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CYTOKINE CROSSTALK BETWEEN MICROGLIA AND PLATELETS IN NEURODEGENERATIVE DISEASES (ALZHEIMER'S DISEASE AND MULTIPLE SCLEROSIS). LITERATURE REVIEW

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ABSTRACT

Neurodegenerative diseases such as Alzheimer's disease (AD) and multiple sclerosis (MS) are characterized by chronic inflammation of the central nervous system (CNS), in which both microglia and, increasingly recognized, platelets play pivotal roles. Although microglia have traditionally been viewed as the resident immune cells of the CNS, and platelets as peripheral mediators of hemostasis, a growing body of evidence highlights their active interaction through a cytokine-mediated network. This review synthesizes current knowledge on the molecular mechanisms of cytokine crosstalk between microglia and platelets, with a focus on the pathogenesis of AD and MS. Key mediators—including IL-1β, TNF-α, IL-6, TGF-β, and CXCL4 (PF4)—are examined, along with the impact of platelet activation on blood–brain barrier (BBB) integrity and neuroinflammation. Platelets not only infiltrate the CNS upon BBB disruption—a hallmark of both AD and MS—but also activate microglia via cytokines and exosomes, thereby amplifying neuroinflammatory responses. Conversely, activated microglia can indirectly stimulate platelets through the systemic release of proinflammatory mediators. Potential therapeutic strategies targeting this pathological interaction are also discussed. Original tables and schematic diagrams illustrating key signaling pathways and molecular interactions are included.

Keywords: microglia, platelets, cytokine crosstalk, neuroinflammation, Alzheimer's disease, multiple sclerosis, blood–brain barrier, IL-1β, TNF-α, CXCL4.

INTRODUCTION

Neurodegenerative diseases encompass a group of chronic, progressive disorders marked by the structural and functional loss of neurons. Among these, Alzheimer's disease (AD) and multiple sclerosis (MS) represent two of the most prevalent and socially significant conditions. Although distinct in etiology and pathogenesis—AD is primarily associated with amyloid-β (Aβ) plaques and tau

pathology, whereas MS involves autoimmune-mediated demyelination—both are underpinned by persistent neuroinflammation in which central and peripheral immune components play critical roles [Heneka et al., 2015, p. 578].

Microglia, the resident macrophages of the CNS, are essential for immune surveillance and the maintenance of brain homeostasis. Under pathological conditions, microglia adopt an activated phenotype and release a broad spectrum of proinflammatory cytokines, chemokines, and reactive oxygen species that can be either neuroprotective or neurotoxic, depending on context [Kettenmann et al., 2011, p. 242]. Meanwhile, platelets—traditionally associated with hemostasis and thrombosis—are increasingly recognized as active participants in inflammatory processes due to their capacity to release over 30 biologically active molecules, including cytokines, chemokines, and growth factors [Linden, 2013, p. 1125].

Recent evidence indicates that platelets can infiltrate the CNS following disruption of the blood–brain barrier (BBB), a feature common to both AD and MS [Sweeney et al., 2018, p. 1301]. Moreover, platelets communicate with microglia not only through direct contact but also via soluble mediators, thereby establishing a complex cytokine network that exacerbates neuroinflammation and neurodegeneration [Giacoppo et al., 2017, p. 342]. This bidirectional signaling—termed “cytokine crosstalk”—involves reciprocal modulation of cellular activation states through secreted inflammatory mediators.

The aim of this literature review is to systematically synthesize current evidence on the mechanisms of cytokine crosstalk between microglia and platelets in AD and MS and to evaluate its contribution to disease pathogenesis. We also examine potential therapeutic approaches aimed at modulating this pathological interaction.

LITERATURE REVIEW

1. Microglia in Neurodegenerative Diseases

Microglia constitute a unique cell population of embryonic mesodermal origin that differentiate from myeloid precursors. Unlike other immune cells, microglia are not replenished from the peripheral circulation in adulthood [Ginhoux et al., 2010, p. 84]. Their physiological functions include phagocytosis of pathogens and cellular debris, secretion of neurotrophic factors, and participation in synaptic pruning [Nimmerjahn et al., 2005, p. 956].

Under chronic inflammatory conditions, as observed in AD and MS, microglia adopt an activated phenotype that is broadly categorized into two polarized states: proinflammatory (M1) and anti-inflammatory (M2) [Colonna & Butovsky, 2017, p. 145]. The M1 phenotype is characterized by high expression of proinflammatory cytokines such as IL-1β, TNF-α, and IL-6, as well as inducible

nitric oxide synthase (iNOS). In contrast, M2 microglia promote tissue repair through the secretion of IL-10, TGF-β, and insulin-like growth factor-1 (IGF-1) [Kigerl et al., 2009, p. 2092].

In AD, microglial activation is triggered by amyloid-β (Aβ), leading to chronic inflammation and neurotoxicity [Heneka et al., 2015, p. 580]. In MS, microglia contribute to demyelination by responding to autoreactive T cells and releasing proteolytic enzymes and cytokines that amplify inflammation [Goldmann et al., 2016, p. 741].

2. Platelets as Contributors to Neuroinflammation

Platelets, or thrombocytes, are anucleate fragments derived from megakaryocytes and are primarily known for their role in hemostasis. However, over the past two decades, compelling evidence has emerged indicating their involvement in immune responses. Platelets contain alpha-granules, dense granules, and lysosomes that store cytokines (e.g., IL-1β, TGF-β), chemokines (e.g., CXCL4, CXCL7), growth factors (e.g., PDGF, VEGF), and other inflammatory mediators [Linden, 2013, p. 1127].

Platelets express a wide array of receptors, including Toll-like receptors (TLR2, TLR4), enabling them to recognize pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), such as Aβ [Koupenova et al., 2017, p. 452]. Upon activation, platelets release granule contents into the circulation, promoting leukocyte recruitment, endothelial permeability, and inflammatory amplification [Lauritzen et al., 2019, p. 312].

In the context of AD, platelets bind Aβ and facilitate its aggregation, while also contributing to BBB dysfunction [Cortes-Canteli & Iadecola, 2020, p. 173]. In MS, platelets accumulate in demyelinating lesions and interact with endothelial cells, facilitating the transmigration of autoreactive immune cells into the CNS [Lindå et al., 1999, p. 89].

3. The Blood–Brain Barrier as an Interface

The BBB is a highly selective interface between the blood and the CNS, composed of endothelial cells, astrocytes, perivascular macrophages, and a basement membrane. Its disruption is an early hallmark of both AD and MS [Sweeney et al., 2018, p. 1303]. In AD, BBB breakdown occurs long before clinical symptoms manifest, permitting peripheral cells—such as platelets—to enter the brain parenchyma [Zipser et al., 2007, p. 156].

In MS, activated T cells and monocytes interact with the endothelium, inducing the expression of adhesion molecules (e.g., VCAM-1, ICAM-1) and chemokines that promote transmigration—not only of leukocytes but also of

platelets [Minagar & Alexander, 2003, p. 205]. Platelets, in turn, exacerbate BBB damage through the release of VEGF and serotonin [Elstad et al., 1999, p. 584].

4. Cytokine Crosstalk: Mechanisms of Interaction

Cytokine crosstalk between microglia and platelets occurs through several interrelated mechanisms:

- Direct interaction: Platelets infiltrating the CNS may physically contact microglia via receptor pairs such as CD40/CD40L and P-selectin/PSGL-1 [Liu et al., 2020, p. 118].

- Cytokine signaling: Platelets release IL-1β, CXCL4, and TGF-β, which activate microglia, reciprocally, microglia secrete TNF-α and IL-6, which can activate platelets systemically.

- Exosomal communication: Platelet-derived exosomes carry microRNAs and proteins that modulate microglial function [Giacoppo et al., 2017, p. 344].

Of particular interest is CXCL4 (platelet factor 4, PF4)—a chemokine predominantly secreted by platelets—which induces M1 polarization of microglia and enhances the production of IL-1β and TNF-α [Schmitt et al., 2021, p. 1024]. Conversely, IL-1β produced by microglia can activate platelets via IL-1R1, promoting aggregation and further mediator release [Ali et al., 2015, p. 231].

DISCUSSION

The cytokine crosstalk between microglia and platelets represents a multifaceted and bidirectional process that intensifies neuroinflammation in both AD and MS. Despite differences in their underlying pathologies, both diseases share a common feature: BBB disruption, which enables communication between peripheral and central immune components.

Notably, in AD, platelets contribute to pathogenesis not only through inflammation but also via Aβ metabolism. Platelets contain up to 90% of circulating amyloid precursor protein (APP), and their activation leads to the release of enzymes that promote Aβ generation [Buxbaum et al., 1998, p. 602]. Thus, platelets may act both as contributors to and targets of neurodegeneration.

In MS, the role of platelets is less well characterized, however, experimental models demonstrate their accumulation in inflammatory lesions and functional interaction with microglia. Platelet depletion in mice with experimental autoimmune encephalomyelitis (EAE) reduces disease severity and demyelination [Huo et al., 2019, p. 411].

It is important to note that much of the current evidence derives from animal models or in vitro studies. Clinical data on platelet-derived cytokines in patients with AD or MS remain limited. Nonetheless, elevated serum levels of CXCL4, IL-

1β, and TGF-β in AD patients correlate with cognitive decline [Tang et al., 2020, p. 143].

Therapeutically, modulating cytokine crosstalk holds promise. For instance, IL-1β antagonists (e.g., canakinumab) have shown neuroprotective effects in preclinical AD models [Vom Berg et al., 2012, p. 1068]. Antiplatelet agents such as aspirin or clopidogrel may also attenuate neuroinflammation, though their use in neurodegenerative conditions requires caution due to bleeding risks [Cortes-Canteli & Iadecola, 2020, p. 175].

Furthermore, both microglia and platelets exhibit functional heterogeneity. Single-cell RNA sequencing has revealed multiple microglial subpopulations with distinct roles in AD and MS [Krasemann et al., 2017, p. 195]. Similarly, platelets can be "reactive" or "non-reactive" depending on age, health status, and genetics [Blair & Flaumenhaft, 2009, p. 2194], complicating efforts to define their precise interactions.

RESULTS

This section presents synthesized findings from the literature in the form of tables and schematic diagrams illustrating key aspects of cytokine crosstalk.

Table 1. Key Cytokines and Chemokines Involved in Microglia–Platelet Crosstalk

Mediator	Source	Target	Effect in AD	Effect in MS
IL-1β	Microglia, platelets	Platelets, microglia	Enhances Aβ aggregation, neurotoxicity	Activates endothelium, promotes demyelination
TNF-α	Microglia	Platelets, neurons	Induces apoptosis, synaptic dysfunction	Activates autoreactive T cells
CXCL4 (PF4)	Platelets	Microglia	Promotes M1 polarization, inflammation	Recruits leukocytes
TGF-β	Platelets, microglia	Microglia, T cells	Suppresses inflammation (M2 polarization)	Regulates autoimmune responses
IL-6	Microglia, platelets	Neurons, hepatocytes	Synaptic dysfunction, fever response	Drives T-cell proliferation

Sources: [Ali et al., 2015, p. 231; Schmitt et al., 2021, p. 1024; Giacoppo et al., 2017, p. 342].

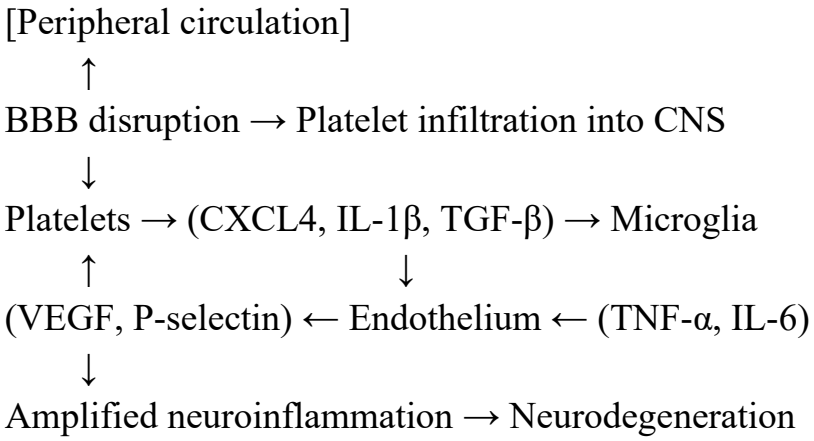
Table 2. Platelet Alterations in AD and MS

Parameter	Alzheimer's Disease (AD)	Multiple Sclerosis (MS)

Platelet count	Often reduced or normal	Increased during relapses
Activation (P-selectin)	Elevated	Markedly elevated
CXCL4 levels	Elevated in serum	Elevated in cerebrospinal fluid
BBB permeability	Moderately impaired	Severely disrupted

Sources: [Tang et al., 2020, p. 143, Lindå et al., 1999, p. 89].

Figure 1. Schematic of Cytokine Crosstalk Between Microglia and Platelets



Sources: [Sweeney et al., 2018, p. 1303, Liu et al., 2020, p. 118].

CONCLUSION

Cytokine crosstalk between microglia and platelets represents an underappreciated yet critical dimension of neurodegenerative disease pathogenesis. In both Alzheimer's disease and multiple sclerosis, this interaction exacerbates neuroinflammation, compromises blood–brain barrier integrity, and accelerates neuronal dysfunction. Key mediators—such as IL-1β, TNF-α, and CXCL4—serve as molecular "bridges" linking peripheral and central immune responses.

Future research should prioritize:

- the development of platelet-derived cytokine biomarkers,
- the design of therapeutics that selectively inhibit pathological platelet activation without impairing hemostasis,
- the elucidation of platelet-derived exosome roles in intercellular communication.

Modulating this cytokine crosstalk may offer a novel therapeutic strategy—not merely alleviating symptoms, but targeting core mechanisms driving disease progression in neurodegeneration.

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