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REVIEW

Platelet Factor 4: A Mysterious Chemokine in Inflammatory Regulation Diseases

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Abstract: Platelet factor 4 (PF4), also referred to as CXCL4, is a significant component of the C-X-C chemokine family, predominantly localized within the alpha granules of platelets. It is recognized for its anti-heparin and anti-angiogenic properties. However, the involvement of PF4 in inflammatory processes has not been extensively investigated. This article aims to explore the diverse functions of PF4 in the context of inflammatory diseases, emphasizing its potential dual regulatory roles across various immune cell types and pathological conditions. Recent research has enhanced our comprehension of PF4, revealing its production not only in platelets but also in macrophages and activated T cells, thereby extending its functional repertoire beyond its conventional roles. Consequently, this review provides a thorough analysis of PF4's influence on inflammatory diseases and offers perspectives and recommendations for future research endeavors.

Keywords: platelet factor 4, inflammatory disease, cellular immune

Introduction

Platelet factor 4 (PF4), also referred to CXCL4, is a prominent member of the C-X-C chemokine family, predominantly expressed in mature platelets.[1] The concentration of PF4 within platelets is notably high, with approximately 20 μg of PF4 present in every 1×10^9 platelet cells. In plasma, PF4 is found at a concentration of approximately 2–10 ng/mL. The synthesis of PF4 is dependent on platelet-specific α granules, which are also known as storage granules. These α granules, which are typically round to oval in shape and measure between 200–500 nm in diameter, constitute about 10% of the total platelet volume. In healthy individuals, mature platelets generally contain around 50–80 α granules each.[2] These granules serve as reservoirs for a variety of proteins, RNA, antimicrobial peptides, and growth factors.[3] PF4, being one of the most abundant proteins within these granules, is released from activated platelets in a manner that is dependent on P-selectin, following platelet activation. The release of PF4 influences various cell types. Traditionally, platelets have been regarded as the sole source of PF4 production; however, recent research has indicated that PF4 can also be synthesized in macrophages and activated T cells.[4,5] The precise role of PF4 in these alternative cell types, however, remains to be fully clarified.

Inflammation is a fundamental immune response to injury and infection, primarily triggered by pathogen invasion and serving as a catalyst for numerous diseases. A critical component of managing inflammatory conditions involves the modulation of the immune response. Recent years have seen the identification and functional characterization of numerous novel proteins, providing new insights into inflammatory diseases. Initial research on PF4 primarily focused on its anticoagulant properties.[6] However, more recent studies have uncovered a wide range of biological functions of PF4 in the onset, progression, and treatment of inflammatory diseases. These functions encompass the promotion of neutrophil adhesion, regulation of megakaryocyte maturation, induction of monocyte differentiation into macrophages,[7] maintaining auxiliary T cell differentiation,[8] maintaining hematopoietic stem cell quiescence,[9] and promoting B cell differentiation in the bone

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marrow environment.[10] Notably, multiple studies have highlighted a dual role of PF4 in inflammatory diseases. PF4 has been associated with the exacerbation of various conditions, including damage to blood vessel walls, promotion of thrombosis,[11] contribution to atherosclerosis, association with multiple sclerosis, and induction of heparin-induced thrombocytopenia. Furthermore, PF4 has been implicated in modulating T cell responses in malignant pleural effusion.[12] It is important to recognize that PF4 may target different organs and physiological environments, potentially exhibiting opposing regulatory effects, which can result in divergent roles in either promoting or inhibiting disease progression. Consequently, this paper seeks to provide a comprehensive review of the advancements related to PF4 in various inflammatory diseases, with the objective of elucidating the complexities surrounding this chemokine.

Structural Characteristics and Receptors of PF4

The Discovery of PF4

The identification of PF4, a platelet protein exhibiting an anti-heparin effect, was first reported in 1955.[13] This protein is characterized by several distinct structural components. At the N-terminus, it features a non-repetitive sequence that is rich in glutamic acid, followed by a relatively hydrophobic region that comprises three anti-parallel β-sheets (Figure 1A and B). At the carboxyl-terminal end, PF4 contains an amphiphilic β-helix structure characterized by two pairs of adjacent lysine residues, which are separated by two amino acids (Figure 1A). Extensive research has been undertaken to examine the homology of human PF4 across various animal species, including mice, rats, rabbits, cattle, pigs, and sheep. The structure of rat PF4, derived from its cDNA, exhibits significant homology with the amino acid sequence of human PF4 obtained through

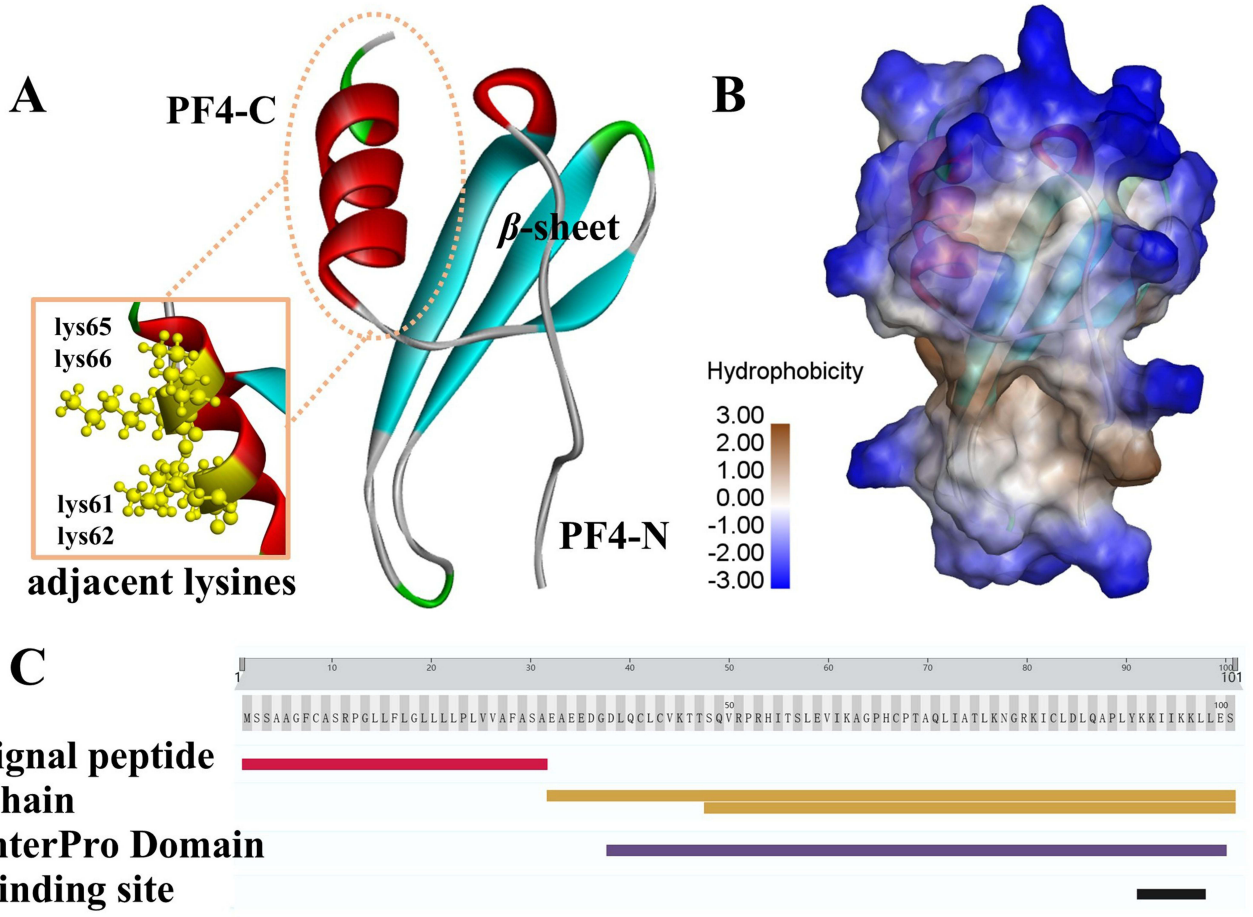

Figure 1 Structural of human PF4 (PDB: 1F9Q; UniProt: P02776). (**A**) Structure of PF4. PF4 consists of an N-terminal non periodic sequence rich in glutamic acid, a relatively hydrophobic sequence containing three antiparallel β-folds (blue bands), and a carboxyl terminal β-helix amphiphilic structure containing two adjacent lysine pairs separated by two amino acids. (**B**) Hydrophobicity of PF4. The brown part in the picture represents hydrophobicity and the blue part represents hydrophilicity. (**C**) PF4 signaling peptide chain and InterPro Domain Binding site.

classical protein chemistry techniques. Twenty-eight of the C-terminal residues in the carboxyl-terminal region of rat and human PF4 are identical. The sequence of the N-terminal region of rabbit PF4 protein is highly consistent with that of human PF4 protein. The bovine carboxy-terminal region extends three residues compared to human PF4. Bovine PF4 and human PF4 share sequence similarity, particularly in the lysine-rich carboxy-terminal putative heparin-binding domain of both proteins. Purified sheep serum shows 71% homology to human PF4, which has been demonstrated to be highly homologous across humans and various animals in multiple studies. These investigations have yielded significant insights into the similarities and differences of PF4 among different organisms.[14–18] The initial discovery of PF4, along with the subsequent elucidation of its structural characteristics, has facilitated further research into its biological functions and its involvement in various physiological and pathological processes, particularly in relation to inflammatory diseases.

The Structure of PF4

The human PF4 gene has been mapped to the q13.1 region of chromosome 4. This region also contains seven additional CXC chemokine genes, which also harbors seven additional CXC chemokine genes, including interleukin-8 (CXCL8/IL-8), granulocyte chemotactic protein-2 (CXCL6/GCP-2), growth-related oncogenes (CXCL1/GRO-a, CXCL2/GRO-b, CXCL3/GRO-g), neutrophil-activating peptide-2 (CXCL7/NAP-2), and epithelial-derived neutrophil-activating peptide-2 (CXCL5/ENA-78). The complete human PF4/CXCL4 protein, inclusive of its signaling peptide, comprises 101 amino acids (Figure 1C). In contrast, the mature form of the CXCL4/PF4 chemokine monomer is a 7.8 kDa protein consisting of 70 amino acids (Figure 1C). Importantly, this protein is devoid of tryptophan and methionine residues, yet it contains four cysteine residues that establish two disulfide bonds.[19] These structural attributes are integral to the stability and functionality of PF4 in various biological processes. A comprehensive understanding of the structural characteristics of PF4 is essential for clarifying its involvement in inflammation and disease progression, as well as for investigating its potential therapeutic applications (Figure 1).

The Affinity and Isolation of PF4

PF4 demonstrates a pronounced affinity for glycosaminoglycans (GAGs) present on proteoglycans, particularly binding to heparin and heparan sulfate (HS), which are principal constituents of GAGs. This interaction is mediated by a cluster of positively charged amino acid residues situated in the C-terminal helix of PF4. Notably, PF4 exists as a tetramer under physiological conditions. The binding affinity of PF4 for negatively charged molecules is significantly augmented by the introduction of additional basic amino acid residues within the β-sheet ring, leading to the distribution of positively charged residues throughout the molecule.[19]

PF4 exhibits anticoagulant properties akin to those of heparin and was isolated from the chondroitin sulfate complex released by platelets. Its strong affinity for heparin-agarose facilitated its isolation[20] with elution typically necessitating a salt concentration of approximately 1.2–1.4 M NaCl. The affinities of PF4 for various glycosaminoglycans are ranked as follows: heparin > heparan sulfate > dermatan sulfate > 6-chondroitin sulfate > 4-chondroitin sulfate.

Cellular Immune Regulation Function of PF4 in Physiological Process

PF4 is a significant chemokine in the field of hematological research, playing a pivotal role in various multi-step differentiation processes, including hematopoiesis and angiogenesis. Evidence indicates that PF4 facilitates the differentiation of hematopoietic stem cells into megakaryocytes, which are essential for platelet production. Additionally, PF4 contributes to angiogenesis by enhancing the migration and proliferation of endothelial cells. Recent studies have established that PF4 is integral to the regulation of cellular immune responses across a range of physiological processes. It has been identified as having strong associations with several immune cell types, including monocytes, phagocytes, neutrophils, NK cells, and T cells. The interactions between PF4 and these immune cells can modulate opposing inflammatory responses depending on the specific context. In summary, the role of PF4 in cellular regulation during physiological processes is intricate and multifaceted.

Regulatory Function of PF4 on T Cells

PF4 demonstrated a significant migratory effect on T cells, comparable to that of the chemokine CXCL10/IP-10 at a concentration of 1 μg/mL when administered at 8 μg/mL.[21] Additionally, PF4, in conjunction with CXCL4L1/PF4var at 2.5 μg/mL, exhibited a similar migratory effect on activated human and murine T cells. Notably, CXCL4L1/PF4var at 3 μg/mL produced effects comparable to those of CXCL11 at 100 ng/mL.[22] These findings underscore the role of PF4 in T cell migration.

PF4 is most notable for its role in immune, as a crucial component of the adaptive immune system. The immunomodulatory activity of PF4 is primarily concentrated in the tridecapeptide segment located at the carboxyl end of PF4, and the polypeptides composed of amino acids in the middle or amino end of PF4 are inactive.[23] Furthermore, GAGs facilitate the binding of PF4 to T cells, suggesting that the interaction of PF4 with GAGs extends beyond neutrophils and endothelial cells to encompass a variety of cell types.[24] The following section elaborates on the role of PF4 in the immune system, focusing on the correlation between PF4 and different phenotypes of T cells (Figure 2).

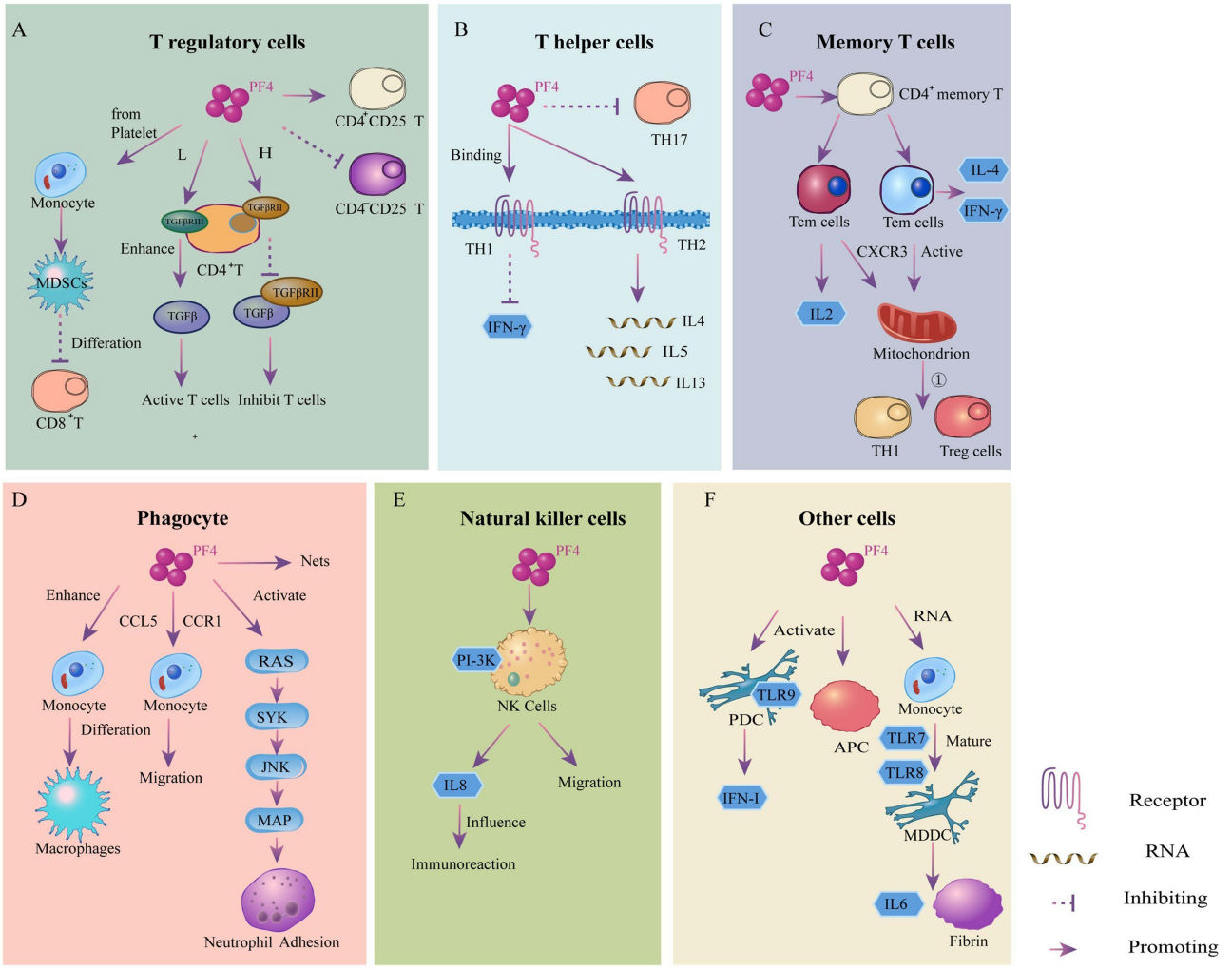

Figure 2 Platelet factor 4 (PF4) regulates several immune cells. (**A**) PF4 regulates T regulatory cells. 1). PF4 promotes the differentiation of monocytes into myeloid suppressor cells (MDSCs), which will inhibit $CD8^+$ T cell. 2). At low concentrations (L), PF4 binds to TGFBRIII to amplify the TGFβ signaling pathway and enhance the response of $CD4^+$ T cells. At high concentrations (H), PF4 directly binds to TGFBRII, hindering the interaction between TGFβ-TGFBRII and exerting the opposite regulatory effect. 3). PF4 inhibits the proliferation of $CD4^+CD25^+$ Treg cells while stimulating the proliferation of $CD4^+CD25^-$ Treg cells. (**B**) PF4 regulates T helper cells. 1). PF4 inhibits the differentiation of Th17 cells in T helper cells (Th). 2). PF4 reduces the IFN-γ in Th1 and increase IL-4, IL-5, and IL-13 in Th2 at mRNA levels. (**C**) PF4 regulates CD4+ memory T cells, including Tcm cells and Tem cells. PF4 activation of CXCR3 receptors enhances mitochondrial biosynthesis and leads to proliferation and activation of effector Th1 and Treg cells. (**D**) PF4 regulates phagocyte. 1). PF4 binds to the chemokine CCL5 and promotes the its differentiation into macrophages. 2). PF4 acts as an agonist of the chemokine receptor CCR1 to promote human monocyte migration. 3). PF4 activates neutrophil adhesion through various intracellular signals and pathways. (**E**) PF4 regulates NK killer cells. PF4 has been shown to induce NK cell migration at certain concentrations. (**F**) PF4 regulates other immune cells, such as plasmacytoid dendritic cells (PDC) and monocyte derived dendritic cells (MDDC).

Regulation of PF4 on T Regulatory Cells (Treg)

$CD8^+$ T regulatory cells (Treg) in the human body mainly comes from $CD8^+CD28^-$ T lymphocytes, which has a significant contribution to inhibit metastasis. Studies have found that when the balance between $CD8^+$ Treg and platelets is disrupted, platelets produce PF4, which induces differentiation of monocytes into myeloid-derived suppressor cells (MDSCs), thereby inhibiting the $CD8^+$ Treg function (Figure 2A). TCGA pan-cancer data confirmed that $CD8^{low}Platelet^{high}$ patients have a significantly lower survival probability compared to $CD8^{high}Platelet^{low}$. Thus, platelets exhibit the immune regulatory functions on $CD8^+$ Tregs through PF4.[25] Moreover, PF4 has been demonstrated to suppress the release of IL-2, hinder the production of inhibitory lymphocytes induced by mitogens, and potentially serve as a mediator for sustained effects in modulating inflammatory processes in vivo, suggesting its potential as a modulator of T cell functionality.[26,27]

$CD4^+$ regulatory T cell (Treg)-mediated active suppression is crucial for attenuating T cell responses to both exogenous and autoantigens. Research has demonstrated that PF4 significantly inhibits T- cell proliferation as well as the secretion of IFN-γ and IL-2 from isolated T cells. At a concentration of 5 μg/mL, PF4 demonstrates the ability to suppress the proliferation of $CD4^+CD25^-$ T cells while stimulating the proliferation of $CD4^+CD25^+$ Treg cells.[28] Furthermore, recent investigations have unveiled a dual role of PF4 in T cell immunity modulation. At low concentrations, PF4 binds to TGFBRIII, amplifying the TGFβ signaling pathway and enhancing the response of $CD4^+$ T effector cells. Conversely, at high concentrations, PF4 directly binds to TGFBRII, impeding the TGFβ-TGFBRII interaction and exerting an opposing regulatory effect (Figure 2A). This discovery opens up new avenues for targeting PF4 to modulate T cell immune responses effectively.[29] PF4 may play a previously unrecognized role in regulating human immune response by inducing Treg cell proliferation and impairing Treg cell function. The complex interactions between PF4 and Tregs highlight its significant role in immune regulation and underscore its potential as a therapeutic target in the treatment of immune-related disorders.

Regulation of PF4 on T Helper Cells (Th)

In the context of T lymphocyte activation, PF4 plays a critical regulatory role in T helper (Th) cells, such as inhibiting the differentiation of Th17 cells.[5,30] It also modulates cytokine secretion patterns, inhibiting the release of various cytokines by $CD4^+CD25^-$ T cells while enhancing the secretion of specific cytokines by Th2 cells. PF4 (at a concentration of 8 μg/mL) also affected the production of cytokines by human Th1 and Th2 cells, especially down-regulation of Th1 cytokine IFN-γ and up-regulation of Th2 cytokines IL-4, IL-5, and IL-13 mRNA levels[31] (Figure 2B).

Regulation of PF4 on Memory T Cells

Recent research has provided significant insights into the role of PF4 in the regulation of $CD4^+$ memory T cells. Specifically, PF4 plays a pivotal role in regulating $CD4^+$ memory T cells, encompassing central memory T cells (Tcm) and effector memory T cells (Tem). It modulates Tcm cells, which produce IL-2 upon reactivation, and Tem cells, known for secreting INFγ and IL-4. By activating the CXCR3 receptor, PF4 enhances mitochondrial biosynthesis in these cells, leading to increased proliferation and activation of effector Th1 and Treg cells[8,32] (Figure 2C). Notably, while both Tcm and Tem cells activate the CXCR3 receptor in response to PF4 to promote mitochondrial biosynthesis, there exists a significant temporal disparity in the activation dynamics of these two subsets.[32] Under PF4 induction, $CD4^+$ Tem cells exhibit a transient enhancement in Th1 effector response, while the Treg response is continuously augmented. In contrast, PF4-induced $CD4^+$ Tcm cells show a delayed enhancement in Treg and Th1 effector responses after 5 days of co-culture.[8] The capacity of PF4 to augment mitochondrial biogenesis and cellular metabolism accelerates the responses of Tcm and Tem cells, thereby reinforcing long-term immunity within the organism.[32]

Regulatory Function of PF4 on Phagocyte

Platelet factor 4 (PF4), which is present in high concentrations within platelets, is instrumental in the activation, differentiation, and migration of monocytes and macrophages. Research indicates that PF4 facilitates the cessation of rolling in monocytes, prompting their differentiation into macrophages during in vivo inflammatory responses.[33] Furthermore, PF4 has the capacity to bind to CCL5, a chemokine, thereby augmenting its effects on monocytes.[34] PF4 also functions as an agonist for the chemokine receptor CCR1, promoting the migration of human monocytes.[35] This evidence suggests that

PF4 may significantly influence the directional movement of monocytes toward areas of inflammation or tissue injury. Furthermore, monocytes treated with PF4 can give rise to macrophages that exhibit heightened non-specific phagocytosis, indicating an increased ability to engulf foreign particles or debris.[36] Collectively, the interactions of PF4 with monocytes and macrophages are pivotal in the processes of activation, differentiation, and migration of these immune cells. By facilitating the differentiation of monocytes into macrophages and enhancing their phagocytic functions, PF4 may play a critical role in the initiation and sustenance of non-specific immune responses.

The recruitment of neutrophils at the site of tissue injury is one of the earliest events in the host defense process. CXC chemokines (PF4 and β-thromboglobulin), which are stored in platelets and released immediately after activation, dominate neutrophil-dependent host defense at the beginning of inflammation.[24] Evidence suggests that PF4, secreted by platelets, serves as a potent stimulant for neutrophil infiltration and contributes to pancreatic tissue damage through the formation of CXCL2. In murine models of acute pancreatitis, it has been demonstrated that inhibiting PF4 levels can diminish neutrophil aggregation, thereby alleviating edema and necrosis of acinar cells during inflammation and potentially mitigating tissue damage.[37] Furthermore, elevated plasma levels of PF4 have been observed in patients with both mild and severe acute pancreatitis, indicating that targeting PF4 may yield clinical benefits for these individuals.[37] Additionally, experimental findings indicate that PF4 is involved in the regulation of neutrophil recruitment and tissue damage in complex inflammatory disease models, such as liver fibrosis and intestinal reperfusion injury.[38,39]

PF4 mediates the formation of neutrophil extracellular traps NETs in ANCA-associated vasculitis.[18,19] The combination of PF4 with NETs limits its ability to damage cultured endothelial cells.[40] According to reports, inhibiting NETs improves the vasculitis model in mice. In small vessel vasculitis, TLR9 agonists induce a significant increase in platelet release of PF4, thereby increasing the formation of NETs.[41] In addition, PF4 activates the adhesion of neutrophils to endothelial cells through a variety of intracellular signals and pathways. In addition to the activation of Src-Kinase, it also requires the synergistic activity of RAS, Syk, and JNK MAP. PF4 induces sequential activation of these elements[42] (Figure 2D).

Regulatory Function of PF4 on NK Cells

It has been reported that free or heparin-bound PF4 induces high-purity human NK cells to produce CXCL8/IL-8, which activates endothelial cells for vascular repair,[43,44] in a time- and dose-dependent manner at concentrations typically found at inflammatory sites. In the context of PF4-induced stimulation of NK cells to produce IL-8, PI-3K has been identified as a crucial mediator in this process.[45–47] Furthermore, both PF4 and PF4 variant have been shown to induce migration of NK cells at concentrations as low as 30 ng/mL.[22] This suggests that PF4, along with its variants, can modulate NK cell behavior and potentially influence immune responses through the production of chemokines like IL-8 (Figure 2E). Eosinophils play a role in allergic inflammation, such as bronchial asthma. Recombinant PF4 (1 mg/mL) is described to induce eosinophil adhesion by enhancing the surface expression of adhesion molecules, namely LFA-1a and LFA-1b.[48]

When basophils were stimulated with 800 ng/mL PF4, histamine release was significantly increased. The synthesized CXCL4/PF4 polypeptide, PF4 enhanced histamine release at 12 mg/mL, and the titer of CXCL4/PF4 was 1% of the complete PF4. Notably, the titers of PF4 and its variants were found to be at or below 0.1% of the concentration of PF4.[49]

Regulatory Function of PF4 on Other Cells

In addition to its various functions within the aforementioned cell types, PF4 has been identified as playing a direct role in the differentiation of B cells within the bone marrow[10] (Figure 2F). Furthermore, studies have revealed that PF4 can induce the overproduction of type I interferon (IFN-I) through the activation of Toll-like receptor 9 (TLR9) in plasmacytoid dendritic cells (PDCs) PF4 mainly targets the IFN-I pathway, resulting in both transcriptional and epigenetic modifications in PDCs. In experimental models of skin inflammation in mice, researchers utilized chemokines and DNA to create nanoparticles, which revealed the presence of DNA-associated PF4 in vivo. These findings indicate that chemokines function as vectors for nucleic acid delivery, thereby inducing TLR-mediated immune inflammation.[50] Physiological concentrations of PF4 stimulated thrombin-dependent activated protein C (APC) production in vitro through cultured endothelial cells and in the primate thrombin infusion model.[51] These findings suggest that PF4 may play a previously unsuspected physiological role in promoting the production of APC.

The Role of PF4 in a Variety of Inflammatory Diseases

Platelets and their derived factors have been demonstrated to modulate various inflammatory responses. In inflammatory conditions, the damage to blood vessels or tissues often leads to the activation and aggregation of platelets, resulting in the formation of a thrombus that is essential for hemostasis. During this process, activated platelets release granules containing a variety of signaling molecules. These signals not only facilitate hemostatic processes but also play a crucial role in the initiation and advancement of inflammation. Of particular note, PF4 has a significant regulatory impact on several inflammatory diseases, including pneumonia, malaria, hepatitis, and atherosclerosis (Figure 3 and Table 1).

Pneumonia

In the context of pneumonia, the regulation of neutrophil recruitment to the infection site through the secretion of specific chemokines is crucial for combating the disease. PF4 plays a significant role in this process. Studies have shown that PF4 is involved in inflammation and innate immunity,[3] particularly in bacterial clearance during Pseudomonas aeruginosa lung infections.[52] PF4 binds to bacteria and activates neutrophils via the synergistic activity of RAS, Syk, JNK, and MAPK pathways under the activation of Src-Kinase[42] (Figure 4A). This recruitment of neutrophils to the lungs and their subsequent bacterial killing are vital in managing Pseudomonas aeruginosa infections.[52]

Conversely, the genetic knockout of PF4 has been associated with reduced clearance of the influenza A virus (H1N1) from the lungs during the initial stages of infection, resulting in decreased neutrophil infiltration and diminished lung inflammation. However, in the later stages of infection, knockout mice exhibit significant aggregation of leukocytes and exacerbated lung tissue pathology compared to their wild-type counterparts. These observations suggest that PF4 deficiency adversely affects neutrophil recruitment to the lungs of infected subjects, thereby influencing the development of lung injury and the mobilization of neutrophils to sites of inflammation.[68] Nonetheless, some studies present a contrary perspective, identifying PF4 as a negative regulator of neutrophil activation, distinct from other classical chemokines, and playing a major role in modulating neutrophil function.[69] Notably, research has shown that the formation of isomers of platelet-derived chemokines, such as CCL5 and PF4 antibodies, can significantly reduce neutrophil influx and permeability, correlating positively with the

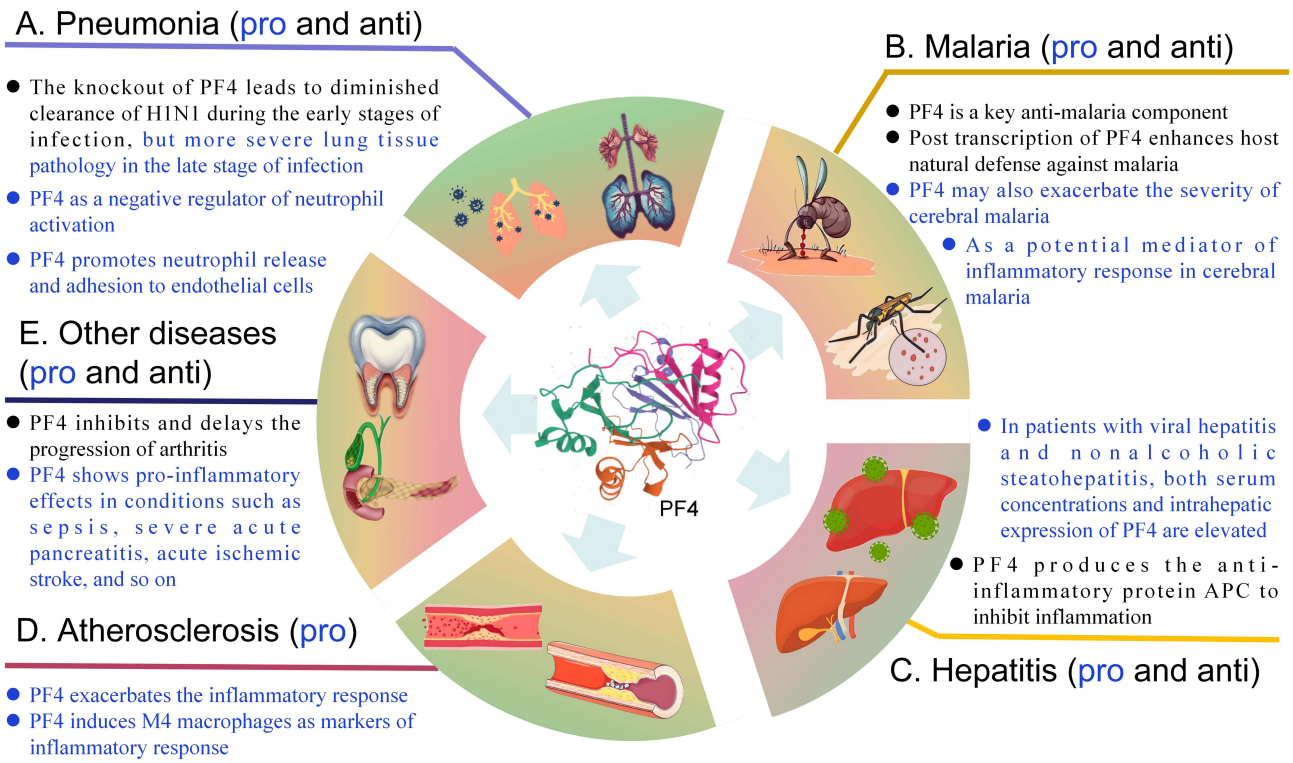

Figure 3 Various regulated roles of platelet factor 4 (PF4) in inflammatory diseases, including pneumonia (**A**), malaria (**B**), hepatitis (**C**), atherosclerosis (**D**), and other diseases (**E**). pro with blue shows the pro-inflammatory actions of PF4, and anti with black shows the anti-inflammatory actions of PF4.

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Table 1 The Role of PF4 in Inflammatory Diseases

Disease	Effect	Reference
Infectious pneumonia	PF4 combines with bacteria to recruit neutrophils into the lungs and kill bacteria inside cells	[52]
Sepsis	Platelets actively participate in microvascular permeability and neutrophil-mediated organ damage and play a critical role	[53]
	Rac1 plays an important role in controlling PF4 in pulmonary inflammation and tissue damage in multi-microbial sepsis	[53]
Acute lung injury	Lowering PF4 levels has a protective effect on the lungs	[53,54]
Malaria	PF4 may increase the severity of cerebral malaria by regulating the inflammatory environment	[55,56]
	PF4 can serve as a predictive biomarker for cerebral malaria	[57]
Hepatitis	Elevated levels of PF4 in serum suggest new targets for anti-fibrotic therapy	[38]
Acute liver injury	PF4 activates resident macrophages in the liver and induces an increase in the production of the anti-inflammatory protein APC, thereby alleviating acute liver injury	[58]
Atherosclerosis	Upregulation of platelet-associated PF4	[59,60]
	Clinical potential of PF4 as therapeutic targets for atherosclerosis	[61]
Pancreatitis	Targeting PF4 may be a useful method to improve AP tissue damage	[37]
Acute ischemic stroke	Activation of cerebral platelets and platelet neutrophil interactions during AIS	[62]
Arthritis	PF-4 derived from octapeptides have anti-inflammatory effects on experimental arthritis in mice	[63]
Periodontitis	PF4 upregulates MMP-1 expression in HGF in a p44/42 MAPK dependent manner	[64]
Dermatitis	The increased expression level of PF4 may play an important role in the etiology of allergic dermatitis	[65]
Mesenteric injure	PF4 may be an important mediator for local and remote tissue damage	[39]
Thrombotic diseases	Platelets activate C5aR1 on their surface and induce PF4 secretion to negatively regulate blood flow remodeling	[66]
Viral myocarditis	PF4 appears to be a potential target for the treatment of VMC	[67]

movement of white blood cells into the lungs.[70] This leads to the proposition that the functional capacity of PF4 may be contingent upon its structural form, a hypothesis that warrants further investigation. Related clinical studies have demonstrated that PF4, as an inflammatory and endothelial biomarker, is significantly elevated in patients with COVID.[71] Additionally, patients with COVID-19 exhibit strong reactivity in the detection of PF4/heparin antigen; however, there is an absence of platelet activation antibodies.[72,73] These findings suggest a significant relationship between PF4 levels and the onset and progression of pneumonia.

Sepsis is characterized by a pronounced systemic inflammatory response that initiates a cascade of pro-inflammatory events, resulting in leukocyte imbalance and host tissue damage. Thrombocytopenia frequently occurs in sepsis, leading to the activation of remaining circulating platelets. Elevated levels of PF4 have been observed in the plasma and bronchoalveolar lavage fluid (BALF) of septic animals. Inhibition of protein kinase C-delta (PKC-δ) has been shown to reduce PF4 levels in both systemic circulation and lung tissue, thereby decreasing neutrophil influx into the lungs and providing a protective effect on pulmonary function.[53] Previous studies utilizing PF4 gene knockout mice in models of acute lung injury (ALI) have demonstrated lung protection, suggesting that a reduction in PF4 levels can mitigate lung damage.[54] In addition, PF4 facilitates neutrophil release and adhesion to endothelial cells,[74] as well as enhances phagocytosis, chemotaxis, and the production of reactive oxygen species in leukocytes.[74] The excessive migration of neutrophils into vascular endothelial cells is a critical factor contributing to inflammation-induced lung injury.

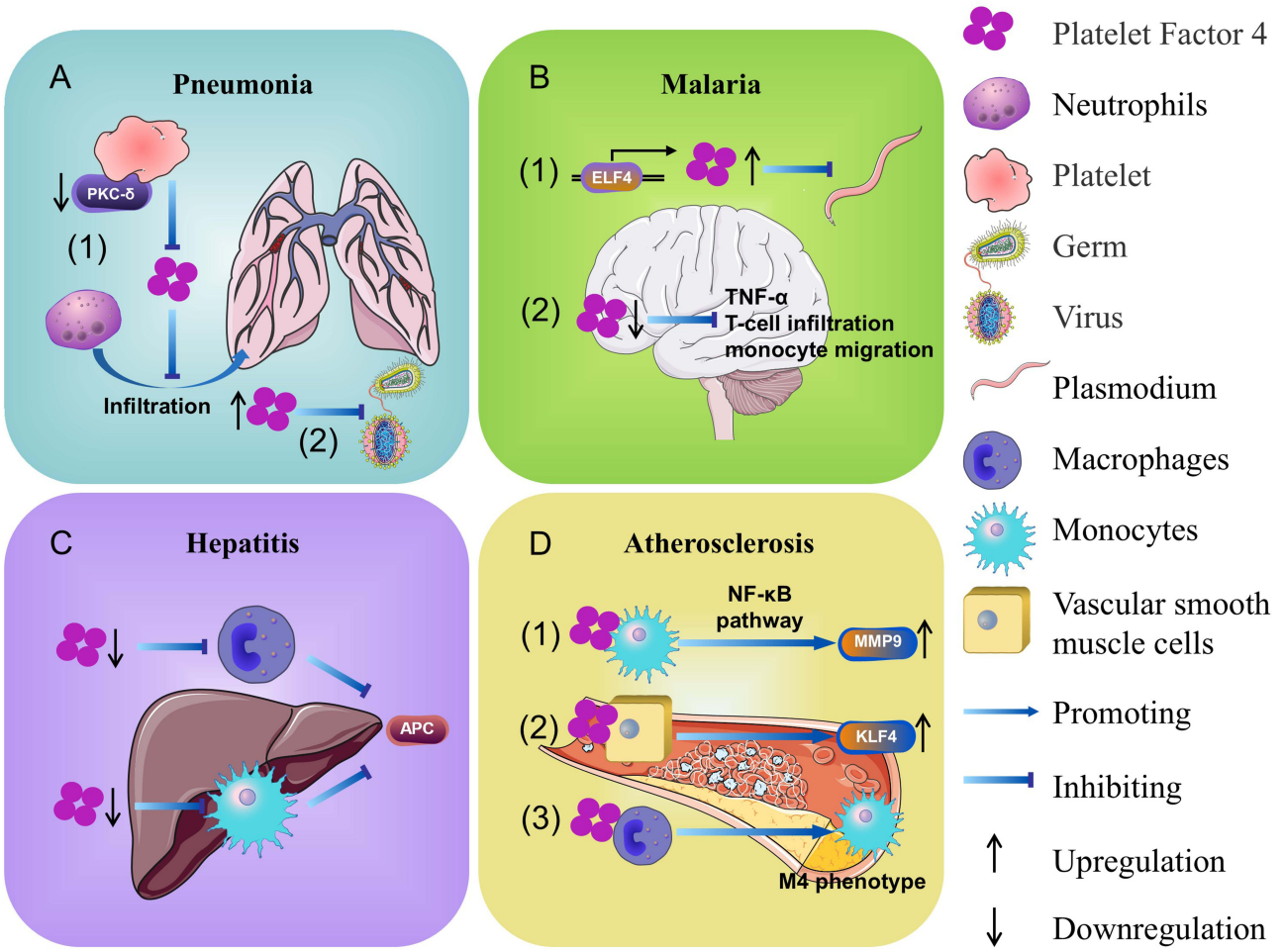

Figure 4 Mechanism of action of PF4 in some inflammatory diseases. (**A**) The reduction of PKC-δ reduces the level of PF4 in the body and lungs, which reduces neutrophil inflow into the lungs and has a protective effect on lung function. PF4, binding to bacteria, activates neutrophils and recruits them to the lungs, where it kills the bacteria to fight inflammation. (**B**) PF4 is activated by ETS transcription factor 4 (ELF4), and down regulates symptoms and reduces mortality in malaria. In the cerebral malaria model of Plasmodium berghei, the decrease of PF4 can inhibit the level of TNF-α, reduce T cell infiltration and reduce brain monocyte migration. (**C**) In liver disease, deficiency of PF4 inhibits protein production with anti-inflammatory activity on monocytes/macrophages (such as APC). Systemic application of PF4 limits the activation of liver resident macrophages and induces increased production of anti-inflammatory protein APC. (**D**) PF4 activates atherogenesis to up-regulate matrix metalloproteinase 9 (MMP9) expression via NF-κB in THP-1 mononuclear-derived macrophages. PF4 increases the expression of transcription factor Krüppel like factor 4 (KLF4), leading to an inflammatory phenotype of VSMCs. PF4 plays a role in influencing monocyte differentiation by inducing different M4 macrophages.

Particularly in the lipopolysaccharide-induced ALI model, the re-accumulation of neutrophils in the lungs has been linked to PF4 dependency, which subsequently contributes to inflammatory damage.[70]

Malaria

PF4 is a significant anti-malarial agent produced by platelets, originating from megakaryocytes, and is released in response to malaria parasite infection. Investigations have indicated that the ETS transcription factor 4 (ELF4) plays a crucial role in enhancing the host's innate immune responses against malaria by promoting the transcription of PF4 and Pro-Platelet Basic Protein (PPBP)[4] (Figure 4B). Nonetheless, PF4 may also intensify the severity of cerebral malaria through its influence on the inflammatory milieu. Srivastava et al revealed that in a cerebral malaria model utilizing Plasmodium berghei, PF4-deficient ($PF4^{-/-}$) mice exhibited milder symptoms compared to wild-type counterparts. This observation included lower mortality rates, reduced TNF-α levels, decreased T cell infiltration, and diminished monocyte migration in the brain. Conversely, reintroducing exogenous PF4 restored mortality rates to those of wild-type animals. Additionally, PF4 is broken down into components within the digestive vesicles of the parasite's organs when Plasmodium infects red blood cells.[55,56] Apart from these findings, PF4 has been identified as a potential mediator of

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the inflammatory response in cerebral malaria and as a predictive biomarker for the condition.[57] This indicates a multifaceted role for PF4 in modulating the immune response to malaria, which may contribute to the pathogenesis of cerebral malaria. Future investigations should aim to clarify the specific functions of PF4 and explore potential therapeutic interventions targeting PF4 to prevent cerebral malaria.

Hepatitis

In individuals diagnosed with viral hepatitis and nonalcoholic steatohepatitis, both serum levels and intrahepatic expression of PF4 are found to be elevated, indicating its potential role in chronic liver diseases.[38] Conversely, recent studies have reported a decrease in serum PF4 levels in patients with acute liver disease and in mice. In experimental models, $PF4^{-/-}$ mice exhibited more severe liver damage compared to controls, associated with increased hepatocyte apoptosis and an enhanced pro-inflammatory response from liver macrophages. In these PF4-deficient mice, there was an inability to produce proteins with anti-inflammatory effects on monocytes/macrophages, such as APC. In addition, systemic administration of PF4 curtailed the activation of liver resident macrophages, improved experimental liver injury, and induced an increase in the production of the anti-inflammatory protein APC (Figure 4C). Consequently, the systemic administration of PF4 emerges as a promising therapeutic strategy for the management of acute liver injuries.[58]

Atherosclerosis

Atherosclerosis is increasingly understood as an inflammatory condition affecting the arterial wall. Platelets, which contain a significant amount of chemokines within their alpha granules, release these inflammatory mediators upon activation. The proatherogenic effects associated with activated platelets are likely mediated by the release of these proinflammatory substances, which promote the recruitment, activation, and differentiation of various cell types, including endothelial cells and leukocytes. Recent studies have shown that PF4 exacerbates atherosclerosis by enhancing the expression of matrix metalloproteinase 9 (MMP9) in THP-1 monocyte-derived macrophages via the NF-κB pathway.[59,60] In the context of vascular remodeling, inflammatory cells such as macrophages, mast cells, and neutrophils are important sources of MMP-9 in vascular tissue.[75] Importantly, a recent investigation revealed that inhibiting the interaction of heterophilic chemokines with specifically designed small molecules could impede the progression of atherosclerosis in $APOE^{-/-}$ mice, underscoring the therapeutic potential of targeting platelet-derived chemokines in the management of atherosclerosis.[76]

During the injury and development of atherosclerosis, PF4 is transported through the vascular wall. Within the vascular wall, PF4 exerts regulatory effects on vascular smooth muscle cells (VSMCs), influencing their proliferation, migration, gene expression, and cytokine release.[77] PF4 can stimulate VSMC injury response in mouse carotid artery ligation models in vitro and in vivo. PF4 leads to the inflammatory phenotype of VSMC by increasing the expression of transcription factor Krüppel-like factor 4. This leads to decreased expression of differentiation markers, increased cytokine production, and enhanced cell proliferation in VSMCs.[78]

Monocytes and monocyte-derived cells, commonly known as macrophages, play a pivotal role in the development of atherosclerotic lesions. The main driving force of monocyte-macrophage differentiation is the macrophage colony-stimulating factor (M-CSF). Macrophages stimulated by M-CSF significantly contribute to atherosclerosis, a fact supported by studies on M-CSF and M-CSF receptor knockout mice.[61] In the context of atherosclerosis, PF4 can also prevent monocyte apoptosis and promote the differentiation of macrophages in vitro. This protein is released by activated platelets and exerts its effects on various cell types involved in atherosclerosis. Notably, the deletion of the PF4 gene results in reduced atherosclerosis in $APOE^{-/-}$ mice.[61]

Consequently, the interaction between monocyte-derived cells and platelets is of considerable significance. PF4 is involved in promoting the migration of monocytes to the subendothelial space and modulating their differentiation, leading to the emergence of a distinct M4 macrophage phenotype (Figure 4D). In human atherosclerotic plaques, M4 macrophages are predominantly located in the adventitia and intima, and their presence is associated with plaque instability, suggesting their role as indicators of pro-inflammatory activity. Overall, PF4-induced M4 macrophages may serve as a promising target for the diagnosis and therapeutic management of human atherosclerotic diseases.[79] Researchers have found that ginkgolide B, a drug used to treat atherosclerosis, can effectively inhibit the expression of PF4 and CD40L in thrombin-activated platelets, which may be related to inhibition of Syk and p38 MAPK phosphorylation.[80,81]

Other Inflammatory Diseases

Peptides derived from PF4 exhibit anti-inflammatory properties in the context of arthritis. Collagen-induced arthritis (CIA) is utilized as an experimental model that closely resembles the pathological and immunological characteristics of rheumatoid arthritis. Research has indicated that the PF4-derived octapeptide sequence, referred to as peptide CT-112, is capable of effectively inhibiting and delaying the progression of arthritis.[63] Furthermore, in addition to its anti-inflammatory effects in arthritis, PF4 has been shown to exert pro-inflammatory actions in various conditions, including sepsis, severe acute pancreatitis, acute ischemic stroke, periodontitis, dermatitis, mesenteric ischemia/reperfusion injury, and other inflammatory diseases.[37,39,62,64,65,82]

Discussion

Inflammation is a complex pathological process when tissues are infected or damaged by pathogens, leading to a protective inflammatory response by the body. Platelets, which are cytoplasmic fragments of megakaryocytes, primarily contribute to hemostasis. Increasing evidence suggests that platelet-associated cell surface proteins (such as CD40L, P-selectin, GPVI, and CLEC-2) and secretory molecules (such as PF4 and RANTES) play significant roles in modulating inflammatory responses in various conditions, including cardiovascular and cerebrovascular diseases, inflammatory bowel disease, rheumatoid arthritis, and infection/sepsis.[39,53,63,66] Under normal conditions, platelets remain inactive. However, upon stimulation by inflammation or injury, they quickly adhere to and aggregate at the site of vascular injury, activate, release platelet-derived granules, regulate hemostasis, form thrombi, and interact with pathogens or immune cells to modulate the immune system. Recent developments in anti-inflammatory drugs that target specific platelet-related mechanisms offer new therapeutic strategies for managing inflammatory diseases.[83]

PF4, a predominant protein within platelet alpha granules, is released from activated platelets in a P-Selectin-dependent manner. Recent research indicates that PF4 is also synthesized by macrophages and activated T cells, though its specific functions remain to be fully elucidated. PF4 is involved in regulating immune responses, including the activation, differentiation, and migration of macrophages, activation of neutrophils, host defense mechanisms, and impacts on NK cell stimulation and T cell regulation and inhibition. PF4 exhibits a dual role in the pathogenesis and progression of inflammatory diseases, potentially linked to variations in its forms, concentration, duration of action, or downstream targets. However, the direct targets of PF4 on different immune cells, target organs, and inflammatory pathways have not been elucidated. Therefore, further investigation into the comprehensive regulatory functions and targets of PF4 in the context of inflammatory diseases is of considerable research importance.

Additionally, PF4 plays a crucial role in combating infections, such as those caused by bacteria or viruses. In monocytes, PF4 has been shown to increase the infection rates of dengue virus (DV) and Japanese encephalitis virus (JEV).[84] Platelet activation is a hallmark of DV infection. Research has demonstrated that PF4 inhibits the interferon (IFN) pathway and significantly enhances DV replication in monocytes, both in vitro and in patients. Inhibiting PF4-mediated signaling results in increased IFN production and suppression of DENV and JEV replication in monocytes. Consequently, the PF4-CXCR3-IFN axis presents a promising target for the development of therapeutic strategies against viral infections, including JEV and DV.[85] Its interaction with HIV-1 is concentration-dependent: low levels of PF4 inhibit HIV-1 replication by blocking the virus's attachment and entry through direct binding to the HIV-1 envelope glycoprotein gp120 and its cell surface receptors, whereas high levels enhance replication.[86] For respiratory syncytial virus (RSV), PF4 effectively inhibits the attachment of viral particles to the primary receptor, heparin sulfate (HS), thereby serving as a potent RSV inhibitor. Elevated levels of PF4 in plasma and alveolar lavage fluid samples from RSV-infected mice and patients suggest its role as a limiting factor for RSV, potentially serving as an indicator of clinical severity.[87] Consequently, PF4 plays a significant role in the pathogenesis of infectious inflammatory diseases and represents a promising target for the development of novel therapeutic agents aimed at these conditions.

The complex regulatory functions of PF4 in relation to inflammatory diseases require additional exploration. A comprehensive understanding of the contributions of PF4, whether synthesized by platelets or other cellular sources, in the context of inflammatory conditions may facilitate the development of novel therapeutic strategies aimed at improving the management of such diseases.

PF4 exhibits a broad spectrum of biological functions in the pathogenesis, progression, and treatment of inflammatory diseases. However, its diverse anti-inflammatory mechanisms have been underreported in the literature. Notably, multiple studies have demonstrated that PF4 plays a dual role in inflammation, acting as both a pro-inflammatory and an anti-inflammatory mediator. Consequently, PF4 may employ distinct regulatory mechanisms in different target organs and physiological environments, leading to varied effects on disease progression. This paper aims to elucidate the multi-faceted roles of PF4 in anti-inflammatory immunity through a systematic review, thereby providing a comprehensive foundation for exploring the potential of PF4 as an anti-inflammatory therapeutic target.

Data Sharing Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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Disclosure

The authors have no conflicts of interest to declare in this work.

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