The Migration of Platelets and their Interaction with Other Migrating Cells

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Abstract

Platelets, beyond their well-described role in haemostasis and thrombosis, act as inflammatory cells playing an active role in several inflammatory conditions. As observed with other inflammatory cells platelets can migrate in vitro, either randomly or in the direction of a chemotactic agent, and in vivo, into inflammed tissues in response to different stimuli. In this chapter we will summarize the current knowledge about the mechanisms that regulate platelet chemotaxis, the evidence for the ability of platelets to migrate in vitro and in vivo, and the mechanisms by which platelets influence chemotaxis of other cells.

Introduction

It is now well established that platelets act as inflammatory cells and contribute to both innate and adaptive immune response through several mechanisms, like pathogen binding, trapping and killing, direct modulation of leukocyte and endothelial cell activation, leukocyte recruitment, and activation of antigen presenting cells (APC) (Czapiga et al. 2004; Jenne et al. 2013; Semple et al. 2011; Vieira-de-Abreu et al. 2012) (also see Slaba and Kubes 2017). Platelets are therefore the most abundant circulating cell type (150–400,000/μL) with an immune function and participate in host defence against parasites, bacteria and viruses. Moreover, increasing evidence shows that platelets play a pathogenic role in several chronic inflammatory disorders including atherosclerosis, allergic inflammation (asthma, rhinitis and eczema), chronic obstructive pulmonary disease, rheumatoid arthritis and inflammatory bowel disease.

Several structural and biochemical characteristics allow platelets to act as inflammatory cells (Heijnen and Korporaal 2017; Slaba and Kubes 2017), probably because they retain some functions of their phylogenetic ancestor, the amoebocyte, the unique nucleated cell with defensive and haemostatic functions circulating in the haemolymph of invertebrates (Momi and Wiwanitkit 2017).

One of the crucial functions of "bona fide" inflammatory cells is their ability to migrate through tissues. Platelets display a number of attributes compatible with the ability to migrate: they express receptors for adhesive proteins and chemokines, contain and release matrix metalloproteinases (MMPs) required for extracellular matrix (ECM) degradation, and have the cytoskeletal and enzymatic machinery required for cell locomotion.

In this chapter, we will summarize the in vitro and in vivo evidence of platelet migration in response to chemotactic stimuli and of the role of platelets in tissue recruitment of other cells, including leukocytes and cancer cells.

Chemotaxis is the active movement, or migration, of a cell in the direction of a chemotactic gradient. It is a central event in several physiologic processes, such as embryonic development, tissue repair, angiogenesis and immune response, and the abnormal chemotaxis of the cells contributes to many pathologic conditions, like chronic inflammation, autoimmunity and metastasis. Cell locomotion is a complex and multistep process by which an extracellular chemotactic gradient is detected by a specific cell receptor, a signal is translated to the cell's

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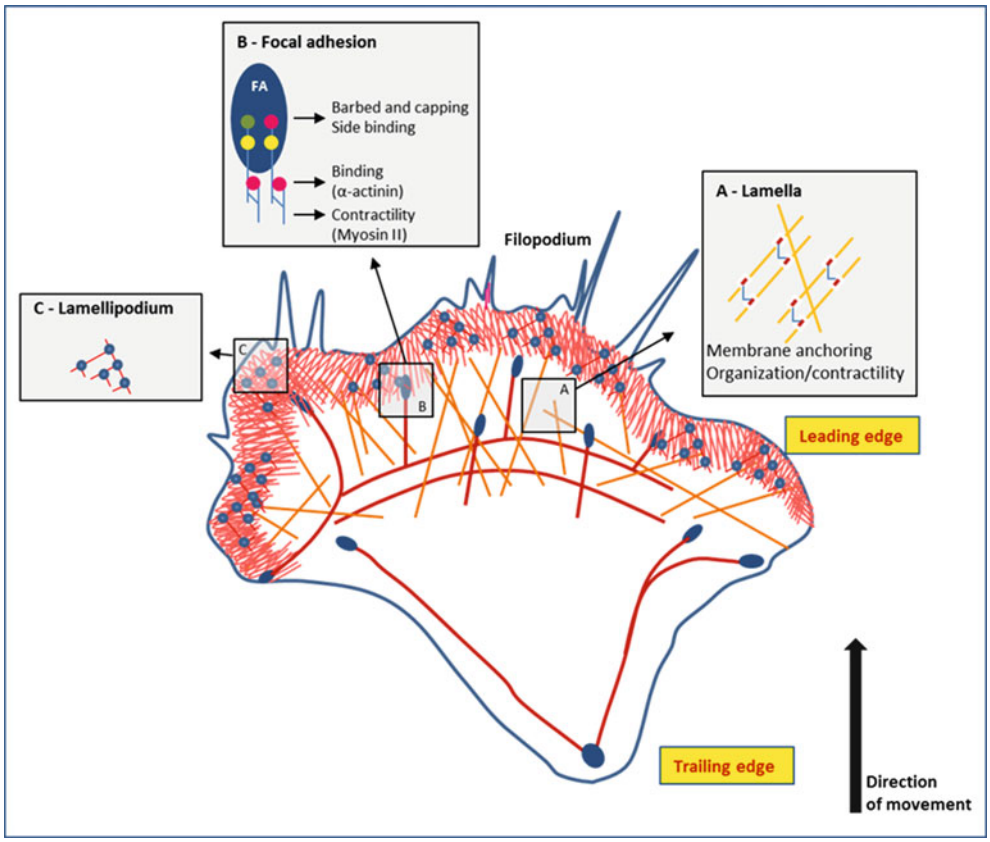

Fig. 1 Cellular polarization. Structural and functional asymmetry of a migrating cell consisting of a leading edge at the front in the direction of movement and a trailing edge at the rear associated with a cytoskeletal organization

motile apparatus and an intracellular functional and structural asymmetry is generated allowing the cell to move towards the detected chemoattractant. Cell polarization is crucial for chemotaxis and consists of the formation of two cellular compartments, the leading edge at the front and the trailing edge at the rear. At the leading edge the cell extends a protrusion, a lamellipodium or filopodium, in the direction of the chemotactic stimulus, which establishes new adhesion sites with the substratum, while at the trailing edge the cell contracts, adhesion sites detach and the uropod, a protrusion at the rear of the cell, retracts. In each of these steps several proteins and intracellular signaling pathways are involved and a fundamental role is played by the cytoskeleton and its ability to rapidly assemble and disassemble (Fig. 1) (Charest and Firtel 2007; Germena and Hirsch 2013; Jin 2013; Raftopoulou and Hall 2004).

Structural Characteristics Ascribing to Platelets the Ability to Migrate

Platelets possess all the structural characteristics required for chemotaxis. They express on their surface several functional chemokine receptors, such as CCR1, CCR3, CCR4, CXCR1, CXCR4, CXCR6, CXCR7 and CX3CR1 (Abi-Younes et al. 2000, 2001; Borst et al. 2012; Chatterjee et al. 2014; Clemetson et al. 2000; Kowalska et al. 1999, 2000; Postea et al. 2012; Rath et al. 2014; Schafer et al. 2004; Suttitanamongkol and Gear 2001; Wang et al. 1998) and other receptors involved in leukocyte migration, like Toll-like receptor 4 (TLR4) and formyl peptide receptors (FPR) (Andonegui et al. 2005; Cognasse et al. 2005; Czapiga et al. 2005).

Platelets possess the central components of chemotaxis-related intracellular signaling, and in particular phosphatidylinositol 3-kinase (PI3K) and phosphatase and tensin homologue deleted on chromosome 10 (PTEN) that regulate the production and cellular localization of phosphatidylinositol 3,4,5-trisphosphate (PIP3), which is crucial for the generation and maintenance of cell polarity (Van Keymeulen et al. 2006), and the Rho family of small GTPases that activate a plethora of effector molecules modulating actin cytoskeleton dynamics (Germena and Hirsch 2013; Worthylake and Burridge 2001; Yan and Jin 2012).

Platelets contain a cytoskeletal framework that allows cell movement. The discoid shape of platelets is maintained by a membrane skeleton that coats internally the plasma membrane, composed by a network of actin filaments, spectrin, adducin, and actin-associated proteins, and by a rigid cytoplasmic scaffold made of actin and filamin A. Actin-associated proteins and filamin A link the platelet cytoskeleton to integrins. Platelet activation induces changes

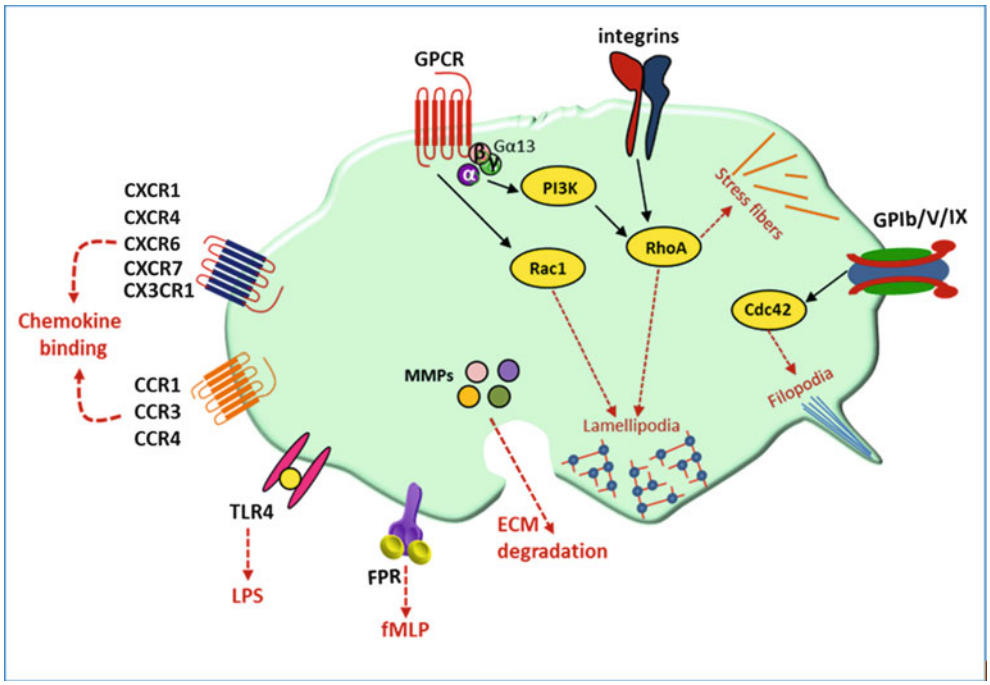

Fig. 2 Structural characteristics ascribing to platelets the ability to migrate. Platelets express on their surface several receptors triggering chemotaxis. Platelets possess the main components of chemotaxis-related intracellular signalling, involved in cell polarization and cytoskeletal re-organization. Platelets contain and release upon activation different MMPs involved in the ECM degradation required for their passage through the basement membrane

in the cytoskeletal organization with the formation of focal adhesion complexes, dynamic structures linking integrins to the actin cytoskeleton and which together with stress fibres contribute to a contractile response (Goggs et al. 2015; Hartwig 2006).

Platelets contain, and release upon activation, several MMPs, including MMP-1, -2, -3, and -14 (Seizer and May 2013; Busti et al. 2010), which may accomplish the extracellular matrix degradation required for the passage of migrating cells through the basement membrane (Fig. 2).

Platelet Migration: Studies In Vitro

The first in vitro observations on the ability of platelets to migrate date back to the early 70s. Before then, platelets were considered cell fragments passively drifting in the circulation until a contact with an area of damaged endothelium stopped them. The motion of platelets occasionally observed under a light microscope was considered as passive diffusion or Brownian movements, i.e. a temperature-dependent, erratic, not directional movement of particles smaller than 4–5 μm observed in colloidal suspensions (Chamot and Mason 1947).

The first studies on platelet migration in vitro assessed the optimal conditions to study platelet movement showing that several factors, such as temperature, pH, anticoagulant, platelet concentration and buffer composition, influence this process (Lowenhaupt et al. 1977; Nathan 1973; Valone et al. 1974) (Table 1).

Methods

Lowenhaupt and Valone were the first to study platelet migration (Lowenhaupt et al. 1973, 1977; Lowenhaupt 1978; Valone et al. 1974). Lowenhaupt adapted the capillary tube migration chamber previously described by George and Vaughan for the study of macrophage migration (George and Vaughan 1962). This consisted of an incubation chamber with a capillary tube immobilized at the bottom. The incubation chamber was composed of a stainless steel slide (75 × 25 × 3 mm) with a center hole 20 mm in diameter and one side sealed by a siliconized glass slide to form a dish and two small channels connecting it to the edge of the slide (Fig. 3a). A siliconized micro-hematocrit capillary tube, fire-sealed at one end, was filled with platelet-rich plasma (PRP) (300,000 platelets/μL) and centrifuged for 5 min. The capillary tube was then cut at the meniscus between platelet poor plasma (PPP) and the platelet pellet and secured to the bottom of the incubation chamber. The chamber was then filled with autologous PPP, covered with a siliconized cover glass and incubated at 22 °C for 18 h in a CO_2 incubator in order to maintain pH between 7.2 and 7.4. To investigate platelet chemotaxis, in the same incubation chamber, a thread-like piece of collagen or a fine-collagen-packed capillary tube was placed at a distance of about 5–6 mm from the platelet-packed capillary tube. The end point was the area of platelet migration out of the capillary tube visible by a stereomicroscope and measured with a planimeter (Lowenhaupt et al. 1973).

Table 1 Methods used to study platelet migration in vitro and optimal experimental conditions

Parameter	Optimal condition	Method	References
Temperature (°C)	22	Capillary tube[a,b]	Lowenhaupt et al. (1973, 1977, 1982) and Lowenhaupt (1978)
		7-compartment chamber[a]	
	25	Capillary tube[b]	Duquesnoy et al. (1975)
	30	Capillary tube[b]	Nathan (1973)
	37	Boyden chamber[b]	Valone et al. (1974)
		Transwell migration and videomicroscopy[a]	Czapiga et al. (2005)
		Boyden chamber[a]	Pitchford et al. (2008)
		Transwell migration and videomicroscopy[a]	Kraemer et al. (2010)
pH	5–6.5	Boyden chamber[b]	Valone et al. (1974)
	7.0	Capillary tube[b]	Nathan (1973)
	7.2–7.4	Capillary tube[a,b]	Lowenhaupt et al. (1973, 1977) and Lowenhaupt (1978)
	7.4	Transwell migration and videomicroscopy[a]	Kraemer et al. 2010
Anticoagulant	Heparin	Capillary tube[b]	Nathan (1973)
	Citrate	Boyden chamber[b]	Valone et al. (1974)
		Capillary tube[b]	Duquesnoy et al. (1975)
		Boyden chamber[a]	Pitchford et al. (2008)
	3.8 % trisodium citrate dihydrate or ACD 15 % v/v	Capillary tube[a]	Lowenhaupt et al. (1973)
		Capillary tube[b]	Lowenhaupt et al. (1977)
	ACD	Transwell migration and videomicroscopy[a]	Kraemer et al. (2010)
Incubation time (hrs)	0.25	Micromaze[a]	Lowenhaupt (1978)
	1.5	Boyden chamber[a]	Pitchford et al. (2008)
	2	Transwell migration[a]	Czapiga et al. (2005)
	3	Boyden chamber[b]	Valone et al. (1974)
		7-compartment chamber[a]	Lowenhaupt (1982)
	8	Transwell migration[a]	Kraemer et al. (2010)
	12	Capillary tube[b]	Duquesnoy et al. (1975)
	18	Capillary tube[a, b]	Lowenhaupt et al. (1973, 1977) and Lowenhaupt (1978)
	24	Capillary tube[b]	Nathan 1973
Platelet suspension	300,000/μL (PRP)	Capillary tube[a,b]	Lowenhaupt et al. (1973, 1977) and Lowenhaupt (1978)
	100,000/μL (WP)	Boyden chamber[b]	Valone et al. (1974)
	^{111}In-oxine-labeled (PRP)	7-compartment chamber[a]	Lowenhaupt (1982)
	3333/μL	Transwell migration[a]	Czapiga et al. (2005)
	300,000/μL (PRP)	Boyden chamber[a]	Pitchford et al. (2008)
	2000/μL (WP)	Transwell migration[a]	Kraemer et al. (2010)
Pore size of the filter (μm)	0.4	Transwell migration[a]	Kraemer et al. (2010)
	2	Transwell migration[a]	Czapiga et al. (2005)
	3	Boyden chamber[a]	Pitchford et al. (2008)
	8	Boyden chamber[b]	Valone et al. (1974)
Endpoint of the test	Area of migration (planimeter)	Capillary tube[b]	Nathan (1973)
			Duquesnoy et al. (1975)
	Area of migration, (stereomicroscope and planimeter)	Capillary tube[a,b]	Lowenhaupt et al. (1973, 1977) and Lowenhaupt (1978)
	Microphotographs of platelet movement	Micromaze[a]	Lowenhaupt (1978)
	Radioactive counts	7-compartment chamber[a]	Lowenhaupt (1982)
	Platelet count per microscopic field		Valone et al. (1974)
			Pitchford et al. (2008)
	Platelet count in the bottom well and image sequences of platelet movement		Czapiga et al. (2005)
			Kraemer et al. (2010)

PRP platelet rich plasma, WP washed platelets
[a]Migration in the direction of a chemotactic agent
[b]Random migration

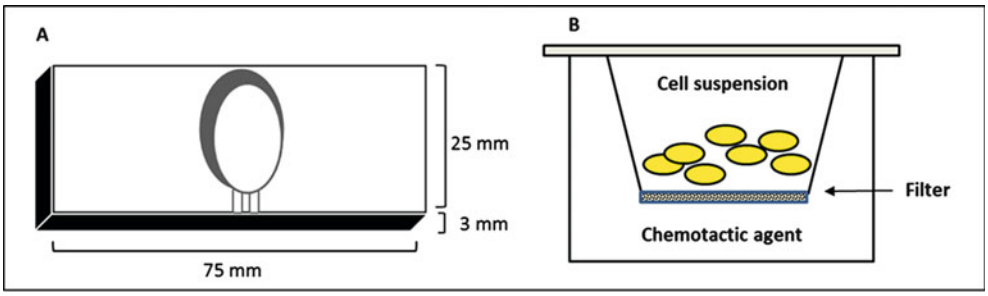

Fig. 3 (**A**) Diagram of the stainless steel slide. (**B**) Boyden chemotaxis chamber

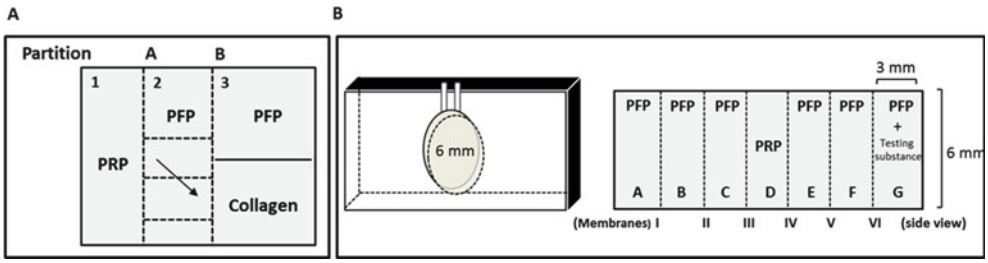

Fig. 4 (**A**) Diagram of the micromaze. PRP is placed in compartment 1, PFP in compartments 2 and 3 and collagen suspended in PFP in compartment 4. (**B**) Seven-compartment chamber. (*sx*) A basic unit of the seven-compartment chamber. (*dx*) The linearly connected 7-compartment chamber showing contents in each compartment

Valone instead studied platelet migration by adapting the Boyden chamber initially developed for the study of leukocyte chemotaxis (Boyden 1962) (Fig. 3b). This is a perspex chamber composed of two compartments separated by a filter membrane 100 μm thick with pores of 8 μm size. A platelet suspension in standard buffer (0.005 M KH_2PO_4, 0.005 M Na_2HPO_4, 0.1 M NaCl, 0.2 g/100 mL glucose and 0.5 g/mL gelatin) (100,000/μL) was placed in the upper compartment and buffer medium in the lower compartment. After 3 h of incubation the filter was removed, washed, fixed in 10 % formalin, stained, cleared and mounted on a glass slide. Platelets migrated into the filter were counted in 10 high-power fields by phase-contrast microscopy at a fixed level (40–70 μm from the top of the filter) (Valone et al. 1974).

Directional migration of platelets towards a chemotactic gradient was also studied with the micromaze method (Lowenhaupt 1978) or the 7-compartment chamber using indium^{111}-oxine-labeled platelets (Lowenhaupt et al. 1982). The micromaze is a chamber formed by four compartments connected by thin slits to permit cell passage between compartments; collagen was placed in compartment 4 (Fig. 4a). Platelet movement was visualized by an inverted phase-contrast microscope by following the leading edge of the platelet mass or by viewing the passage of individual platelets between compartments through the slits: time-lapse image sequences were taken at fixed intervals (Lowenhaupt 1978). The 7-compartment chamber consists of seven identical compartments linearly connected and separated by Nucleopore or Millipore filters of different pore size (III and IV 3 μm, II and V 1 μm, I and VI 0.45 μm); collagen was placed in compartment G (Fig. 4b). Gel-filtered platelets were labeled with ^{111}In-oxine, resuspended in autologous platelet-free plasma (PFP) and filtered through two sterile nylon mesh filters to remove aggregates. Platelet chemotaxis was expressed as a ratio of the radioactive counts of the two-end compartments (Lowenhaupt et al. 1982).

More recently platelet chemotaxis has been studied using several further modifications of the original Boyden chamber, namely:

1. The NeuroProbe 96-well ChemoTx microplate, with the upper and lower compartments separated by a 2 μm pores filter. After 2 h of incubation, platelets migrated into the lower compartment were counted by light microscopy (Czapiga et al. 2005).
2. The Nucleopore single wells, with the upper and lower compartments separated by a 3 μm pore size filter, loaded with murine or human PRP. After 1.5 or 3 h incubation, respectively, filters were stained and platelets were counted at various depths below the filter surface (0–100 μm for murine and 40–70 μm for human platelets) (Pitchford et al. 2008).
3. The transwell inserts, with a polyethylene terephthalate (PET) membrane with 0.4 μm pores. Platelets were added in the upper compartment, allowed to migrate

for 8 h and then counted in the lower compartment by flow cytometry (Kraemer et al. 2010).

Horizontal migration of platelets has been studied in a delta T culture dish placed on a microscope with a heated stage and platelet movements were recordedbefore and during the addition of either fMLP or PBS (as a control) every 5 s for 15 min (Czapiga et al. 2005), or in a migration chamber consisting of a fibrinogen-coated slide with a central spot of low-melting agarose containing the chemotactic agent and platelet movement were recorded using a polarization microscope for 3 h (Kraemer et al. 2010).

The assays used to study platelet migration are summarized in Table 1.

Chemotactic Agents

Platelets can detect an extracellular chemotactic gradient and move along this gradient. The first platelet chemotactic agent to be described has been collagen. Various types of collagen (bovine, equine, human from skin or from achilles tendon) elicit platelet chemotaxis, although with different potency. Only native collagen, and not heat-denatured or dinitrofluorobenzene-treated collagen, induces platelet chemotaxis. Interestingly, the structural features of collagen required for platelet aggregation, i.e. the fibrillar structure, are not required for chemotaxis. Collagen-induced platelet chemotaxis does not require a direct contact with platelets, given that migration was still observed when a filter impermeable to the large polymerized collagen molecules was interposed between platelets and the stimulus. Thus, the generation of "chemotaxins", low molecular weight substances produced by the interaction between collagen and plasma, was postulated (Lowenhaupt 1982). Platelets migrated in the direction of collagen for a long distance (3000 times their diameter, i.e. 6 mm) in a very short time (15 min) (Lowenhaupt 1978).

Formyl peptides, cleavage products of bacterial and mitochondrial proteins, induce platelet chemotaxis via binding to formyl peptide receptors (FPR), seven transmembrane receptors coupled to Gαi stored in α-granules and expressed on the platelet surface after activation (Czapiga et al. 2005). Platelet movement towards fMLP at a velocity of 13.07 ± 1.10 μm/min has also been recorded in time-lapse (Czapiga et al. 2005).

Recently, platelet chemotaxis towards a conventional chemokine of the CXC family, CXCL12 or stromal cell-derived factor-1α (SDF-1α), has been shown (Kraemer et al. 2010). This chemokine induced platelet migration upon binding to its specific receptor CXCR4 expressed on platelets, given that the CXCR4-receptor antagonist AMD3100 inhibits it. Platelets also trans-migrate through an IL-1β-activated layer of human umbilical vein endothelial cells (HUVEC) in the direction of SDF-1α (Kraemer et al. 2010). In time-lapse studies platelets accumulated around the source of SDF-1α after 3 h, with a speed of migration variable depending on the number of focal adhesion contacts. In the early stages of migration (fast migration: 200 μm/3 h) platelets have only few focal adhesion contacts, while their number increases as migration speed slows down (Kraemer et al. 2010).

Molecular Mechanisms Regulating Platelet Migration

Platelet migration is an active, energy-consuming process that requires viable and metabolically intact platelets. Infact, fixation with formalin or pre-treatment with iodoacetic acid (IAA) and sodium fluoride (NaF), which interfere with the glycolytic pathway, with 2,4-dinitrophenol (DNP), which uncouples oxidative phosphorylation, and with 6-aminonicotinamide, which suppresses the hexose monophosphate shunt, blocks platelet migration (Valone et al. 1974; Lowenhaupt et al. 1977). As expected cytochalasin B, which disrupts actin filaments, inhibited migration, while colchicine, which interferes with the polymerization of microtubules, did not (Lowenhaupt et al. 1977).

Platelet migration triggered by SDF-1α is mediated by PI3K, given that the PI3K inhibitors wortmannin and LY294002 significantly inhibited it. PI3K phosphorylates Wiskott-Aldrich syndrome protein (WASP) that induces the rearrangement of the actin cytoskeleton (Kraemer et al. 2010). Downstream signaling linking PI3K to platelet migration involves the serum- and glucocorticoid-inducible kinase 1 (SGK1), known to be involved in endothelial cell and monocyte/macrophage migration (Borst et al. 2015; Zarrinpashneh et al. 2013). The importance of SGK1 in platelet migration seems to be connected to its ability to regulate the actin cytoskeletal architecture in fact WASP and vinculin, two proteins interacting with actin, are SGK1-sensitive. WASP activates the Arp 2/3 complex that binds actin, thus inducing its polymerization, and vinculin is an actin-binding protein that, when phosphorylated, stabilizes the focal adhesions (Kraemer et al. 2010; Schmidt et al. 2012). SGK1-deficient platelets show impaired migration, reduced WASP activation and enhanced vinculin phosphorylation (Schmidt et al. 2012).

Platelet migration is dependent on the increase of intracellular Ca^{2+} via the Ca^{2+} channel Orai1, the pore forming unit of the store-operated Ca^{2+} entry (SOCE) channel, and on K^+ efflux via the Ca^{2+}-activated K^+ channel SK4 (Schmidt et al. 2011).

Platelets adhering to a fibrinogen-coated surface and then exposed to high shear conditions ($1500\ s^{-1}$) undergo

polarization, cytoskeletal reorganization with increased WASP phosphorylation and redistribution of intracellular focal adhesion kinases (FAK) to areas of dynamic focal adhesions, and migration in the direction of flow at a speed of approximately 10 μm/h (Kraemer et al. 2011).

Platelet Migration in Disease

Platelet migration has also been studied in disease conditions and/or in response to various pathologic stimuli. Duquesnoy in 1975 described a platelet migration inhibition (PMI) assay to detect antibodies in serum directed against the human leukocyte antigen (HLA) and the platelet-specific antigen Pl-A1 (Duquesnoy et al. 1975), or alloantibodies against platelets in platelet-transfused patients (Levine and Brubaker 1983). This assay was a modification of the capillary tube chemotaxis chamber used by Lowenhaupt et al. (1973) and it tested the capacity of antibodies to inhibit platelet migration by mixing control PRP with patient's serum. The sensitivity of the PMI test was reported to be comparable or even greater to that of several other methods used for the detection of platelet antibodies, such as the platelet lysis assay, complement fixation, platelet aggregometry and platelet factor-3 release (Duquesnoy et al. 1975; Levine and Brubaker 1983).

Platelets from allergic asthmatic subjects, but not from healthy donors, concentration-dependently migrated in vitro in response to the specific sensitizing allergen and in response to a monoclonal anti-human IgE antibody. In asthmatic subjects allergen-specific IgEs, produced upon previous contact with the allergen and bound to the platelet high-affinity receptor for IgE, FcεRI, bind the allergen inducing the cross-linking of contiguous receptors thus triggering platelet chemotaxis (Pitchford et al. 2008). The same phenomenon is triggered by an anti-IgE antibody that, binding to contiguous Fc portions of FcεRI-bound IgEs, induces the cross-linking of the receptors. The crosslinking of IgE receptors on platelets was previously shown to trigger other platelet functional activities, such as cytotoxicity (Polack et al. 1991), oxygen radical formation (Vargas et al. 1999) and release of chemokines (Hasegawa et al. 2001; Klouche et al. 1997). Migration of platelets from ovalbumin (OVA)-immunized mice in response to the sensitizing allergen was also demonstrated (Pitchford et al. 2008).

Platelet Chemotaxis: Studies in Animal Models

Studies in animal models confirm the ability of platelets to migrate into inflammed tissues. Extravascular accumulation of platelets in bronchial tissue and in lungs, associated with bronchospasm, has been observed by electron microscopy or

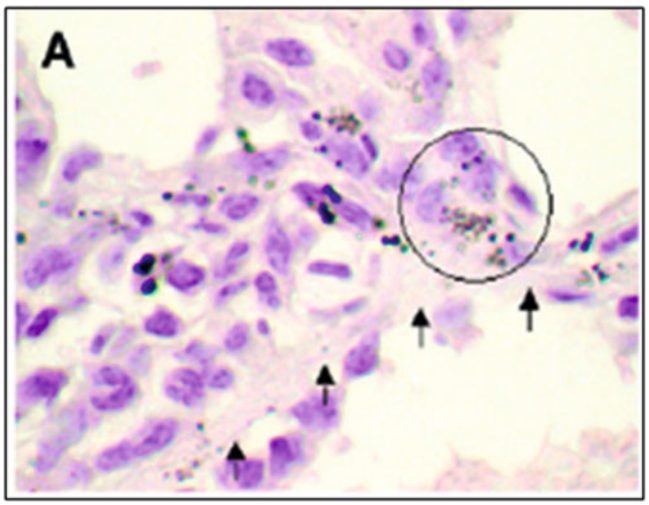

Fig. 5 Individual platelets (*arrows*) migrated in lung parenchyma after mouse allergen challenge. Reprinted with permission of the American Thoracic Society. Copyright (c) 2016 American Thoracic Society. Pitchford SC et al., 2008, Allergen induces the migration of platelets to lung tissue in allergic asthma, Am Respir Crit Care Med 177; 604–612. The American Journal of Respiratory and Critical Care Medicine is an official journal of the American Thoracic Society

by the accumulation of ^{111}In-oxine-labelled platelets in guinea pigs and baboons after intravenous challenge with platelet-activating factor (PAF) and other platelet agonists, like ADP or collagen. The penetration of platelets in tissue was not the consequence of blood extravasation, as no other blood cells were concomitantly found (Arnoux et al. 1988; Lellouch-Tubiana et al. 1985; Page et al. 1984; Robertson and Page 1987). The presence of platelets in skin accompanied by neutrophils was also described after the intradermal injection of PAF in rats (Pirotzky et al. 1984).

Platelets have also been detected in bronchoalveolar lavage (BAL) fluid of mice with chronic allergic airway inflammation (Pitchford et al. 2004) and from rabbits with experimental asthma, following allergen-challenge (Coyle et al. 1990).

Platelets from OVA-immunized mice were observed to migrate out of blood vessels after allergen inhalation and to localize in lung parenchima, directly underneath the airways (Fig. 5). Platelet influx in tissue preceded leukocytes and was largely independent of the latter (Pitchford et al. 2003, 2005). Platelet migration into inflammed lung was shown to be mediated by the binding of allergen to FcεRIγ-bound allergen-specific IgEs on the platelet surface (Pitchford et al. 2008), a phenomenon previously described for other inflammatory cells such as eosinophils, basophils and mast cells (Ishizuka et al. 2001; Orida et al. 1983; Svensson et al. 2004).

Transendothelial migration of platelets into the skin of guinea pigs induced by the subcutaneous injection of fMLP was demonstrated by serial electron-microscopy of thin tissue sections (Feng et al. 1998b). In that study it was shown

that platelets crossed endothelial cells not at the level of interendothelial cell junctions, which remained closed. However, platelets have been demonstrated to extend pseudopods suggesting active diapedesis. Moreover, single platelets enclosed within endothelial cytoplasmic vacuoles, generally located close to interendothelial cell junctions, were observed and the platelet-containing vacuoles were observed to open to the abluminal surface whereupon platelets were discharged into the underlying basal lamina. Following transmigration across the basal lamina, platelets were found free in dermal connective tissue, together with neutrophils and other white cells. Interestingly, migrating platelets did not display the ultrastructural features of a release reaction, suggesting that conventional platelet activation is not required for platelet migration (Feng et al. 1998b).

The mechanism of transmigration observed in this model, i.e. that platelets cross undamaged endothelium by a process similar to pinocytosis, has been previously described for neutrophils (Feng et al. 1998a). This mechanism does not necessarily apply to all stimuli-inducing diapedesis and active migration through interendothelial cell junctions may also take place (Laitinen 1993; Marchesi 1966).

Platelet translocation into the Disse spaces of the liver and their active penetration into hepatocytes have been reported by immunostaining for 5-hydroxytryptamine (5-HT), a sensitive method to detect platelets in tissue as platelets contain large amounts of 5-HT, and by electron microscopy (Nakamura et al. 1998). Platelets in the Disse spaces of lipopolysaccharide (LPS)-treated mice were in contact with Kupffer cells (hepatic macrophages) (Nakamura et al. 1998; Yamaguchi et al. 2006). This process seems to involve biochemical pathways different from those involved in aggregation, given that anti-platelet agents, including aspirin, did not prevent hepatic platelet accumulation (Nakamura et al. 1998).

In a murine model of corneal abrasion, diapedesis of platelets out of vessels was demonstrated with accumulation of platelets in the limbus where they actively contribute to corneal nerve regeneration. The accumulation of platelets was mediated by P-selectin (Li et al. 2011), an adhesion molecule that also plays a role in the accumulation of platelets in glomeruli in a murine model of glomerulonephritis (Zachem et al. 1997). Activated platelets, alone or together with neutrophils, were found by immunofluorescence within glomeruli of rats with nephritis induced by the selective perfusion of the renal artery with the lectin concanavalin A (Zachem et al. 1997).

In a model of ligation of intestinal arteries in mice, green fluorescent protein (GFP)-labeled platelets were observed in areas of post-ischemic inflamed tissue, where they could function as pilot cells that guide the invasion of other inflammatory cells. This mechanism was mediated by SDF-1α involving signalling through PI3K and activation of SGK-1 (Kraemer et al. 2010). Furthermore, SGK-$1^{-/-}$ mice showed decreased platelet transmigration into the ischemic intestinal vascular wall (Schmidt et al. 2012).

Platelet Chemotaxis: Studies in Humans

Despite the difficulty in detecting platelets in tissue using histology with conventional staining techniques, due to the small dimensions and the lack of a nucleus, observations using electron microscopy and/or immunological staining confirm the ability of platelets to transmigrate into tissues in humans with inflammatory conditions.

Platelets were found in BAL of patients with allergic asthma following allergen challenge without the concomitant presence of erythrocytes, confirming active diapedesis and not passive transfer due to blood extravasation, with some degranulated platelets and free granules in the lavage (Metzger et al. 1985, 1987). Platelet aggregates have also been observed in the lamina propria of the microvasculature of lungs of asthmatic subjects by transmission electron microscopy during late-onset airways obstruction following allergen provocation, in apposition to areas of bronchial smooth muscle, underneath the epithelium, and in areas of eosinophil infiltration (Beasley et al. 1989).

Extravascular platelets, colocalized with leukocytes, have been detected by immunofluorescence in surgically excised nasal polyps from patients with aspirin-exacerbated respiratory disease (AERD), a chronic inflammatory disorder characterized by nasal polyposis and asthma triggered by the ingestion of aspirin (Laidlaw and Boyce 2012).

Platelets were also identified by immunohistochemistry in brain tissue sections from patients with multiple sclerosis with active demyelinating plaques and by confocal immunofluorescent microscopy in a chronic active type 1 lesion (active inflammation and demyelination) (Langer et al. 2012).

Electron microscopy of the synovium of patients with rheumatoid arthritis (RA) showed platelet thrombi obliterating the lumen of vessels and platelets were observed in the vicinity of gaps between endothelial cells of the joint vasculature (Schumacher 1975). Positive staining for $\alpha_{IIb}\beta_3$ outside the vasculature was detected using immunohistochemistry of the synovium from patients with RA, representing either platelets or platelet-derived microparticles (PMPs) (Konttinen et al. 1989; Palmer et al. 1986). Moreover, platelets, platelet aggregates and platelet-leukocytes complexes have been shown in the synovial fluid of patients with RA suggesting active migration into extravascular sites (Endresen 1981; Endresen and Forre 1992; Farr et al. 1984; Ginsberg et al. 1978; Yaron and Djaldetti 1978).

Platelet Contribution to the Chemotaxis of Other Cells

Platelets influence the migration of other cells by releasing soluble chemotactic mediators, by liberating PMPs, or by direct contact with the involved cells (Fig. 6).

Platelet lysates enhanced cell migration of several hepatocellular carcinoma cell lines (Carr et al. 2014) and fibroblasts (Carducci et al. 2016; Senior et al. 1983), and adherent activated platelets stimulated the migration of murine embryonic endothelial progenitor cells (EPC) (Langer et al. 2006).

Platelets contain and release upon activation several soluble mediators influencing cell migration (Table 2). Among them chemokines, which represent a significant fraction of the platelet α-granules content, are released upon platelet activation and mediate the recruitment of several cells to sites of inflammation, including leukocytes, cancer cells and hematopoietic cells, thus favouring neointima formation and atherosclerosis, vessel repair and regeneration after vascular injury (Gleissner et al. 2008). CXCL4/platelet factor 4 (CXCL4/PF4), the first member of the chemokine family discovered in platelets and the most abundant platelet chemokine (Deuel et al. 1977), and CXCL7/neutrophil-activating peptide-2 (CXCL7/NAP-2) purified from supernatants of thrombin-stimulated platelets induce neutrophils to undergo firm adhesion on an endothelial cells monolayer in a concentration-dependent manner. CXCL7 also stimulates neutrophil transendothelial migration (Petersen et al. 1999; Schenk et al. 2002). Furthermore, CXCL7 and CXCL5/epithelial neutrophil-activating protein 78 (ENA-78), secreted by activated platelets upon contact with tumor cells, induce

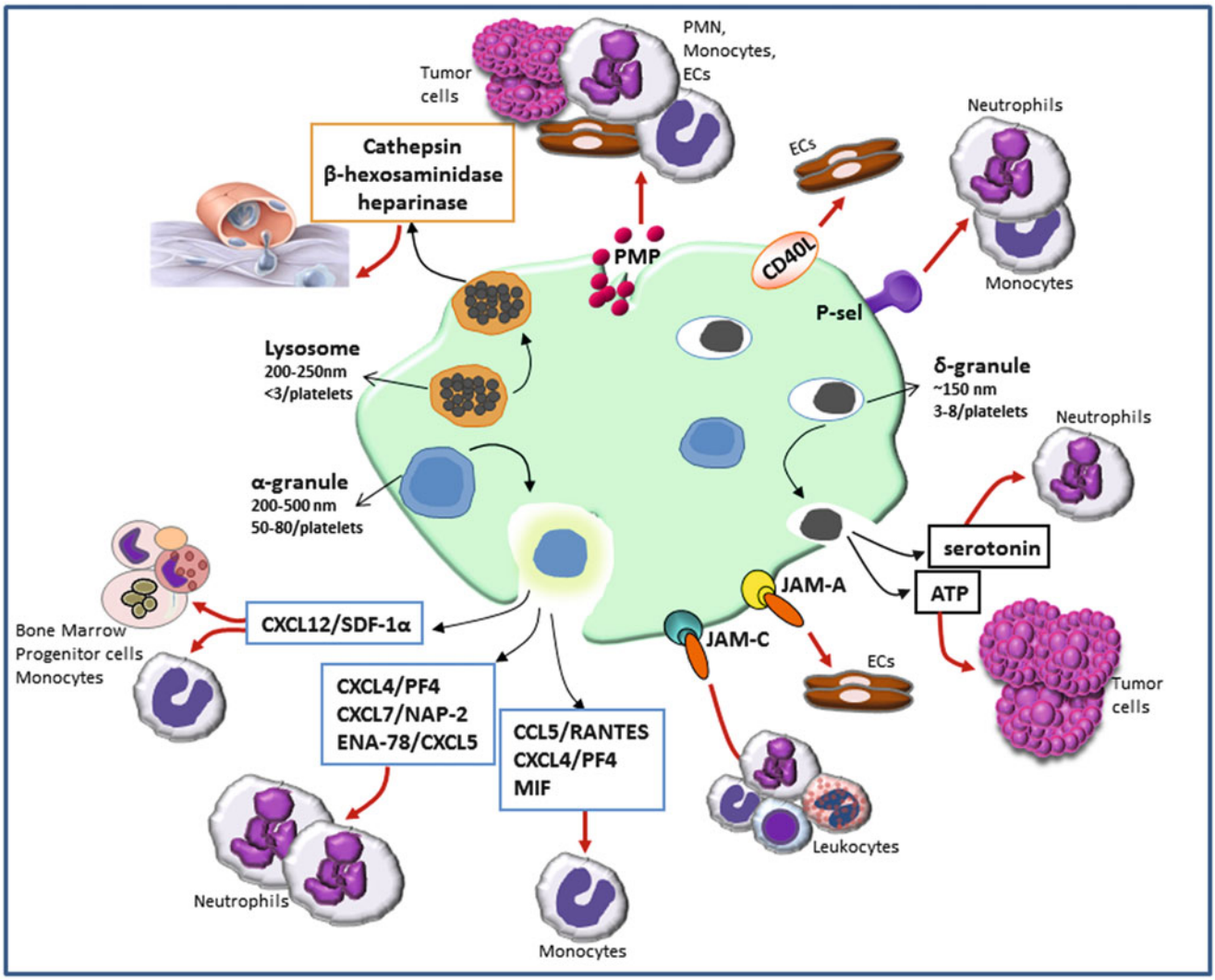

Fig. 6 Platelet contribution to the chemotaxis of other cells. Platelets play an active role in the induction of chemotaxis of other cells by releasing, upon activation, soluble mediators contained in their granules (α, δ and lysosomes), by liberating PMPs, and by expressing surface receptors favouring cell–cell interactions

Table 2 Soluble platelet-derived inflammatory mediators and platelet surface proteins that modulate cell migration

Soluble platelet-derived mediators	Responding cells
α-granules	
CXCL4/PF4	Neutrophil firm adhesion on the endothelium
CXCL7/NAP-2	Neutrophil firm adhesion on the endothelium and trans-migration
	Formation of the early metastatic niche
CXCL12/SDF-1α	Adhesion and migration of bone marrow progenitor cells
	Monocyte adhesion and chemotaxis
CXCL5/ENA-78	Neutrophil migration
	Formation of the early metastatic niche
CCL5/RANTES	Monocyte adhesion on the endothelium and recruitment
MIF	Monocyte arrest on the endothelium and chemotaxis
Dense granules	
Serotonin	Neutrophil and T-cell recruitment
ATP	Tumor cell transendothelial migration and metastasis
Lysosomes	
Cathepsin, heparinase, β-hexosoaminidase	Cell diapedesis by remodeling the inflammed tissue
PMPs	Neutrophil and monocyte adhesion to the endothelium
	Chemotaxis and invasion of breast and lung cancer cells
	Chemotaxis of hematopoietic stem/progenitor ($CD34^+$) and various myeloid and lymphoid cells
Platelet surface proteins	
CD40L/CD154	Endothelial cell activation
CD40	T cell recruitment
P-selectin	Monocyte and neutrophil rolling and adhesion to the endothelium
JAM-A	Platelet adhesion to the endothelium
JAM-C	Firm adhesion of leukocytes on adherent platelets

granulocyte migration and guide the formation of the early metastatic niche (Labelle et al. 2014). Activated platelets are a major source of CXCL12/SDF-1α (Chatterjee and Gawaz 2013). Platelet-derived CXCL12 supports adhesion of CD34+ human progenitor cells (PCs) under static conditions and facilitates the rolling and firm adhesion of CD34+ cells onto platelets adhered to a layer of human aortic endothelial cells (HAEC) under high shear rate in vitro and in vivo (Stellos et al. 2008). Platelet-derived CXCL12 also enhances the adhesion and migration of bone marrow progenitor cells to sites of vascular injury thereby promoting repair (Massberg et al. 2006). Furthermore, CXCL12 released by activated platelets induces monocyte chemotaxis by acting on CXCR4 and monocyte adhesion under static and dynamic arterial flow conditions by acting on CXCR7 (Chatterjee et al. 2015). CCL5/regulated on activation normal T cell expressed and secreted (CCL5/RANTES) secreted by activated platelets and immobilized on the inflamed/activated endothelium of atherosclerotic arteries induces adhesion of monocytes (Mause et al. 2005; Schober et al. 2002; von Hundelshausen et al. 2001). Platelets under shear flow deposit CXCL4 and CCL5 on atherosclerotic or IL-1β-activated HAEC, enhancing the recruitment of monocytes to the endothelium (Baltus et al. 2005; Huo et al. 2003). Moreover, platelet-derived macrophage migration inhibitory factor (MIF) stimulates monocyte arrest on endothelium and chemotaxis (Wirtz et al. 2015).

Platelet-derived IL-1β induces the secretion of CCL2/monocyte chemottractant protein-1 (MCP-1) and increases the expression of intracellular adhesion molecule-1 (ICAM-1) by endothelial cells, promoting the adhesion of monocytes to the endothelium and their chemotaxis; in fact MCP-1 is a potent chemotactic factor for monocytes (Gawaz et al. 2000). Platelet-derived IL-1 induces the release of CXCL1 and CXCL8 from endothelium, which in turn induces neutrophil recruitment (Page and Pitchford 2013; Kaplanski et al. 1993; Thornton et al. 2010).

Platelet dense-granules contain serotonin, a vasoactive inflammatory mediator that can induce vascular permeability and promotes the recruitment of neutrophils into lung and peritoneum, after intraperitoneal and intratracheal LPS administration, and in aseptic skin wounds (Duerschmied et al. 2013), and the recruitment of T cells into the liver during viral hepatitis-induced hepatic injury (Lang et al. 2008). Platelet-derived ATP promotes tumor cell transendothelial migration and metastasis via stimulation of P2Y2 receptors (Schumacher et al. 2013).

Platelet release lysosomal enzymes, such as cathepsin, β-hexosoaminidase and heparinase, in vivo in humans at a localized site of vessel wall damage (Ciferri et al. 2000; Vlodavsky et al. 1992), and these may participate in cell diapedesis due to their tissue-degrading activity and by remodelling the inflammed tissues, a role already demonstrated to be involved in the migration of fibroblasts,

cancer and endothelial cells (Mohamed and Sloane 2006; Palka et al. 1997; Schraufstatter et al. 2003)

PMPs play an important role in tissue recruitment of inflammatory cells by the interaction between P-selectin expressed on their surface and P-selectin glycoprotein ligand-1 (PSGL-1) on neutrophils (Forlow et al. 2000) and simultaneously by their adhesion to the subendothelial matrix through integrin $\alpha_{IIb}\beta_3$ (Merten et al. 1999). PMPs stimulate monocyte adhesion also by inducing endothelial cells (ECs) to express ICAM-1 and by delivering chemokines, such as RANTES, to the endothelium (Barry et al. 1998; Mause et al. 2005). In addition, PMPs transport cytokines (e.g. IL-1β) that stimulate polymorphonuclear cells (PMNs) adhesion to ECs and miRNAs that may modify the phenotype of endothelial cells (Gidlof et al. 2013) and macrophages (Laffon et al. 2016). PMPs enhance the chemotaxis of invasive breast and lung cancer cells and stimulate their invasion across Matrigel by inducing MMPs production. Furthermore, PMPs act as chemotactic agent for hematopoietic stem/progenitor ($CD34^+$) cells as well as for various myeloid and lymphoid cells (Baj-Krzyworzeka et al. 2002; Janowska-Wieczorek et al. 2005, 2006).

Platelets express upon activation a number of surface proteins involved in heterotypic interactions with endothelial cells and leukocytes, mediating the rolling and adhesion of leukocytes to the endothelium and the subsequent transmigration into inflammed tissue (Gawaz et al. 2005; Weyrich and Zimmerman 2004). The formation of platelet-neutrophil and platelet-monocyte complexes, the subsequent neutrophil and monocyte adhesion to the endothelium and recruitment into the inflammed tissue is dependent on platelet P-selectin (Page and Pitchford 2013), mediated by its binding to the high affinity counter ligand PSGL-1 (Hamburger and McEver 1990; Moore et al. 1995; Kuijper et al. 1998). High-resolution videomicroscopy has revealed the existence of membrane tethers involving P-selectin/PSGL-1 bonds that regulate neutrophil rolling on platelets (Schmidtke and Diamond 2000). The importance of platelet P-selectin/PSGL-1 axis has been determined by the use of P-selectin-deficient mice, by the blockade of P-selectin or with PSGL-1 antibodies (Abdulla et al. 2012; Diacovo et al. 1996; Mayadas et al. 1993; Pitchford et al. 2005).

Platelet CD40 ligand (CD40L/CD154) binds CD40 on endothelial cells and enhances the release of IL-8 and MCP-1, the expression of E-selectin (CD62-E), Vascular Cell Adhesion Protein-1 (VCAM-1) and ICAM-1, and the release of matrix metalloproteinases (e.g., MMP-1, -2, -3, and -9). Furthermore CD40L-positive T cells activate platelets through a CD40-dependent pathway resulting in CCL5 release and T cell recruitment (Danese et al. 2004; Henn et al. 1998; Giannini et al. 2011).

Platelet Junctional Adhesion Molecule (JAM-A) can support homophilic interactions with endothelial-cell JAM-A, mediating platelet adhesion to the endothelium (Babinska et al. 2002), thus facilitating the deposition on endothelium of platelet CCL5/RANTES (Zernecke et al. 2006). Platelet JAM-C functions as a counter-receptor for the β2-integrin Mac-1 on neutrophils mediating firm adhesion of leukocytes to adherent platelets (Santoso et al. 2002).

Conclusions

Among the functions that characterize platelets as inflammatory cells, one which is little considered but is probably crucial is the ability to migrate into tissue in the direction of a chemotactic stimulus. This allows platelets to actively participate in the tissue inflammatory process by releasing stored or newly synthesized mediators acting both on other platelets and/or on other cell types. Furthermore, platelets influence and sometimes are essential for the migration of other inflammatory cells, including leukocytes and cancer cells.

This "non-classical" platelet activity is an example of the existence of a dichotomy in platelet function, i.e. the ability of platelets to display an inflammatory or a haemostatic/thrombotic response depending on the stimulus and on the environment, recently elegantly demonstrated investigating the role of different purinergic receptor subtypes on platelets (Amison et al. 2015).

Further investigation into the mechanisms regulating platelet migration, and in general the characterization of the mechanisms regulating this dichotomy of platelet function, may be crucial for the discovery of new therapeutic approaches to inflammatory diseases by the development of drugs able to interfere with the inflammatory but not with the haemostatic function of platelets.

Take Home Messages

- Platelets possess several characteristics that allow them to migrate: the expression of receptors for chemokines and for other chemotactic agents, the presence of all the signaling pathways responsible for the transduction of the extracellular chemotactic signal to the motile apparatus, a dynamic cytoskeleton and the relase of several enzymes (MMPs, cathepsins, β-hexosoaminidase, heparinase) responsible for ECM degradation.
- The ability of platelets to migrate in vitro, both randomly and in the direction of a chemotactic stimulus, such as collagen, fMLP, SDF-1α, IgE and allergens, has been confirmed using different assays.
- The penetration of platelets in inflammed tissues has been described in several animal models and in human disease conditions.

(continued)

- Platelets can induce the migration of other cell types by several mechanisms, including the shedding of PMPs, release of granular materials (chemokines, cytokines, growth factors, ATP, enzymes), and the expression of surface receptors involved in platelet heterotypic interactions with leukocytes, endothelial and cancer cells.

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