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Platelets and platelet-derived vesicles as an innovative cellular and subcellular platform for managing multiple sclerosis

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Abstract

Introduction Multiple sclerosis (MS) is a progressive inflammatory autoimmune disease that involves young individuals. The drug delivery systems now are available for this disease have chronic and non-targeted effects on the patients. Because of the presence of BBB (blood-brain-barrier), their concentration in the CNS (central nervous system) is low. Because of this flaw, it is critical to use innovative active targeted drug delivery methods.

Result Platelets are blood cells that circulate freely and play an important role in blood hemostasis. In this review, we emphasize the various roles of activated platelets in the inflammatory condition to recruit other cells to the injured area and limit inflammation. Besides, the activated platelets in the different stages of the MS disease play a significant role in limiting the progression of inflammation in the peripheral area and CNS.

Discussion This evidence indicates that a platelet-based drug delivery system can be an efficient biomimetic candidate for drug targeting to the CNS and limiting the inflammation in the peripheral and central areas for MS therapy.

Keywords Multiple sclerosis · Platelet, · Inflammation · BBB · Platelet-based drug delivery system · CNS

Introduction

Multiple sclerosis (MS) is an autoimmune disease featuring chronic inflammation [1]. The degradation of the blood-brain barrier (BBB), multifocal and chronic inflammation, oligodendrocyte loss and demyelination, axon degeneration, and reactive gliosis are all part of the pathological process of MS. These abnormalities result from the infiltration of peripheral inflammatory and immune cells into the central nervous system (CNS), including macrophages, T cells (both CD4 and CD8 cells), B cells, and plasma cells [2, 3]. Even though MS's etiology remains elusive, many studies indicate that genetic and environmental factors are involved [4]. This disease is usually diagnosed between the ages of 20 and 40 and affects 2.5 million people globally, impairing the lives of young people due to its severe economic and social implications [5, 6]. Relapsing-remitting MS (RR-MS) is present in 85% of cases, where patients experience recurrent episodes of disease symptoms followed by remission. However, remission is not always accrued; after years, some patients face the secondary progressive course of the disease, and a smaller number of patients experience the primary progressive course of the disease [7, 8].

Drug-modified therapy (DMT) is currently available to treat MS by managing the disease progression, suppressing the inflammation process mediated by the immune system, and decreasing the attack rate [8]. Because of the chronic and non-specific effects on the immune system, this strategy is not effective in all patients. Therefore, an urgent need for new drug delivery systems is evident [9].

Nowadays, platelets play critical roles in suppressing inflammatory processes and facilitating recovery in injured

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and inflamed organs [10]. These processes are regulated by suppressing inflammatory cytokines like tumor necrosis factor (TNF)-α, which induces the inflammatory phenotype of macrophages and monocyte, and by secreting IL-10, which triggers an anti-inflammatory phenotype in the mentioned cells [11]. Thanks to the presence of various receptors and different molecules in their membrane, platelets may connect with other cells, such as endothelium and immune cells. Meanwhile, these chemicals and receptors assist platelets in crossing the BBB and concentrating in inflammatory areas, slowing the evolution of the inflammatory process [12, 13]. Hence, platelet utilization as a cellular vehicle for the delivery of drugs to the brain could be an effective delivery system for MS treatment.

Pathogenesis

Recent studies showed that despite the uncertainty of the etiology of MS, environmental factors like deficiency of vitamin D3, smoking, history of Epstein-Barr virus infection, obesity, Western diets, and genetic factors might affect MS progression and increase differentiation in the immune system and production of inflammatory cytokines [14, 15]. These substances stimulate antigen-presenting cells (APCs) and pathogen recognition receptors including toll-like receptors (TLRs), which play a key role in host defense and identifying signals from necrotic and injured tissues. The immune system's activation depends on these receptors, which recognize pathogenic substances and unusual signals. These are expressed in various immune and non-immune cells, including most CNS cells like microglia, astrocytes, neurons, and oligodendrocytes. Activation of subsequent pathways with TLRs could trigger the production of pro-inflammatory cytokines like IL-1, IL-12, and TNF-α and induce the pro-inflammatory NF-κB and MAPK pathways [16, 17]. Different stimuli activate the NF-κB pathway, which then translocates to nuclei. The activation of transcription factors plays a key role in the production of pro-inflammatory genes and leads to the transformation of innate immune cells like macrophages into the M1 pro-inflammatory phenotype, as opposed to the M2 anti-inflammatory phenotype. This produces pro-inflammatory cytokines like IL-12, IL-1, IL-6, and TNF-α and induces activation of adaptive immune cells like CD4 T cells, which differentiate to Th1, Th2, and Th17. Th17 secretes IL-17, which activates neutrophils and monocytes and recruits them to the damaged organ [18, 19, 24]. The presence of NF-κB subunits in the nuclei of damaged astrocytes and infiltrated macrophages was shown in active MS plaques, and the upregulation of NF-κB related genes was detected in MS patients compared with control groups [20]. These findings indicate that dysregulation of the inflammatory pathway significantly affects MS progression.

It is believed that APCs activate autoreactive T cells and inflammatory cascades and recruit other T cells and macrophages to initiate inflammatory lesions. Macrophages secrete toxic and pro-inflammatory cytokines like matrix metalloproteinase, TNF-α, IL-6, and IL-1. These cells migrate to the CNS and induce myelin loss, axonal damage, and neuronal dysfunction [21]. Compared to healthy controls, myelin-reactive T cells in MS patients are more active, exhibit a Th1 phenotype, and have a greater affinity for myelin-binding protein. CD8 and CD4 cells have been seen in MS lesions, and they may bind to and destroy cells that express major histocompatibility complex (MHC) class 1, such as neurons and oligodendrocytes [22]. Th1 cells produce inflammatory cytokines like interferon (IFN)-γ and TNF-α. These cytokines induce the production of IL-6, which indirectly leads to the expression of vascular adhesion molecule 1 (VCAM I) on the surface of endothelial cells in the BBB and have a crucial role in the production of Th17.

Th17 produces IL-17, IL-22, IL-21, and IFN-γ, which can kill oligodendrocytes. IL-17 induces the secretion of pro-inflammatory cytokines, such as IL-6, TNF-α, and granulocyte-monocyte colony-stimulating factor (GM-CSF), and chemokines, including CCL20, CXCL2, and CXCL8, which can activate microglia and recruit lymphocytes, macrophages, and neutrophils [21, 24]. Furthermore, IL-17 contributes to the breakdown of BBB integrity by down-regulating occludins. IL-17 stimulates the synthesis of IL6, CXCL8, and CCL2 by BBB endothelial cells, allowing peripheral lymphocytes and monocytes to migrate to the CNS. Activated microglia, infiltrating dendritic cells, and macrophages generate IL-23, which promotes Th17 proliferation [23].

Pro-inflammatory cytokines produced by Th1 and Th17, like GM-CSF, IFN-Ɣ, and TNF-α cause macrophage polarization to the M1 phenotype. In an experimental autoimmune encephalomyelitis (EAE) model study, it was observed that M1 macrophages produced inflammatory cytokines like IL-6, IL-8, IL-12, TNF-α, and IL-1β, which caused tissue injury, in addition to the production of CD86, CD40, IL12, and MHC class 2 (24). IL-12 has a potential link with the high-level production of IFN-Ɣ, which has an essential role in inflammation progression and tissue damage [25]. IL-6, IL-12, and IL-23 are implicated in differentiating T cells to Th1 and Th17 and have a significant role in the progression of inflammatory conditions in MS [26].

Anti-inflammatory cytokines such as IL-13, IL-4, and IL-10 cause macrophages to polarize to the anti-inflammatory M2 phenotype. The presence of INOS and CD4 + macrophages in the active lesions of axonal injuries was shown in EAE model studies. Furthermore, the presence of IL-10 and the M1 phenotype of macrophages in the recovery phase indicates the macrophage's dual role in different disease stages [27].

Blood-brain barrier dysfunction and receptors in inflammatory conditions

In a healthy person, peripheral substance movement to the CNS is restricted by the BBB, and infiltration of immune cells is restricted by the sealed tight junctions of endothelial cells (EC) and the end feet and pericytes of astrocytes. In the early stage of MS, peripheral leukocytes infiltrate the CNS, and BBB dysregulation plays a significant role in multifocal lesion formation [28]. Th1 and Th17 are pathogenic lymphocyte T cells. Pro-inflammatory cytokines and chemokines produced by pathogenic activated T cells, such as the VLA-4 integrin and leukocyte functional antigen (LFA-1), may cause leukocyte infiltration and transendothelial migration. ICAM1 and VCAM1 are overexpressed on ECs by various inflammatory stimuli, and pathogenic lymphocyte T cells have a high affinity for attaching to them. Furthermore, transmembrane glycoprotein selectin subsets including the P, E, and L glycoproteins are overexpressed under inflammatory conditions in ECs and have a significant role in leukocyte-EC interaction and transendothelial migration. Expression of P-selectin is upregulated in neuroinflammatory conditions by all CNS vasculature [29]. Many active cells, including T cells, macrophages/microglia, and astrocytes present in active MS lesions, release Th1 cytokines like INF-γ, IL-12, 1 L-6, IL-8, TNF-α and IL-1β, which promote expression of intracellular adhesion molecules (ECAM), including ICAM1, E-selectin, and VCAM1. The expression of VCAM1 is elevated during relapses and decreased in remission of MS or following a high dose of a corticosteroid. These cytokines are the essential stimuli for the production of α (CXC) and β (CC) chemokines, which are chemotactic for neutrophils and monocytes/macrophages [30, 31].

Astrocytes account for 30% of the CNS's glial cells; in addition to contributing to the integrity of the BBB, these cells help produce neurosteroids and generate anti-inflammatory conditions by secreting anti-inflammatory cytokines such as IL-10 and TGFβ in healthy individuals. Nevertheless, in MS, astrocytes differentiate to the reactive A1 phenotype and secrete inflammatory cytokines like IL-1β, IL-10, VEGF, and chemokines like CXCL10, CCL2, and CCL20. By the high level of expression of intracellular adhesion molecules like and ICAM1, this phenotype increases the CNS infiltration of immune cells and supports B cell survival with the secretion of IL-15 and IL-6 [32]. Reactive astrocytes produce matrix metalloproteinase (MMP), which alters the BBB integrity and increases permeability by boosting the expression of cell adhesion molecules, resulting in enhanced immune cell recruitment to the active MS lesion [33].

Microglia

Microglia are glial cells comprising 5–12% of total brain cells during embryonic development. They originate from myeloid precursor cells and migrate to the CNS, serving an important role in the CNS immune system by phagocytosing pathogens and dead cells, maintaining neuronal function, and regulating synaptic plasticity. Microglia, like macrophages, have many phenotypes and functions in inflammatory situations (Fig. 1) [34].

In the EAE model and MS, in the acute phase of the disease, infiltrated macrophages and microglia transform into the activated M1 phenotype and release pro-inflammatory cytokines like TNFα, IL-1β, IL-23, IL-6, IL-12, and chemokines like CCL5, CCL8, CCL4, CXCL12, CXCL9, CXCL10, CXCL4. This situation upregulates MHC class 2 and CD40 and increases nitric oxide (NO) synthesis through enhanced expression of nitric oxide synthase (INOS), all of which contribute to CNS tissue damage, neuronal dysfunction, and demyelination. However, the recovery state macrophages and microglia with the M2 phenotype secrete anti-inflammatory cytokines like IL-13, IL-23, IL-10, IL-4, and TGFβ, which affect EAE suppression and induce T cell differentiation to T regulatory and Th2 cells, which have a beneficial effect on the regulation of inflammation [35].

Another type of glial cell is the oligodendrocyte, responsible for myelination and axon transport, maintaining axon integrity, and neuronal survival in the CNS. These cells regenerate oligodendrocyte-producing cells (OPCs) in the adult brain, which regenerate oligodendrocyte-myelinated cells. Inflammatory cytokines like TNF-α promote oligodendrocyte apoptosis. Inducing the production of nitrogen and oxygen-free radicals, IFN-γ affects OPCs and directly affects microglia and astrocytes. Because oligodendrocytes need a substantial quantity of adenosine triphosphate and oxygen for appropriate myelination and have a high metabolite rate that indirectly influences the myelination process, these chemicals increase mitochondrial damage [36]. Oligodendrocytes secrete IL-6, IL-8, and CCL2, which recruit immune cells to the active inflammatory site. Indeed, by secretion of IL-1β, they induce secretion of COX2, which is responsible for forming prostanoids that contribute to the immune response at the site of inflammation. Microglia and macrophages trigger anti-inflammatory responses by phagocytosis of myelin debris and cytokine production

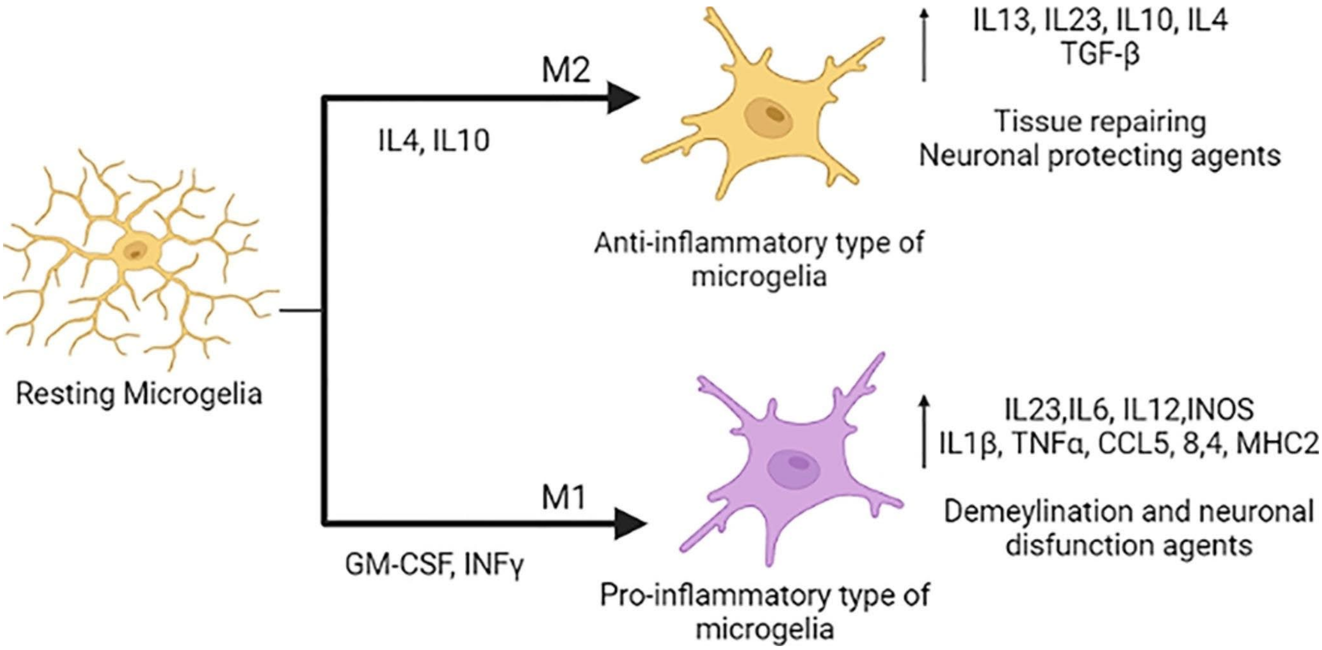


Fig. 1 In the acute phase of the disease, microglia transform to the activated M1 phenotype and release pro-inflammatory cytokines, which play a significant role in central nervous system tissue damage, neuronal dysfunction, and demyelination. The recovery state microglia with the M2 phenotype secrete anti-inflammatory cytokines that induce T cell differentiation to T regulatory and Th2 cells, which have a beneficial effect on the regulation of inflammation (created with BioRender.com).

(IL-10 and TGFβ), blocking tissue damage. Furthermore, TGF-β induces myelinating oligodendrocyte maturation and migration to the damaged area, also increasing the secretion of anti-inflammatory cytokines like hepatocyte growth factors by microglia. These growth factors, including insulin-like growth factor 1 (IGF-1), platelet-derived growth factor (PDGF), and vascular endothelial growth factor (VEGF), drive cell differentiation and migration and play essential roles in the remyelination process [37].

Platelets

Platelets are small, anucleate cells that are abundantly circulating in the blood. Platelets' life span is 7 to 10 days; megakaryocytes produce these cells daily. The fundamental role of platelets is hemostasis, bleeding cessation, and thrombosis [38]. During bleeding conditions, platelets adhere to von Willebrand factor with glycoprotein (GP) 1ba and collagen with GP VI and α2β1. In this situation, activated platelets change their shape and release granules like adenosine diphosphate (ADP), platelet-activating factor (PAF), and thromboxane A2, thereby activating more platelets and fibrinogen receptors (GP IIb/IIIa). By changing their shape, activated platelets spread and generate platelet plugs, binding with the plasma membrane via GP IIb/IIIa [39, 40].

Platelets in resting status do not interact with other cells. After activation following pathogen invasion, endothelial dysfunction, and physical damage, they may interact with other cells, such as ECs, and then release chemokines, which induce changes in the adhesiveness and proteolytic effects of ECs [41]. The α granule, dense granule, and lysosome are three kinds of granules in activated platelets. ATP, ADP, and serotonin are found in dense granules, whereas proteins including cathepsin E and D and CD63 are found in lysosomes. Every platelet has 60 to 80 α granules that contain chemokines like CCL5, CCL3, and CXCL1 and growth factors like PDGF, VEGF, and epidermal growth factor (EGF) [42]. The α granules have a fundamental role in inflammatory conditions. These mediators promote activated platelets to interact with other cells like immune cells, triggering the recruitment and differentiation of T cells and phagocytosis by macrophages and activated neutrophils [43]. The α granules also produce P-selectin, known as a platelet activation marker. The connection between P-selectin and P-selectin glycoprotein-1 ligand (PSGL-1) induces the adhesion of platelets to leucocytes and monocytes and recruits leukocytes to the inflammatory region [44]. Because of these effects, recent studies have indicated that platelet has other functions like immunity, inflammation, and wound healing. In addition, the expression of receptors for various mediators, including TLRs (1–9) and other inflammatory cytokines like RANTES, IL 1-β, CD 40 L, and P-selectin on the platelet surface, confirms the platelet's important function in the immune system, inflammatory response, and tissue repair [10, 45, 46].

Table 1 Some of the ways that platelets have been used as a novel means of medication delivery

Coating materials	Disease	Core materials	Result	Reference
Platelet	Lymphoma	Doxorubicin nanoparticle	The accumulation of the drug in tumor cells was increased, with favorable drug loading (46.3%) and encapsulation efficiency (86.6%)	[48]
Platelet membrane	Lung cancer	Docetaxel/PLGA* nanoparticles	The average size of nanoparticles was 98.3 nm; the presence of the coating material increased the blood circulation time, controlled the drug release, increased targeting to the tumor cells, and controlled the EPR effects	[49]
Platelet membrane	Rheumatoid arthritis	FK506 PLGA* nanoparticles	Coating with the platelet membrane increased the nanoparticle's stability, modified the circulation time, and increased the drug accumulation in the inflamed organ.	[50]

* PLGA: Poly(lactic-co-glycolic acid)

5 – 1.

Platelets contain proteins that are presorted in megakaryocytes. Despite lacking a nucleus, activated platelets can produce proteins, including anti-inflammatory and pro-inflammatory mediators that participate in inflammatory responses. For example, IL-1β promotes a response to the inflammatory process by cells like leukocytes and ECs [46]. Platelets directly act against bacteria, viruses, and fungi by presenting TLR2, TLR4, and TLR9 on their surface. TLR4 activates against lipopolysaccharide (LPS) and consequently releases TNF-α and CD154. These cytokines enhance the function and migration of APCs. Signals from TLRs are critical components to activate the innate immune system and cause a direct effect on the adaptive immune system. T cells activate platelets by interacting with CD40/CD154 to produce RANTES (regulated upon activation, normal T cell expressed and secreted), increasing T cell recruitment [47]. Platelets have been employed in illnesses like cancer because of their many functions in immune cells and the inflammatory phase. Table 1 shows some ways that platelets have been used as a novel means of medication delivery.

Platelet and immune cell interaction

Platelet activation quickly occurs after membrane receptors like TLRs recognize a pathogen. In this situation, platelets change their shape from discoid to circular with enormous pseudopodia and release mediators like IL-1β and membrane glycol proteins like CD40L and CD54 [51]. These mediators are secreted in the soluble form (s CD40L). Besides, overexpression of receptors like the P-selectin receptor on the platelet surface indicates the activity of platelets and their ability to interact with most leukocytes, especially neutrophils and monocytes. This interaction activates leukocyte and neutrophil transendothelial migration and triggers the neutrophil extracellular trap (NET) formation, a kind of cell death (distinct from apoptosis) based on granule attachment to the nuclear membrane. In addition, interactions with neutrophils result in the synthesis of bioactive lipids such as resorcin and lipoxin, which are implicated in inflammation [52, 53]. Platelets can interact with and recruit dendritic cells to the injured area through intermediates like CD38 and CD11b (54). Platelets bind only 3% of lymphocytes in the resting state, but this interaction is increased when lymphocytes are activated during inflammatory conditions or dysregulated hemostasis. In the active form, upregulation of receptors like P-selectin, CD40, GpIIb, and IIIa promotes this interaction in platelets. The proof of interaction with platelets is the presence of scavenger receptors like CD36 on the surface of T cells. Activated platelets secrete molecules like CCL5, RANTES, serotonin, CXCL4, or platelet factor 4 (PF4), leading to T cells' activation and differentiation

[55]. They can also interact with dendritic cells by interaction of CD40L and CD40, inducing the maturation and proliferation of these cells. Indeed, the production of cytokines like IL-6 and IL-12 against pathogens like *Staphylococcus aureus* eventually limits the infection [56]. IL-6 is a multifunctional cytokine with pro and anti-inflammatory effects, regulating the immune responses and acute inflammation. An in vivo study indicated that IL-6 induced platelet hyperactivation via the platelet-derived IL-6 trans-signaling pathway. Then, activated platelets induced leukocyte survival and activation [57, 58].

Activated platelets may physically interact with phagocytes like macrophages via several molecular pathways, in addition to secreting cytokines that directly or indirectly trigger the activation and recruitment of phagocytes. This cooperation improves the adaptive immune system, contributing to antimicrobial activity [59].

Platelets and inflammation

P-selectin, GP Ib, and PSGL1 (P-selectin glycoprotein ligand 1) can induce platelet-EC interactions. By molecules like ICAM1 and α5β3, firm adhesiveness with them is accrued. By the secretion of CD54 or CD40L, activated platelets increase the secretion of molecules like ICAM-1, VCAM1, IL-8, and MCP-1 (monocyte chemotactic protein 1) on the surface of ECs and increase vascular permeability. This leads to the recruitment of leukocytes and their attachment to ECs [55]. In inflammatory or infectious conditions, activated platelets may participate in the acute phase response (APR) by secretion of intermediates like IL-1β, IL-8, and IL-6. Meanwhile, through TLRs (mainly TLR4), they induce adherence with neutrophils and induce the neutrophil extracellular trap, which traps bacteria and limits the progress of these conditions [60]. Activated platelets help to clear up germs in staphylococcal infections by activating neutrophils and macrophages. They can also cause monocytes to differentiate into dendritic cells, promoting their activation and maturation. They induce the production of cytokines like IL-12, IL-6, and TNFα, which kill *S. aureus*, proving the participation of platelets in adaptive immune responses [56].

Activated platelets bind to the intermediate phenotype of monocytes (CD16+) and, by activating the NF-κB signaling pathway and upregulating TGF-β (which activates the P38 MAPK signaling pathway), induces the production of this phenotype, augmenting the inflammatory response. In vitro study performed with Chinese hamster ovary cells indicated that the interaction of platelets and monocytes induces the production of pro-inflammatory cytokines like IL-8, IL-6, TNFα, and MCP-1 [61]. A study by ED Hottz indicated that in patients with severe COVID-19, platelet activation and platelet-monocyte aggregation increased the disease severity and mortality rate with tissue factor expression [62]. A cross-sectional study in patients with pulmonary tuberculosis indicated that monocyte activation with CD11b, CD16, and CCR5 expression augmented inflammatory responses, whereas platelet activation had a beneficial effect. Furthermore, the in vitro study indicated that activated platelets decreased the expression of IL-1β, TNF-α, and IFN-Ƴ in the peripheral blood of these patients [63]. In cardiovascular diseases, platelets are activated to a greater extent and induce platelet-monocyte and platelet-neutrophil aggregation via P-selectin, leading to increased tissue damage and cardiovascular disease progression [64]. A clinical study also proved that platelet inhibition reduced monocyte-platelet interaction and plasma levels of cytokines like TNF-α, and platelet inhibition with a P2Y12 inhibitor decreased the mortality in sepsis [65]. Platelets can produce inflammatory cytokines in a P2Y12-dependent pathway and directly change the inflammatory process. Hence, antagonists of the P2Y12 receptor may alter the immune response [66].

The interaction of platelets with dendritic cells causes dendritic cells to proliferate and mature. The active type of platelets not only inhibits the production of inflammatory mediators like TNF-α and IL12P70 by dendritic cells but also increases the production of anti-inflammatory mediators like IL-10 [67, 54]. In vitro and in vivo studies indicate that activated platelets could alter adaptive immunity in inflammatory conditions by increasing B cells' production of IgG1, IgG3, and IgG2 [68–70]. T lymphocytes may induce platelet aggregation, stimulated by lymphocyte CD11b and platelet GpIIb/IIIa and CD154. CD154 activates T cells to remove viruses, and the contact between platelets and T cells attracts these cells to the inflammatory site. Activated platelets affect T cell activity by inhibiting Th17 differentiation and function via mediators such as PF4 (CXCL4) and RANTES, as well as promoting the activation and proliferation of naive T cells by secreting serotonin [71]. Besides, CD40L expression induced B cell differentiation and antibody class switching [72]. Platelets always express MHC class 1 intracellularly and in the plasma membrane. When stored in a blood bank, these molecules induced an immunosuppression effect on CD8 + T cells. This effect is known as the transfusion effect; activated platelets with intracellular MHC class 1 can present antigens to CD8 + T cells and activate them [73].

In various inflammatory conditions like autoimmune diseases, stroke, diabetes, atherosclerosis, and immune thrombocytopenia, there is increased platelet activation and elevated CD154 surface expression. Furthermore, the expression of CD154 on the surface of T and B cells promotes the activation of dendritic cells for the production of CD8 + T cells and has a fundamental role in CD4 + T helper cell function. This evidence indicates a significant relationship between the activity of the T and B cells and platelets in inflammatory diseases [47]. Microparticles produced by platelets act like active plateletsand overexpress sCD40L or CD154, which activate B lymphocytes. This may boost the expression of receptors such as CD86 and CD27, reflecting the activation state of these cells and causing B cells to produce IgG [74]. Under inflammatory conditions, activated platelets secrete intermediates like ADP and TX2 by activated granules, promoting the recruitment of platelets and inducing the movement of other immune cells to the injured site [75].

Platelets play inflammatory and anti-inflammatory roles in different stages of inflammation. This dual effect is controlled by the secretion of intermediates like NAP2 (neutrophil-activating peptide), PF4, TNF-α, RANTES, and growth factors like PDGF and VEGF. PF4 is a positively charged protein with both hemostasis and thrombosis functions and a chemotactic effect for neutrophils and monocytes. Furthermore, it prevents monocyte apoptosis and induces differentiation to macrophages, production of reactive oxygen species, and phagocytosis. Activated platelets increase the production of IL1-β, IL6, and TNF-α. TNF-α induces monocyte and leukocyte mobilization [73]. Besides, the receptors on the platelet surface directly and indirectly recruit leukocytes, especially neutrophils and monocytes, to the inflammatory site. This evidence indicates that platelets significantly affect inflammatory hemostasis and participate in wound repair stages. Therefore, it confirms the beneficial effects of platelets and PRP (platelet-rich plasma) in the wound repair process [76].

The presence of inflammatory and anti-inflammatory mediators in platelet granules indicates this dual role of platelets in inflammatory conditions, with this concept being named inflammatory hemostasis. Activated platelets can interact with monocytes, induce their survival, promote anti-inflammatory mediators like IL-10, and stimulate macrophages' anti-inflammatory phenotype [77]. Several cytokines secreted by activated platelets, such as PF4, RANTES, P-selectin, CD40L, and IL-1β, were recently considered molecular targets in inflammatory condition treatments. The monoclonal IL-1β antibody canakinumab reduced the risk of cardiovascular disease progression in high-risk patients. Activated platelets can also induce an inflammatory cascade via the JAK/STAT pathway. Different inflammatory diseases depend on this signaling pathway, so the inhibition of this pathway with JAK inhibitors can represent a novel therapeutic target [73]. Activated platelets can interact with inflammatory cells and induce a pro-inflammatory status; however, these interactions ultimately limit the progress of inflammation (60). The different functions of activated platelets are summarized in Fig. 2.

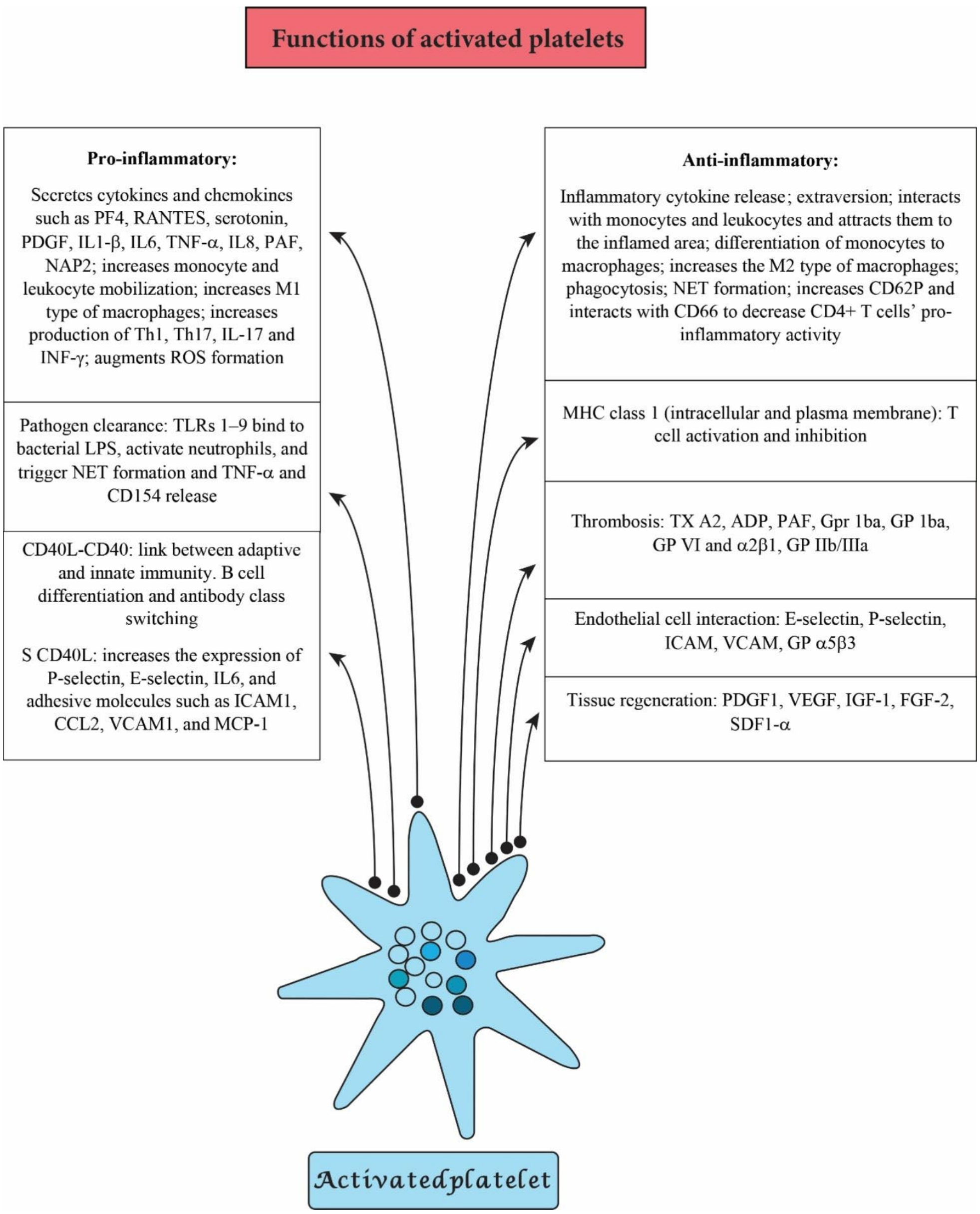
Platelets and the brain

The interaction between neurons and immune cells in the CNS sustains synaptic plasticity and environmental integrity. Activated platelets harm the integrity of the BBB via the overexpression of receptors and the increased production of different molecules and enzymes such as ICAM, VCAM1, and MMPs. These platelets can cross the BBB consecutively with activated monocytes and, by platelet-monocyte aggregation, can activate microglia. By the expression of CD40L, activated platelets contribute to neuro-inflammation, but by secretion of different growth factors like PDGF1, VEGF, IGF-1, fibroblast growth factor two (FGF-2), and SDF1-α (stromal cell-derived factor 1α), they contribute to tissue regeneration. Indeed, by secretion of serotonin, platelets increase neuronal activity and neuronal survival by inducing gene expression, which is associated with the plasticity of neuronal synapses [13]. Beyond acute brain damage, active platelets have been demonstrated to promote neuronal survival and activity and boost the expression of genes that regulate neuronal plasticity near the injury site through serotonin production [78]. An in vitro study indicated that platelet-activating factors could temporarily disrupt BBB tightness and increase the infiltration of leukocytes to the inflammatory site [77]. Activated platelets in inflammatory conditions can secrete different MMPs to attract neutrophils to the inflammatory site, which may disrupt BBB functions [79]. A recent hypothesis study was performed on the increased BBB permeability of drugs by a platelet vehicle for glioblastoma disease [80]. Another study declared that a platelet-based carrier increased the brain uptake clearance of a hydrophilic drug, dimethyl fumarate, and increased the drug's brain concentration and accumulation compared to a free drug solution [81].

Platelets and multiple sclerosis

One of the indicators of BBB breakdown and disease activity is the number of adhesion molecules like PECAM1 in the serum of individuals with active multiple sclerosis lesions. PAF (platelet-activating factor) levels in the plasma and cerebrospinal fluid of a patient with RRMS increased, suggesting BBB breakdown. Furthermore, the receptors for PAF in multiple sclerosis lesions are upregulated, and the activity of PAF is greater in RRMS compared with secondary progressive MS [82, 83].

A recent hypothesis study stated that the interaction of activated platelets with leukocytes at the endothelium of the BBB initiates the secretion of PECAM1, which induces the infiltration of leukocytes. Besides, activated platelets directly activate lymphocytes and dendritic cells and, by secreting PAF, induce the disruption of the BBB junctions



Functions of activated platelets

Pro-inflammatory:

Secretes cytokines and chemokines such as PF4, RANTES, serotonin, PDGF, IL1-β, IL6, TNF-α, IL8, PAF, NAP2; increases monocyte and leukocyte mobilization; increases M1 type of macrophages; increases production of Th1, Th17, IL-17 and INF-γ; augments ROS formation

Pathogen clearance: TLRs 1–9 bind to bacterial LPS, activate neutrophils, and trigger NET formation and TNF-α and CD154 release

CD40L-CD40: link between adaptive and innate immunity. B cell differentiation and antibody class switching

S CD40L: increases the expression of P-selectin, E-selectin, IL6, and adhesive molecules such as ICAM1, CCL2, VCAM1, and MCP-1

Anti-inflammatory:

Inflammatory cytokine release; extraversion; interacts with monocytes and leukocytes and attracts them to the inflamed area; differentiation of monocytes to macrophages; increases the M2 type of macrophages; phagocytosis; NET formation; increases CD62P and interacts with CD66 to decrease CD4+ T cells' pro-inflammatory activity

MHC class 1 (intracellular and plasma membrane): T cell activation and inhibition

Thrombosis: TX A2, ADP, PAF, Gpr 1ba, GP 1ba, GP VI and α2β1, GP IIb/IIIa

Endothelial cell interaction: E-selectin, P-selectin, ICAM, VCAM, GP α5β3

Tissue regeneration: PDGF1, VEGF, IGF-1, FGF-2, SDF1-α

Fig. 2 Once stimulated by invading pathogens, endothelial dysfunction, or physical damage, platelets are activated and express different cytokines and chemokines with thrombotic, pro-inflammatory, or anti-inflammatory effects. insulin-like growth factor 1 (IGF-1), platelet-derived growth factor (PDGF), and vascular endothelial growth factor (VEGF), PAF (platelet-activating factor), fibroblast growth factor two (FGF-2), and SDF1-α (stromal cell-derived factor 1α), NAP2 (neutrophil-activating peptide)

[84]. A study about platelets' role in the pathogenesis of MS was conducted by Nathanson, indicating increased adhesiveness of platelets in patients with MS [85]. Another study revealed increased platelet activity in blood circulation in such patients [86]. Platelets were also found to have a role in the breakdown of the BBB and disease development in the EAE model [83]. Furthermore, platelet RNA may be employed as a diagnostic material in MS progression, according to research by Sol et al. Platelets with distinct RNA profiles have greater activity in these individuals [87]. Platelets are the critical source of IL-1α, which activates the endothelial cells of the BBB and causes trans-endothelial migration of neutrophils. IL-1α is involved in chronic inflammations of the CNS, one instance of which is MS [88]. The adhesiveness of activated platelets toward endothelial cells leads to platelet-leukocyte aggregation and plays a vital role in the inflammatory process. As a result, it is thought that these aggregated complexes play a key role in the rupture of the BBB and the progression of disease stages, resulting in an increase in lymphocyte infiltration into the CNS [89]., Activated platelets interact with neutrophils and monocytes by interfering with molecules such as CD62P and CD162 on their surface and bind to T cells via the ICAM2/CD11a interaction [90]. Interaction of platelets with the endothelial cells can induce the production of CD62P and leukocyte recruitment to the injured area in the BBB. CD40 is present on the surface of monocytes, B cells, endothelial cells, and macrophages; its interaction with s CD40L (soluble CD40 ligand) on the surface of activated platelets could promote the pathogenesis of MS via different mechanisms.

A recent study found that in RRMS patients, the level of s CD40L in the CSF is increased. Platelet-monocyte interactions induce the release of inflammatory cytokines like IL-6, TNFα, and IL-1, and increase the secretion of MMP9 and MMP14. Platelet interactions with neutrophils increase the expression of MMP2, MMP14, and MMP9 within endothelial cells. MMPs have a role in inflammatory reactions and tissue damage; they also enhance immune cell infiltration [90].Degradation of extracellular matrix proteins, BBB tight junctions, and myelin components increases their presence in the CNS. The expression levels of MMPs 9, 7, 3, and 1 in circulating blood monocytes in a patient with an acute lesion of MS were increased [91]. It is evident that platelets are involved through various mechanisms in the initiation and development of MS. In the early stage of MS, activated platelets secrete pro-inflammatory cytokines like serotonin, PAF, and PF4, inducing the activation and proliferation of Th1 and Th17 cells, which produce IL-17 and INF-γ. The production of pro-inflammatory cytokines and serotonin decreases as the disease stage progresses, while the expression of CD62P on the platelet surface and aggregation with CD4 + T cells increases. Platelets suppress CNS inflammation by interacting with CD66 molecules on their surface and down-regulating CD4 + T cell release of pro-inflammatory cytokines such as INF-γ [92].

Conclusion

Multiple sclerosis (MS) is a progressive autoimmune disease with chronic inflammation that mostly involves young individuals and disables them. Currently, approved drugs only reduce the number and severity of attacks; therapy focuses on reducing assaults, reducing CNS damage, and changing immune system reactions to the CNS. On the other hand, this therapeutic strategy's persistent and non-specific targeting of the immune system raises concern regarding the danger of therapy for an extended time. Furthermore, this therapeutic approach will not be helpful for everyone. These reasons increase the necessity of developing a new treatment strategy. The stability of the drug delivery system in blood circulation is greatly affected by the absorption of non-specific proteins, which cause rapid drug clearance from the blood. Therefore, designing an ideal drug delivery system with suitable stability and safety with high permeability to BBB is essential for treating MS [93].

In recent years, the utilization of natural body cells like erythrocytes, macrophages, and platelets has been considered due to their stability, safety, and durability. Moreover, because they are normal body cells, they could be developed as effective drug carriers while preventing rapid clearance by the reticuloendothelial system [81, 94]. One of these innate cells is the platelet, which can penetrate the BBB and meaningfully target the site of inflammation in the CNS under inflammatory conditions. Platelets give efficiency in the targeted operation of drug delivery systems for anti-inflammatory action due to their interactions with the receptors of cells present at the site of inflammation. Furthermore, they may enhance anti-inflammatory effects in peripheral blood circulation through the absorption of leukocytes. Platelets, by limiting the accumulation of the other inflammatory cells, prevent the progress of the inflammatory process, and activated platelets can secrete anti-inflammatory intermediates. Activated platelets can affect immune cells like macrophages by interacting with them and inducing an anti-inflammatory phenotype. They can eliminate the production of inflammatory cytokines that cause injury to CNS and the BBB in MS's inflammatory processes, ultimately preventing the entry of inflammatory agents into the brain. The different activities of platelets in inflammatory conditions in MS indicate that these cells can perform both as an inflammatory limiting agent, controlling the inflammatory processes, and as a targeted vehicle for the inflammatory and injured area in the peripheral and central nervous systems. The reviewed evidence indicates that a platelet-based drug delivery system could be an efficient biomimetic candidate for targeted drug delivery to the CNS and inflammation suppression in MS therapy.

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Declarations

Conflict of Interest The authors declare no conflict of interest.

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