies from patients with depression (Williams, 2012).

The role of BDNF, a protein that controls the formation of neural circuits in the nervous system and has a well-known antidepressant effect at the onset of MDD is also significant. Platelets are the main source of BDNF storage, and platelet count directly correlates with serum BDNF levels (Boukhatem et al., 2024). The disease is associated with low levels of platelet granules that express BDNF. This finding explains the decreased BDNF levels that lead to the exacerbation of emotional and psychological disorders (Dwivedi, 2009).

Furthermore, elevated levels of dopamine, adrenaline, and noradrenaline have been found in patients with psychogenic disorders, supporting the strong association between catecholamines and the severity of depression (Lake et al., 1982; Peacock et al., 2017). Platelets express adrenergic and dopaminergic receptors. Elevated catecholamine levels promote platelet recruitment, PF4 and β-thromboglobulin release, and accumulation. In particular, adrenaline increases platelets' expression of Thromboxane A2, strengthening fibrinogen binding to platelets (Wu et al., 2021). Subsequently, platelets release several chemokines, such as RANTES, TNF-α, and Stromal Cell–Derived Factor–1 (SDF–1), which affect the neurobiological processes associated with the symptoms of the disease (Amadio et al., 2020).

Recent studies have demonstrated that patients with depression have altered leptin's metabolic pathway and genetic expression (Jow et al., 2006). Because of the high levels of leptin in MDD, platelets express the leptin receptor LEPRL, which enables activation and platelet aggregation (Giandomenico et al., 2005). Depression has been linked to the suppression of platelet and neuron mitochondrial function, which severely impairs brain activity. Clinical studies showed increased levels of antioxidant enzymes and oxidative damage products in depressed patients compared to healthy controls, suggesting that mitochondrial dysfunction induces oxidative stress and a high release of ROS (Black et al., 2015).

7.2 Platelets and comorbidities of depression

Cardiovascular diseases

The most common comorbidities of depression that increase mortality are cardiovascular diseases (Glassman, 2007). Elevated serotonin levels induce a significant platelet accumulation in atherosclerotic arteries, ultimately leading to clot formation and the development of cardiovascular disease (Williams et al., 2019). Studies in patients with depression revealed an unusual expression of GPIIb/IIIa and P-selectin when they were in an orthostatic position. Therefore, platelet hypersensitivity may be a contributing factor to ischemic heart disease, cerebrovascular disease, or death after an infarct (Williams, 2012).

Schizophrenia

Schizophrenia can be described as the progression of depression. Since the mitochondrial enzyme MAO is reduced in schizophrenic individuals, there has been a strong correlation between MAO, neurotic behavior and bipolar disorder, which characterize the disease (Bortolato et al., 2009; Aji et al., 2023). Brain cells express primarily MAO-B and secondly MAO-A. In contrast, platelets secrete only MAO-B, whose decrease indicates a direct involvement in the paranoid type schizophrenia (Repovecki et al., 2022). Research findings suggest that in patients with Schizophrenia, there is a significant activity of the platelet's mitochondrial complex I (COI), which has been linked to recurrent psychotic episodes. In addition, patients with chronic Schizophrenia had higher concentrations of Glutamine Synthetase-Like Protein, which regulates glutamic acid metabolism in platelets, and higher titers of autoantibodies against platelets in the prefrontal cortex (Asor, 2012).

Intense stress

Research in humans indicates that chronic stress promotes hyperstimulation of the hypothalamus–hypophysis axon, leading to the dysfunction of the central sympathetic and serotoninergic system, and platelets' activation (Haroon et al., 2011). Consequently, due to the increased concentration of β-thromboglobulin, PF4, CD63, the high rate of platelet-monocyte aggregates, and the severe fibrinogen-GPIIb/IIIa binding, there is an increased risk of cardiovascular disease (Patterson et al., 1995; Koudouovoh-Tripp, 2012). Platelets' strong reactivity to patients experiencing meta-traumatic stress, as measured by ADP, stimulates P-selectin's surface expression and the formation of platelets and neutrophil aggregates (Rust et al., 2023).

The correlation between platelet serotonin and post-traumatic stress disorder development is controversial. The study of Li and colleagues (Li et al., 2016), demonstrated reduced serotonin concentration in post-traumatic stress disorder patients, while the study of

Pivac and colleagues (Pivac et al., 2006), claims high levels. Additionally, patients with psychogenic complications caused by post-traumatic stress disorder showed high activity of platelet MAO-B, suggesting that the enzyme could be linked with the disorder (Koudouovoh-Tripp, 2012).

8.0 FUTURE PROSPECTS

Platelets have multifaceted functions and interact with multiple cells due to their granules' reservoir of anti-inflammatory, neuroprotective, and antioxidative molecules. The interaction between platelets and the brain parenchyma will probably result in the development of new diagnostic biomarkers for neurodegenerative diseases. Numerous microRNAs (miRNAs) that regulate the neuroinflammatory processes in MS have been linked to the disease's duration and activity. MicroRNAs have also been identified as potential biomarkers for both progressive and relapsing-remitting MS (Mehdi-Alamdarlou et al., 2023). According to a current study, patients with PD have significantly higher plasma PEV-Aβ1-42 levels. Regarding cognitive decline in PD, the plasma PEV-Aβ1-42/PEV ratio could be a promising biomarker (Wang et al., 2023). Recent reports have also indicated that patients experiencing recurrent depression who are resistant to treatment have elevated platelet distribution width (PDW), suggesting PDW as a new, potential biomarker of depression (Gialluisi et al., 2019). Platelets' ability to interact with neural cells will probably lead to the development of novel therapies for preventing or managing CNS disorders.

In recent preclinical studies neurotrophin-rich platelet lysates have been developed using human platelet-rich plasma or platelet concentrates as source materials for treating the central nervous system disorders (Burnouf & Walker, 2020). Due to platelet PEVs capacity to transfer trophic factors, cross tissue barriers and diffuse into target cells, there is growing interest in their therapeutic use as drug carriers (Dantzer, 2018; Burnouf & Walker, 2020). Furthermore, there is increasing evidence that antiplatelet drugs are effective in treating neurodegenerative diseases (Puricelli et al., 2023).
BDNF levels are affected in multiple neurodegenerative disorders. BDNF is considered as a possible therapeutic agent because of the negative correlation between low BDNF levels and cognitive disorders. Despite the positive outcomes of cerebral injection of BDNF in animal models, its short half-life and the inability to effectively cross the BBB, limit its potential for therapeutic use (Boukhatem et al., 2024). Moreover, given the significant role of mitochondria in the development of PD, antioxidants that target mitochondria have gained interest (Ma et al., 2023). Although further preclinical and clinical investigation is required, the possibility of administering drugs targeting platelet function and platelet-derived preparations to the brain may offer a novel therapeutic strategy for CNS disorders.

9.0 CONCLUSIONS

The expression of membrane receptors, which promote intercellular communication, and the release of numerous soluble molecules are two processes that determine platelet activation. As a result, platelets develop new functions and migrate to the cerebral parenchyma. Due to their ability to mimic the structure and function of neurons and their direct involvement in neuroinflammation processes, platelets play a significant role in the pathogenesis of neuropsychiatric and neurodegenerative diseases. The data regarding the correlation between platelets and neurodegenerative diseases (AD, PD and MS), or neuropsychiatric disorders (depression and its comorbidities), has significantly increased recently. Many studies demonstrate platelets' hyperactivation in these diseases and their interaction with numerous cells within the brain parenchyma, including immune cells, astrocytes, and microglia, resulting in vascular damage and cerebral homeostasis loss. Additional studies of platelet functions are required to elucidate the pathophysiology of various neurological diseases and to develop novel, more efficacious therapies.

Author Contributions: VK conceptualized, designed and supervised the study. VK, DF, IC and KG prepared the manuscript. All authors have read and approved the final manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

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