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Platelet-derived chemokines in inflammation and atherosclerosis

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ABSTRACT

Platelets are inflammatory anuclear cells with a well-established role in the development and manifestation of atherosclerosis. Activated platelets secrete a plethora of chemokines including CXCL4 or platelet factor 4 (PF4), CCL5, CXCL12 or stromal cell derived factor-1α (SDF-1α), CXCL16 and others, which initiate or promote local inflammatory processes at sites of vascular injury. These processes are mainly mediated by the recruitment of circulating haematopoietic stem cells, neutrophils, monocytes or lymphocytes on vascular wall. Under acute ischemic conditions platelet-derived chemokines may promote the mobilization of bone marrow-derived progenitor cells and their homing at lesion sites. This review focuses on the role of platelet-derived chemokines in inflammation and atherosclerosis. Further, we discuss the clinical value of plasma levels of chemokines in the prognosis of atherosclerotic heart disease.

1. Introduction

Atherosclerosis represents a complex immune response to oxidized low-density lipoprotein or other unknown antigens facilitated by interplay between various cell populations in atheromatous plaque. This cellular interaction on vascular wall is fired or enhanced by a plethora of chemokines, which are secreted or expressed in the surface of all vascular and blood cells including platelets [1]. A constantly growing number of data are indicating platelets as an actively involved cell population in atherosclerosis, as well as a crucial crosslink between inflammation and thrombosis [2]. Though platelets do not adhere to the vascular endothelium under normal (physiological) conditions, endothelial cell activation towards a pro-inflammatory phenotype or disruption of the endothelial layer, leads to platelet adhesion on vascular wall. Subsequently, platelet activation induces the release of chemokines, which mediate the recruitment of leukocytes to the vascular endothelium favoring atherogenesis and in later stages atheroprogression and atherothrombosis [3].

Inflammation is the key pathophysiological mechanism driving atherosclerosis initiation and progression, plaque rupture and thrombosis [1]. *In vitro* and *in vivo* data showed that inflamed endothelial cells, mainly via von Willebrand Factor (vWF), but also via the adhesion receptors intercellular adhesion molecule 1 (ICAM-1) and vitronectin receptor interact with circulating activated platelets, even under high shear stress conditions, leading to platelet adhesion to vascular wall [4–7]. Upon adhesion, platelets release a plethora of pro-inflammatory chemokines, which attract circulating leukocytes favoring the recruitment of the latter to vascular wall [8]. Moreover, inflammatory mediators released from activated platelets promote vascular inflammation at lesion sites. Specifically, the chemokine CCL5 (also known as RANTES) and the dyad CD40-CD40L promote the recruitment of other platelets and inflammatory cells, thus contributing to the progression of atherosclerosis [3,8,9]. In addition, platelet released platelet factor-4 (PF4; also known as CXCL4) or stromal cell-derived factor-1 (SDF-1) favor the uptake of oxidized LDL from macrophages promoting the formation of foam cells and contributing to the development of the lipid core of atherosclerotic plaques [10–12].

Beyond their role in orchestrating the inflammatory process at the sites of atherosclerotic lesions, platelets also seem to play a key role in plaque rupture and subsequent local thrombus formation. Rupture of an atherosclerotic lesion exposes extracellular matrix proteins, which in turn trigger a rapid recruitment of circulating platelets to vascular wall causing thrombosis. Further, activated platelets secrete matrix metalloproteinases (MMP), such as MMP-2 or MMP-9 contributing to extracellular matrix degradation and local activation of factors favoring plaque rupture and thrombus formation [13,14]. Given that the local

Abbreviations: HSC, haematopoietic stem cells; Mo, monocytes; Neu, neutrophils; $CD4^+$T, $CD4^+$T cells; EC, endothelial cells; MΦ, macrophages; ENA78, epithelial-derived neutrophil-activating protein-78; SDF-1α, stromal cell derived factor-1α

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microenvironment of ruptured atherosclerotic plaques is highly thrombotic, platelets are not only activated but also orchestrate the thrombosis cascade crucially participating in the creation of local thrombi occluding vessels and leading to myocardial infarction or stroke.

Various receptors play a key role in intercellular interactions between platelets and other cell types. For instance, platelet P2 receptors, such as the P2Y12 receptor, are expressed on platelet membrane playing a key role in thrombosis and inflammation [15]. Data from P2Y12 knockout mice demonstrated the active involvement of this receptor in favoring the release of platelet chemokines and monocyte recruitment at the sites of vascular injury [16,17]. Selectins and integrins are also key groups of receptors mediating platelet interactions. P-selectin glycoprotein ligand-1 mediates platelet rolling on endothelium, as well as leukocyte tethering on activated platelets, participating in pro-inflammatory and pro-thrombotic processes. Moreover, integrins such as αIIβ3 and αvβ3 mediate firm adhesion of platelets under high shear rates [3,18]. The collagen receptor GPVI favors platelet aggregation and activation during vascular inflammation [19–21]. A number of clinical studies demonstrated the potent prognostic and diagnostic role of GPVI and its circulating form in disease states such as stable coronary artery disease (CAD) or acute myocardial infarction (MI), as well as in stroke [22–26]. Another type of receptor, known to form strong intercellular junctions, localized in platelets, as well as in other cells, is the junction adhesion molecules (JAMs), namely JAM-A and JAM-C [27]. Data from *in vivo* platelet-specific JAM-A knockout hyperlipidemic mice models demonstrated the potent role of this receptors, as JAM-A deficient platelets led to accelerated neointima formation and inflammatory activity at the lesion site [28,29]. This is in line with our previous report suggesting a pro-regenerative effect of platelet-derived JAM-A in the recruitment of $CD34^+$ haematopoietic stem cells and the differentiation of the later to endothelial cells [30]. In addition, we have previously indicated a potent involvement of JAM-C in the recruitment of circulating CD34 + progenitor cells towards immobilized platelets, a mechanism that may be enhanced in patients with known CAD [31]. Taken together, there is a plethora of ligands and receptors involved in the interaction of platelets with vascular endothelial cells and circulating blood cells. However, the purpose of the present review is to elucidate the pivotal role of platelet-derived chemokines in inflammation and atherosclerosis *in vitro*, *in vivo* as well as in various clinical conditions linked to atherosclerosis.

1.1. Platelets "sense" the presence of cardiovascular risk factors

Platelet activation is a pivotal step in the pathophysiology of atherosclerosis. Recent data demonstrated that beyond acute phase activating factors such as collagen, there are clinical states and factors favoring platelet susceptibility to activation.

Obesity is considered as one of the most important cardiovascular risk factors and is associated to the increased risk of atherosclerotic vessel disease. Various clinical and experimental data indicate that obesity is linked to disturbed platelet function and increased mean platelet volume (MPV), a parameter connected to increased platelet reactivity in obese subjects [32]. It has been also demonstrated that increased MPV could be an independent predictor for vascular events in obese individuals [32,33].

Diabetes mellitus, one of the major cardiovascular risk factors, has been associated with increased platelet activity and elevated inflammatory factors like CD40L compared to healthy individuals [34]. Interestingly, increased platelet reactivity was strongly associated with higher mortality in patients with diabetes undergoing percutaneous coronary intervention, while improvement of the metabolic status of diabetic patients could improve platelet reactivity [35,36]. Furthermore, in subjects with diabetes, elevated levels of platelet-derived micro-particles correlated with atherosclerosis and thrombosis [37]. Further to diabetes, patients with metabolic syndrome, a chronic inflammatory state strongly associated with atherosclerosis, exhibited higher P-selectin expression [38]. Healthy individuals with known history of metabolic syndrome, without any clinically overt cardiovascular disease, have increased platelet activation and elevated RANTES plasma levels [39]. Similar evidence supports the critical role of activated platelets in the development of thromboembolic stroke or transient ischemic attack in patients with metabolic syndrome [40].

Arterial hypertension, a classic risk factor for cardiovascular diseases, is also associated with increased platelet activation. Patients with resistant as well as controlled hypertension had higher MPV compared to individuals with normal blood pressure [41]. A large clinical study, which included more than 80,000 apparently healthy subjects, demonstrated that there is significant platelet activation even in patients with pre-hypertension [42].

One of the most important parameters affecting platelet affinity to endothelium is shear stress, which is defined as the longitudinal force per unit area applied onto the vessel wall while blood flows through the arterial vessel lumen. Under high shear stress conditions, platelet adhesion is enhanced, a process that is mediated firstly by the interaction between vWF and GPIb-V-IX and secondly through interaction with collagen as well as through other well characterized adhesion molecules expressed by endothelial cells such as the platelet and endothelial cell adhesion molecule 1 (PECAM-1), as recently demonstrated [43]. At a more advanced level, activated platelets morphologically alter into a shear-stress-depending manner favoring the formation of thrombi at the sites of high shear stress [44].

2. Platelet chemokines in inflammation and atherosclerosis

Extensive research activity has revealed a number of chemokines released from activated platelets. These chemokines orchestrate the development and progression of inflammation and atherosclerosis by enhancing the interaction of platelets with endothelial cells and circulating leukocytes and their progenitor cells (Fig. 1). It is crucial to mention that in many experimental studies global knockout mouse models are used, meaning that the existing data are not platelet specific. Similarly, in clinical studies chemokine circulating levels reflect their production from various cell types, therefore rarely are platelet specific.

The position of the first two cysteine residues defines the subgroups of chemokines, which are termed CC, CXC, C, CX3C [45]. Chemokines, a family of chemoattractant cytokines, are stored in alpha granules in platelets. However, the production of cytokines and other mediators, e.g. IL-1β take place in the cytosol. A critical role of chemokines released from platelets is to recruit and activate immune cells, such as monocytes, neutrophils and T-lymphocytes during vascular injury.

One of the highly expressed chemokines of platelets upon activation is CCL5, also referred to as RANTES, which activates CCR5, CCR3 and CCR1 receptors. Early *in vitro* and *in vivo* data demonstrated that RANTES mediates monocyte arrest on inflamed endothelium. In $ApoE^{-/-}$ mice, RANTES released from activated platelets favored platelet-monocyte aggregate formation on atherosclerotic lesions [46,47]. On the other hand, the use of Met-RANTES, a RANTES receptor antagonist, in an $LDLR^{-/-}$ mice model of atherosclerosis, decreased leukocyte infiltration, resulting in more stable atherosclerotic plaques [48]. Very recent data also demonstrated that CCR5 and CCL5 play crucial role in orchestrating T-cell homing in atherosclerotic lesions [49]. Specifically, it has been shown that the interaction between CCR5 and CCL5 is crucial for mediating CD4T-cells homing to atherosclerotic aortic lesions in high fat diet-treated $ApoE^{-/-}$ mice, which regulates local inflammatory processes and atherosclerosis progression [49]. These data also led to the detection of a specific CCR5-positive CD4T-cells [49]. Transcriptomic analysis of these T-cell subtype, demonstrated that these T-cells are able to secrete interferon-γ (IFN-γ), interleukins and tumor necrosis factor-α (TNF-α), factors known for their atherogenic activity [49]. Clinical data also indicate RANTES as a chemokine with a potent clinical significance. Elevated RANTES plasma

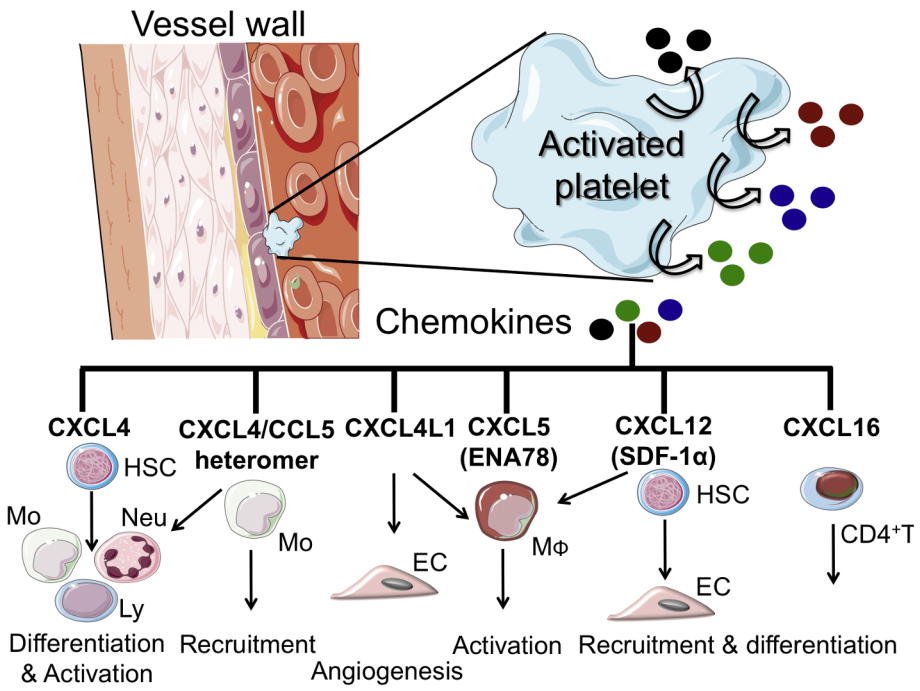

Fig. 1. Platelet-derived chemokines in inflammation. Upon platelet adhesion on vessel wall, platelets become activated changing their shape and releasing a plethora of chemokines (depicted as black or other coloured circles) to blood or the local environment. Platelet adhesion is induced either by exposure of platelets to subendothelial matrix or to inflammatory endothelium. Most of the chemokines are stored in alpha-granules, sometimes packaged in distinct alpha-granules, which are in turn released to platelet environment upon platelet activation. Other major triggers of platelet activation, apart from adhesion, are the thrombogenic molecules ADP (adenosine diphosphate), collagen and thrombin. The figure depicts the release of few platelet-derived chemokines upon platelet adhesion on vascular wall and its potential consequences for the neighboring vascular cells and circulating blood cells. Due to simplifying reasons we show here only a selection of chemokines and their actions. Further information is available in the Table. (Cell type illustrations included in the figure were modified from SMART).

levels were associated with metabolic syndrome in apparently healthy subjects, while increased RANTES circulating levels were also shown to correlate with the progression of CAD in patients with ACS [39,50]. On the other hand, in patients with known or suspected CAD undergoing coronary angiography, baseline RANTES levels were strongly associated with cardiac mortality, particularly in diabetic patients [51]. Nevertheless, the source of RANTES in patients' blood cannot be attributed only to platelets. Further studies evaluating the association between RANTES and platelet activation status are needed. Moreover, large clinical prospective studies are needed to evaluate the exact prognostic significance of RANTES in coronary artery disease.

The chemokine CXCL4, also known as platelet factor 4 (PF4), plays a crucial role in atherosclerosis. PF4 binds to CXCR3 activating various intramolecular pathways, which play a significant role in the development and progression of atherosclerosis and other cardiovascular diseases [52,53]. *In vitro* cell culture experiments demonstrated that CXCL4 mediates T-cell interaction with platelets promoting atherosclerosis by limiting neutrophil and monocyte apoptosis under pro-inflammatory conditions [54]. Cell culture experiments using macrophages have shown that PF4-induced macrophage differentiation led to downregulation of CD163 atheroprotective receptor and to an inability of macrophages to express heme oxygenase-1 [55]. Using immunofluorescence studies in human atherosclerotic plaques, an increased expression of PF4 and decreased expression of CD163 were observed [55]. Of great interest PF4 knockout ($PF4^{-/-}$) mice alone or combined with ApoE deletion, demonstrated reduced atherosclerosis indicating the crucial role of PF4 in atherosclerosis development [56]. Additionally, *in vitro* experiments showed that PF4 binds to oxidized-LDL (ox-LDL), and mediates its uptake and the esterification by macrophages promoting the formation of foam-cells [11]. Immunohistochemical analysis of atherosclerotic lesions from human carotid arteries also demonstrated that PF4 is co-localized with ox-LDL, supporting the hypothesis that PF4 favors ox-LDL uptake [11]. Histologic and immunohistochemical analysis of atherosclerotic lesions from human carotid arteries revealed the presence of PF4 in endothelium and macrophages at the sites of the lesions [57]. Interestingly, the presence of PF4 in endothelial cells and macrophages was associated with the severity of atherosclerosis in atherosclerotic lesions from human plaques of patients with carotid stenosis [57]. The same study demonstrated that the presence of PF4 in the macrophages, as assessed through immunostaining, was associated with the severity of symptoms related to atherosclerotic disease [57]. Moreover, recent data demonstrated that CXCL4 chemokine is among the key proteins "loaded" on platelet-derived exosomes [58]. According to the results of this study, platelet-derived exosomes from patients with cerebrovascular disease contain proteins and chemokines, such as CXCL4, in higher amount compared to healthy control subjects [58]. Of note, CXCL4 contains a recent discovered subtype, which is known as CXCL4L1 and differs structurally in three amino acids in the C-terminal [59,60]. Lately, it has been demonstrated that CXCL4 and CXCL4L1 could differentially affect monocyte differentiation [61]. *In vitro* exposure of macrophages to both chemokines shown that exposure to CXCL4L1 led to a differential monocyte activation, as defined by the capacity of the latter to produce CCL2 and CXCL8 [61]. Data from human studies demonstrated that CXCL4L1 circulating levels are associated with outcome in patients with stable CAD [60]. Nevertheless, the exact role of CXCL4L1 in cardiovascular disease remains to be elucidated.

Strikingly, CXCL4 forms heteromers with CCL5 with synergistic activity. By enhancing CCL5 activity, CXCL4 triggers monocyte recruitment and adhesion. Structural properties of CCR1 receptor enable the binding of CXCL4-CCL5 complexes causing the formation of atherosclerotic lesions [47]. Targeting CXCL4-CCL5 in mice resulted in attenuation of the formation and progression of aortic aneurysms and in protection against stroke-induced brain injury [62,63]. Specifically, western-blot analysis of the ischemic region of mice brain demonstrated an increased expression of CCL5 and its receptor, compared to the non-ischemic region [63]. Injection of MKEY, an inhibitor of CXCL4-CCL5 heteromers, led to reduced size of the infarct regions after stroke, as well as reduced macrophage infiltration, resulting in diminished neurologic deficits [63]. The aforementioned data indicate that CXCL4-CCL5 heteromers may play a complex role in cardiovascular disease [62,63]. Of great importance, with potent clinical significance, are the results of a recently published study from the research group of Dr. Phillip von Hundelshausen and Dr. Christian Weber on chemokine interactome [64]. Going beyond the known CXCL4-CCL5 heteromers, the authors showed that CCL5 is among the chemokines with a special ability to form heteromers with other chemokines, for example CCL5-CCL17 or CCL5-CXCL12 and others [64]. Striking data demonstrated a synergistic effect of CCL5-CCL17, mediated by affiliated receptors for both chemokines [64]. In addition, CCL5-CCL17 heteromers were detected in the intima and adventitia of human coronary arteries with advanced

atherosclerosis, compared to healthy vessels, as well as in atherosclerotic lesions derived from ApoE$^{-/-}$ mice [64]. On the other hand, knocking in of CXCL4L1 led to the same atheroprotective effects of CXCL4 knockout [64]. These data further support the idea that CXCL4 exhibits its atherogenic actions when forming heteromers with CCL5. Finally it has been demonstrated that CCL5 could drastically affect CXCL12-induced platelet aggregation, as indicated by the *in vitro* use of CCL5 derived peptides, having a favorable effect in reducing thrombogenesis. These data further enhanced the hypothesis that chemokines and chemokines heteromers could serve as potent therapeutic targets [64].

CXCL12, widely known as stromal cell derived factor-1alpha (SDF-1α), embodies a crucial role in atherosclerosis by affecting numerous cells. After being released from alpha granules of platelets, SDF-1α binds to the receptors CXCR4 and CXCR7. Recently published data demonstrated that CXCL12 induced platelet activation is mediated, possibly among other factors, through the regulator G-protein signaling 16 (RGS16) which plays a key role in the signaling of G protein-coupled receptors [65]. RGS16 is involved in inflammatory process, mainly via affecting monocyte function and cytokine production, functions closely associated to CXCL12 roles [65]. Of great interest is also the observation that SDF-1α could act in a paracrine way by binding to CXCR4 expressed on platelet surface [66]. Specifically *in vitro* experimental data showed that SDF-1α produced after collagen-induced platelet activation could act on platelet surface- expressed CXCR4 further inducing platelet activation in an autocrine or a paracrine manner [64]. Furthermore, the release of SDF-1α from platelets seems to play a key role in other cells' chemotaxis, interaction with vascular wall, as well as in cell differentiation [67]. Platelet-derived SDF-1α binds to its counter-receptors CXCR4 and CXCR7 on monocytes surface reducing monocytic apoptosis and promoting macrophage and monocyte transformation into foam cells by enhancing phagocytosis of apoptotic platelets [68]. Interestingly, *in vitro* experiments showed that SDF-1α mediates the differentiation of CD34$^+$ progenitor cells into foam cells by phagocytizing platelets [12]. SDF-1α binding to both receptors affects the expression of other mediators, such as TGF-β, since the inhibition of CXCR4 and CXCR7 reduced TGF-β expression significantly [69]. Beyond SDF-1α direct role in recruiting and engagement of other cells, SDF-1α promotes via binding to CXCR4 the differentiation of CD34$^+$ cells to endothelial progenitor cells [70]. This finding leads to the notion that platelets through expression of CXCL12 enhance vascular and even myocardial regeneration by accelerating the differentiation of circulating progenitor cells towards a pro-angiogenic cell phenotype. Patients with acute coronary syndromes (ACS) presented with significantly increased SDF-1α expression compared to patients with stable angina pectoris, while there was a significant correlation between platelet-bound CXCL12 and the number of circulating CD34$^+$ progenitor cells, underlying a possible role of this chemokine in CD34$^+$ cell mobilization in acute coronary syndromes [71]. Increased platelet expression of CXCL12 was also associated with reduced infarct area size, estimated through late-gadolinium-enhancement magnetic resonance in patients with AMI [72]. Further, we have previously demonstrated that increased baseline platelet/CD34$^+$ progenitor cell co-aggregate formation was associated with a significantly decreased myocardial infarct size and better left ventricular function 3-months after acute myocardial infarction (AMI) [73]. Moreover, formation of platelet/CD34$^+$ progenitor cell co-aggregates favored the homing of CD34$^+$ progenitor cells in the microcirculation after ischemia/reperfusion injury in mice [73]. Additionally, among patients with myocardial infarction, increased baseline expression of platelet SDF-1α was associated with higher left ventricular ejection fraction and stroke volume three months after AMI compared to patients with reduced expression of baseline platelet-bound SDF-1α [72]. Patients with increased SDF-1α levels presented also with increased circulating number of CD34$^+$ progenitor cells, which could at least partially explain the beneficial effect of platelet-bound SDF-1 in AMI [72]. However, this hypothesis needs to be evaluated in large prospective clinical studies.

CXCL5, also termed epithelial-derived neutrophil-activating protein 78 (ENA78), is a platelet derived chemokine highly expressed in patients with atherosclerosis with a proposed atheroprotective role [74]. In an ApoE$^{-/-}$ mouse model, CXCL5 was shown to affect macrophage activation status and via affecting the expression of the regulator protein ABCA1 leads to enhanced cholesterol efflux resulting in reduced accumulation of foam cells [75]. Clinical data demonstrated that there was a positive correlation between serum CXCL5 levels and intima media thickness, as a marker of atherosclerosis, in patients with type 2 diabetes [76]. However, further experiments and clinical data are needed to verify the exact role of CXCL5 in atherosclerosis.

Among the chemokines having a functional role in atherosclerosis, CXCL16 is also expressed by platelets. It has been demonstrated that resting platelets express CXCL16 mRNA and they also express CXCL16 on their surface [77]. CXCL16 expression is increased in response to various platelet stimuli such as ADP or ox-LDL [77]. Interestingly, platelet-derived CXCL16 is involved in ox-LDL binding, while *in vitro* blocking of CXCL16 resulted in reduced adhesion of platelets on a collagen/ox-LDL matrix [77]. The same study also showed that platelets from patients with ACS exhibited enhanced expression of CXCL16 compared to platelets from CAD patients [77]. As for most of the chemokines described here, CXCL16 is not platelet-specific chemokine, CXCL16 and its receptor CXCR6 mediate intercellular interactions including platelets. For instance, CXCL16 expression on inflamed endothelial cells plays a major role in recruiting and activating circulating platelets from blood flow, as well as in the recruitment of mononuclear cells. Thus, CXCL16 significantly contributes to atherosclerosis progression [78,79]. Both CXCL16 and LDLR deficient mice (CXCL16$^{-/-}$ LDLR$^{-/-}$) showed atherosclerotic lesion progression, mainly attributed to the disrupted cholesterol efflux due to impaired CXCL16 receptor function. However, macrophages from CXCL16$^{-/-}$ mice showed a reduced capacity to internalize ox-LDL *in vitro* [77,80]. Accordingly, in ApoE$^{-/-}$ mice fed with a high cholesterol diet, CXCL16 circulating levels were significantly higher and were associated with the formation of vulnerable plaques and increased MMPs. Thus, it was proposed that CXCL16 functions as a biomarker for plaques at risk of rupture, although further evaluation is needed [81].

Early clinical data demonstrated that in patients with acute and chronic coronary artery disease, circulating CXCL16 levels were significantly associated with markers of inflammation and metabolic parameters [82]. Furthermore, in patients with acute coronary syndrome baseline circulating CXCL16 levels were associated with higher mortality risk [83]. This prognostic value of soluble CXCL16 remained even after the adjustment for known risk factors [83]. In the HUNT2 population based study, CXCL16 levels were assessed in 5546 subjects confirming that subjects with higher CXCL16 were at risk of myocardial infarction. However, this prognostic value was lowered after adjustment for known risk factors [84]. Clinical data demonstrated a prognostic value of CXCL16 in patients with acute ischemic stroke, as CXCL16 level significantly increases the first days after acute stroke and associates with increased CV mortality [85].

Platelet microparticles (PMPs) are vesicles with diameters ranging between 0.1 and 1.0 μm, derived from platelets, either via shedding from the platelet membrane or through exocytosis. Various data demonstrated that PMPs play different roles in diseases such as cancer, inflammatory diseases, as well as in atherosclerosis [86]. Early *in vitro* data indicated that PMPs from activated platelets contain a significant amount of RANTES [87]. By using immunofluorescence, Mause et al. demonstrated that RANTES from circulating PMPs could trigger monocyte adhesion to inflamed endothelium [87]. More studies are needed in order to better elucidate the association of PMPs with other chemokines, and their role in atherosclerosis.

Other chemokines stored and/ or released from platelets include CXCL7 (also mainly known as neutrophil-activating peptide (NAP-2)), macrophage migration inhibitory factor (MIF), CXCL3 (also known as GRO- gamma), CCL4 (also known as macrophage inflammatory protein

Table 1
Key experimental and clinical studies focusing on the role of selected platelet chemokines in inflammation and atherosclerosis.

Chemokine	Experimental or clinical modality	Description of outcome
CCL5/ RANTES	Cell culture & ApoE$^{-/-}$ mice [46]	RANTES mediates monocyte arrest on inflamed endothelium promoting atherosclerosis
	Apo E$^{-/-}$ mice [47]	RANTES and PF4 triggers platelets monocyte coaggregate formation on inflamed endothelium
	LDLR$^{-/-}$ mice [48]	RANTES antagonism via Met-RANTES led to the formation of stable atherosclerotic plaques
	LDLR$^{-/-}$ & Abcb6$^{-/-}$ bone marrow transplanted mice [116]	Increased RANTES levels associated with accelerated atherosclerosis, via increased leukocyte activation & platelet-leukocyte coaggregation
	Observational study involving patients with ACS (n = 204) [50]	Higher RANTES levels determined upon admission with ACS and 6 h later, were associated with CAD progression
	Observational study involving patients with known or suspected CAD undergoing coronary angiography (n = 389), followed-up for 24 months [51]	Low baseline plasma RANTES levels were associated with high cardiac mortality. Authors hypothesized that this could be partly attributed to the upregulation of CCR5 in these patients. However future large-scale population studies are needed to further examine this finding
CXCL4/PF4	Cell culture [55]	PF4 (recombinant form) induced macrophage differentiation, and abolished atheroprotection through decreased CD163 expression
	Cell culture [11]	PF4 binds to ox-LDL promoting macrophages uptake, leading to foam cell formation
	PF4$^{-/-}$; ApoE$^{-/-}$ mouse model [56]	Significantly reduced atherosclerosis in PF4$^{-/-}$; ApoE$^{-/-}$ mice
	Atherosclerotic plaques from human carotid arteries (n = 132 patients) [57]	Expression of PF4 in vascular endothelial cells and macrophages was associated with severity of atherosclerotic disease
	Observational prospective study involving patients (n = 217) with suspected CAD undergoing computed coronary artery angiography (CCTA) [117]	No difference in plasma PF4 levels between patients with or without CAD
CXCL12/ SDF-1α	Cell culture [68]	CXCL12 (recombinant form) induced monocyte differentiation and their transformation into foam cells via phagocytosis of apoptotic platelets
	Cell culture [12]	SDF-1α induced CD34^{+} progenitor cells differentiation to macrophages and their transformation into foam cells via platelets phagocytosis
	Cell culture and mouse model of vascular injury [70]	Platelet derived SDF-1α leads to CD34^{+} recruitment at injury site, blocked when Ab versus SDF-1α or CXCR4 is used. Platelet-derived SDF-1α - CXCR4 axis promotes CD34^{+} differentiation to endothelial cells
	Patients with ACS (n = 418) versus patients with stable CAD (n = 486) [71]	Higher SDF-1α levels in patients with ACS compared to stable CAD patients. Lower ejection fraction was associated with higher SDF-1α levels. SDF-1α levels significantly correlated with CD34^{+} progenitor cell number in CAD
	ACS patients (n = 162) vs. SAP (n = 116). Ischemia-reperfusion (IR) injury mouse model [73]	Platelet/CD34^{+} cell co-aggregate formation was positively correlated to SDF-1α. In IR-injury mouse model platelet/CD34^{+} cell co-aggregate formation increased adhesion of CD34^{+} cells to vascular wall
	Prospective study involving patients with AMI (n = 40) [72]	Patients with increased baseline platelet-derived SDF-1α had reduced infarct size, improved ejection fraction and stroke volume 3 months after AMI, as assessed through

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Table 1 (*continued*)

Chemokine	Experimental or clinical modality	Description of outcome
		cardiac magnetic resonance imaging (cMRI)
	Prospective study involving patients with symptomatic CAD undergoing PCI (n = 608) [118], followed up for 12 months	Higher SDF-1α circulating levels were independently associated with higher risk for myocardial infarction, stroke and/ or cardiovascular death
CXCL5/ ENA78	Cell culture and ApoE$^{-/-}$ mouse model [75]	CXCL5 (recombinant form) activated ABCA1 protein resulting in increased cholesterol efflux activity in macrophages, and reduced accumulation of foam cells in atherosclerotic plaques
	Cross-sectional community based study involving patients with type 2 diabetes (n = 730) [76]	Serum CXCL5 levels were positively associated with intima media thickness in patients with type 2 diabetes mellitus
CXCL16	CXCL16 $^{-/-}$ LDLR$^{-/-}$ mouse model [80]	CXCL16$^{-/-}$ LDLR$^{-/-}$ mice demonstrated accelerated atherosclerosis
	ApoE$^{-/-}$ mouse model [81]	CXCL16 was highly expressed in ApoE$^{-/-}$ mice, and CXCL16 circulating levels were associated with more vulnerable plaques
	Observational study involving patients with ACS (n = 28) and stable CAD (n = 33) studying platelet expression of CXCL16 [77]	ACS patients had enhanced platelet expression of CXCL16 compared to CAD patients. The expression of CXCL16 was also associated with platelet activation as measured by P-selectin surface expression
	Prospective study involving patients with ACS (n = 1351) with a median follow-up of 81 months [83]	ACS patients with increased circulating serum baseline CXCL16 levels had higher mortality risk compared to patients with lower levels. Prognostic value of CXCL16 remained even after adjustment for known risk factors
	Cross-sectional study involving general population from the HUNT2 cohort, followed up for 11.3 years (n = 5546) [84]	No significant differences in serum CXCL16 levels between patients with MI and control group. Subjects with higher CXCL16 levels were at higher risk for myocardial infarction
	Prospective observational study involving patients with acute ischemic stroke (n = 244), followed-up for 47 months [85]	Increase of plasma CXCL16 levels the first 4 days after acute ischemic stroke was associated with increased CV mortality risk
CXCL7/NAP-2	Cell culture [119]	CXCL4 and CXCL7 (recombinant forms) significantly promoted neutrophil adhesion and transmigration on endothelial cell culture (HUVEC)
	Cell culture and NAP2$^{-/-}$ mouse model [120]	NAP-2 (recombinant form) from platelets induced neutrophil shape change and polarization. Effects were reversed when NAP-2 was depleted using a specifically targeting antibody. NAP-2 was highly expressed on platelet at sites of vascular injury in mouse model (wire injury). NAP-2$^{-/-}$ mice exhibited major reduction in leukocyte shape change and migration through thrombi to the site of vascular injury
CXCL3/GRO-gamma	Cell culture [121]	CXCL3 (recombinant form), induces monocyte arrest on endothelial cells
CCL4/MIP-1beta	Cell culture and hypertensive patients (n = 551), with an average follow-up of 37.2 ± 19.9 months [122]	*In vitro* CCL4 increases ROS production in THP1 cells, favoring their adhesion on endothelial cells. Higher CCL4 plasma level was independent predictor for future CV events in hypertensive patients
CCL3/MIP-1alpha	STEMI and unstable angina patients (n = 44 STEMI, 54 UAP, 22 controls) and C57Bl/6 mouse model with induced AMI [123]	AMI in C57Bl/6 mice led to increased CCL3 levels, and increased CCL3 associated with increased homing of T-cells at ischemic site. STEMI and UAP patients had

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Table 1 (*continued*)

Chemokine	Experimental or clinical modality	Description of outcome
		increased plasma CCL3 levels compared to apparently healthy age and sex matched subjects

Table abbreviations: Ab: Antibody, ACS: Acute coronary syndrome, AMI: Acute myocardial infarction, CAD: Coronary artery disease, CCTA: Coronary computed angiography tomography, CMR: Cardiac magnetic resonance, CV: Cardiovascular, EPCs: Endothelial progenitor cells, IR: Ischemia/ reperfusion, LDL: Low density lipoprotein, MI: Myocardial infarction, MIF: Macrophage migration inhibitory factor, MIP: Macrophage inflammatory protein, NAP-2: Neutrophil activating peptide, PCI: Percutaneous coronary intervention, PF4: Platelet factor 4, RANTES: Regulated on activation normal T cell expressed and secreted, ROS: Reactive oxygen species, SDF-1α: Stromal cell-derived factor-1, STEMI: ST-elevation myocardial infarction, UAP: Unstable angina pectoris.

(MIP)-1 beta) and CCL3 (also known as MIP-1 alpha). Experimental and clinical data indicate their potent pathophysiological role in atherosclerosis [45,88,89]. However, the effect of platelet origin of these chemokines in atherosclerosis or in interaction with immune cells and vascular wall has not been described till now.

Table 1 summarizes significant experimental and clinical data on platelet chemokines with a known role in atherosclerosis. We must declare, here, that platelets are not the only cells responsible for the production of these chemokines and, thus, studies involving platelet-restricted chemokine knockout mice are needed to elucidate the platelet-specific effects *in vivo*.

3. Role of platelet activation in other inflammatory diseases

Platelets play also a pivotal role in other inflammatory diseases such as in autoimmune and in infectious diseases. It is well-established that bacterial or viral infections affect platelet count in humans [90]. Platelets are abundantly activated in sepsis and release numerous mediators like PF4 participating in the pathology of sepsis [91].

Platelet activation has also a key role in the inflammatory processes involved in the pathophysiology of autoimmune diseases [92]. Patients with rheumatoid arthritis express higher levels of P-selectin and CD40 L, while patients with systemic lupus erythematosus have higher sCD40 L expression levels [93–95]. Increased platelet activation is also common in patients with multiple sclerosis (MS) presenting high P-selectin levels [96]. In addition, higher expression of the activated form of GPIIb/IIIa has been identified in MS patients [97].

Platelets may play also a critical role in the development or progression of Alzheimer's disease (AD) [98,99]. In cerebrospinal fluid from AD patients high amounts of GPVI and beta-thromboglobulin were found, thus indicating increased platelet activation [100]. Interestingly, cognitive impairment significantly correlates to platelet activation [100]. However, the exact mechanisms involved remain elusive. Further mechanistic studies are needed in an effort to understand the role of platelets and anti-platelet therapy in dementia.

Taken together, these data underline the importance of platelets in a large spectrum of inflammatory diseases.

4. Impact of cardiovascular therapy on release of platelet chemokines

Platelets have been over decades a target of pharmacological intervention. However, the current antiplatelet therapy targets the aggregatory function of platelets and not platelet activation per se. However, accumulating evidence suggests that the current antiplatelet therapy may also partially affect the release of platelet chemokines.

One of the first and still in use antiplatelet drugs in atherosclerosis is aspirin, which represents an inhibitor of cyclooxygenase-1. Aspirin affects platelet activation by regulating the expression of surface receptors, such as GPIIb/IIIa and P-selectin, as well as the release of chemokines, mainly by modulating the content of platelet derived exosomes, which contain chemokines such as CXCL4 and CXCL7 [101,102]. The P2Y12 ADP receptor antagonists, acting through inhibition of the ADP-induced activation of the P2Y12 receptor, are considered pivotal agents in currently used therapeutic anti-platelet strategies. Clopidogrel, ticagrelor and prasugrel are among the most common drugs in clinical use. Treatment with P2Y12ADP receptor antagonists led to reduced plasma levels of sCD40 L and RANTES [103].

Statins, one of the most used lipid-lowering agents, are widely known for their pleiotropic actions, especially their anti-inflammatory properties and their role in plaque stabilization [104]. *In vitro* experiments showed that statins inhibit platelet aggregation, lowering platelet thrombogenicity and aggregability, reducing the surface expression of P-selectin, while decreasing the release of pro-inflammatory cytokines, such as CD40 L [105–107]. Knowing that cholesterol influences platelet function, it is tempting to hypothesize that statins indirectly affect platelet function by its ability to lower cholesterol and thus reduce the amount of oxidized LDL [108–110]. Recently, rosuvastatin has been described to lower hyperactivity of platelets and further decrease the membrane cholesterol level in platelets in patients with hypercholesterolemia thereby ameliorating patient outcome [111].

Dabigatran, a direct thrombin IIa inhibitor, apixaban and rivaroxaban, direct factor Xa inhibitors, are new oral anticoagulants used in clinical routine mainly used in patients with atrial fibrillation and for the prevention of venous thromboembolism. Thrombin inhibitors reduce the formation of platelet-leukocyte aggregates, platelet aggregation via inhibiting tissue factor activation and further affect directly vascular inflammation and atherosclerosis *in vivo* [112,113]. Drugs targeting specifically factor X have similar effects as described earlier and thus reduce venous thrombus formation [114,115]. However, their impact on platelet activation and chemokine release remains unknown.

5. Conclusion and future perspectives

Our current knowledge indicates platelets as a key cell population in inflammation and atherosclerosis. Platelets interact with various cell types including endothelial cells, T-cells, monocytes, macrophages, neutrophils, haematopoietic stem cells ($CD34^+$ cells) and other inflammatory cells. Emerging data support the importance of platelet-derived chemokines in cell-cell interaction and, thus, in inflammation and in atherosclerosis. Given that the chemokine interactome may serve as a therapeutic target, future studies are called to evaluate the therapeutic value of interference with platelet chemokine interactome in inflammatory diseases including coronary heart disease.

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