Cancer Metastasis Rev (2017) 36:199–213
DOI 10.1007/s10555-017-9682-0

Platelet "first responders" in wound response, cancer, and metastasis

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Published online: 20 July 2017

Abstract Platelets serve as "first responders" during normal wounding and homeostasis. Arising from bone marrow stem cell lineage megakaryocytes, anucleate platelets can influence inflammation and immune regulation. Biophysically, platelets are optimized due to size and discoid morphology to distribute near vessel walls, monitor vascular integrity, and initiate quick responses to vascular lesions. Adhesion receptors linked to a highly reactive filopodia-generating cytoskeleton maximizes their vascular surface contact allowing rapid response capabilities. Functionally, platelets normally initiate rapid clotting, vasoconstriction, inflammation, and wound biology that leads to sterilization, tissue repair, and resolution. Platelets also are among the first to sense, phagocytize, decorate, or react to pathogens in the circulation. These platelet first responder properties are commandeered during chronic inflammation, cancer progression, and metastasis. Leaky or inflammatory reaction blood vessel genesis during carcinogenesis provides opportunities for platelet invasion into tumors. Cancer is thought of as a non-healing or chronic wound that can be actively aided by platelet mitogenic properties to stimulate tumor growth. This growth ultimately outstrips circulatory support leads to angiogenesis and intravasation of tumor cells into the blood stream. Circulating tumor cells reengage additional platelets, which facilitates tumor cell adhesion, arrest and extravasation, and metastasis. This process, along with the hypercoagulable states associated with malignancy, is amplified by IL6 production in tumors that stimulate liver thrombopoietin production and elevates circulating platelet numbers by thrombopoiesis in the bone marrow. These complex interactions and the "first responder" role of platelets during diverse physiologic stresses provide a useful therapeutic target that deserves further exploration.

Keywords Platelet · TCIPA · Metastasis · Thrombosis · Extravasation · CTC

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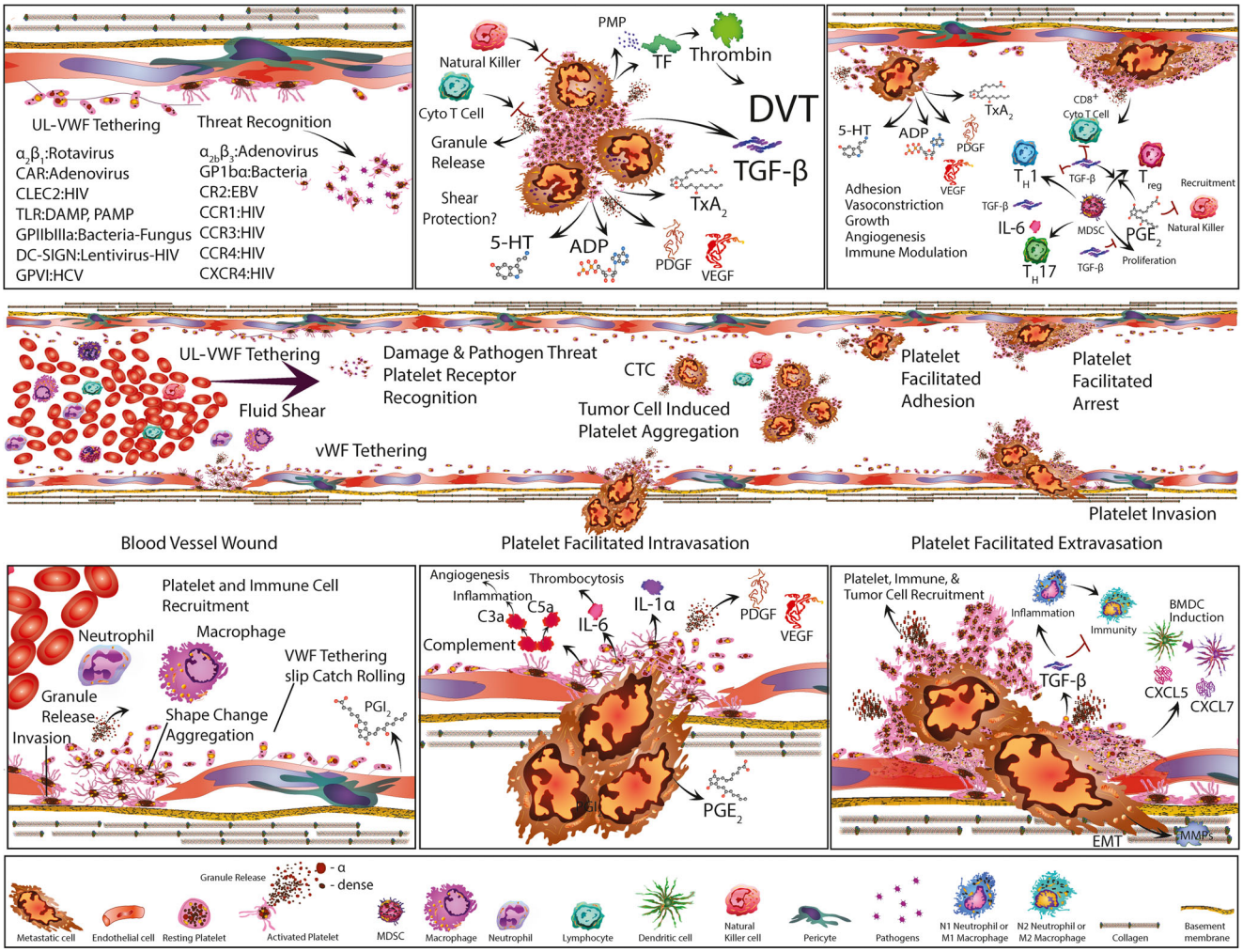
1 Platelet "first responder" properties

"First responders" describe platelets as active participants in the hemostasis, wounding, immune, and metastatic processes (Fig. 1) [1, 2]. Platelets often remain unheeded during *in vivo* experimental studies or pathologic observations. The primary reason is due to small size/volume (mean platelet volumes



range is 9.7–12.8 femtoliter or spheres 2 to 3 μm in diameter) and the lack of a nucleus makes identification more difficult compared to the typical nucleated cell. Although platelets are visible by high magnification light microscopy, ultrastructural analysis is typically done to effectively observe subcellular morphologic or activational structural changes and newer methods may prove even more observationally effective [3–6]. Individual and aggregates of activated platelets can be detected by immunohistochemistry at the microscopic level but this is not a routine approach for pathologists.

Biophysically, resting platelets exhibit a plate-like discoid shape that maximizes planar surface interactions [7–9]. These physical characteristics facilitate their segregation toward the outer fluid shear fields of flowing blood [10–17]. Normal human platelets range between 150,000–400,000 per microliter (μl) in numbers with those that concentrate near vessel walls being 2–3 times greater than at the central fluid stream. Platelet flow patterns, near wall excess, and proximity enhance encounters and recognition of any vascular wall lesions or wounds. These platelet recognition properties include the exposure of the subendothelial basement membrane or underlying matrix induced by wounding or endothelial retraction [18–23]. The rapid formation of filopodia facilitated by a variety of adhesion receptors linked to a highly reactive cytoskeleton helps maximize dynamic surface contacts and the rapid response rate of platelets [24–31].

2 Platelet "first response" facilitated clot/wound biology

Normally, platelets serve as "first responders" during the wounding process and hemostasis. A lacerated blood vessel exposes platelets to subendothelial elements that initiate their first response through receptor-based recognition of extracellular matrix. This recognition triggers platelet activation and aggregation. Once activated, within a matter of seconds, platelets begin to change shape, degranulate, and release proteins, growth factors, bioactive lipids, and other factors that recruit additional platelets and immune cells along with initiating thrombogenesis and clotting to fill any exposed gaps.

This process occurs in response to an injury that exposes collagen and extracellular matrix proteins, which results in

◀ **Fig. 1** Platelet "first responders" facilitate wound response, threat recognition, immune function, cancer progression, and metastasis. Platelets elicit the initial response to any wound or breach in blood vessels. Platelets respond first by adhering to the perivascular extracellular matrix basement membrane and collagen. This causes resting platelets to change shape, aggregate, and release both alpha and dense granule components that attract and activate more platelets as well as immune cells. Anucleate platelets are key bone marrow stem cell-megakaryocyte derived subcellular product that are attracted to leaky angiogeneic vessels and can invade into perivascular spaces. The platelet aggregation process is held in check by prostacyclin (PGI_2). Platelets can also slow down in the presence of shear stress of rapidly flowing blood by forming slip-catch bonds with von Willebrand factor (VWF) that causes rolling behavior at the endothelial cell surface. A local inflammatory response that follows involves complement (enzymatically processed to C3a and C5a), prostaglandin E_2 (PGE_2), interleukin-6 (IL-6), IL-1alpha (IL1α), and other inflammatory cytokines. Platelets can also interact with ultralarge VWF to form tethers. Another first responder behavior is the recognition of damage by toll-like receptors (TLRs), sialic acid-binding immunoglobulin-type lectins (Siglecs), damage-associated molecular patterns (DAMPs), infectious pathogens harboring pathogen-associated molecular patterns (PAMPs). Other platelet threat receptors include C-type lectin-like type II transmembrane receptor (CLEC-2), complement receptor type 2 (CR-2), C–C chemokine receptors (CCR 1,3 and 4), dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN), and coxsackie adenovirus receptor (CAR) and integrins. Primary tumors secrete IL6, which induces thrombospondin release in the liver and initiates thrombocytosis in the bone marrow. Platelets also induce physical and molecular wounding damage signals. This can lead to further platelet activation and cyclic inflammatory release of tumor and platelet microparticles and exosomes that molecularly and biologically cross-educate one another along with additional pro-inflammatory and angiogenic factors. After full intravasation into the blood stream, direct contact with circulating tumor cells (CTCs) initiate tumor cell induced platelet aggregation (TCIPA) that causes further platelet activation and alpha (α) and dense granule release. Alpha granules contain numerous proteins, growth factors such as platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VGEF) that stimulate tumor growth and angiogenesis. Dense granule release includes platelet G-protein coupled receptor stimulants such as adenosine diphosphate (ADP) and serotonin (5-HT, 5-hydroxytryptamine). Platelet activation also leads to thromboxane A_2 (TxA_2) synthesis and release. Direct platelet-tumor cell contact glycoproteins such as P-selectin and tissue factor (TF) or via microparticles bearing procoagulants stimulate thrombin production and fibrin clot formation. The heterotypic platelet-tumor cell aggregates help protect them from vascular shear forces and may mask them from other immune cells along with providing a reservoir for growth factors. Following hematogenous spread additional platelets are engaged at secondary sites facilitating and stabilizing the adhesion and arrest of heterotypic emboli prior to extravasation. Released molecules also recruit granulocytes by bone marrow derived cell induction and immune cell differentiation. Transforming growth factor beta (TGF-β) from platelets and PGE_2 release stimulate marrow derived stem cells (MDSC) and T-cell differentiation or inhibition, which includes cell cluster of differentiation 8 positive ($CD8^+$) cytotoxic T-cells, T-helper1 (T_H1), and T-helper17 (T_H17) T-regulatory cells (T_{reg}). Concurrently, bone marrow derived dendritic cells (BMDC) induction can occur in response to cytokines, C-X-C motif chemokine 5 (CXCL-5), and CXCL-7. Secreted TGF-β induces epithelial-mesenchymal-transition (EMT) genes and also facilitates myeloid polarization of macrophages and neutrophils toward immunosuppressive phenotypes. This may occur within the tumor or in the circulation at platelet facilitated arrest sites during the establishment of metastasis. Thus, these platelet-tumor cell microenvironmental niches may direct tumor-associated macrophages (TAMs) toward a protumor (M2) from an antitumor (M1) phenotype. Similarly, tumor-associated neutrophils (TANs) TANs may acquire a protumor phenotype (similar to M2), largely driven by TGF-β to become "N2" neutrophils

interactions with the exposed subendothelium. These first responder interactions are driven by a variety of platelet glycoprotein receptors that can fail in many congenital platelet disorders [2, 32]. These receptors can bind extracellular matrix factors that include proteoglycans, laminin, fibronectin, and vitronectin along with various isoforms of collagen. von Willebrand factor (VWF) binds to exposed collagen I, III, and VI fibers. VWF is also recruited into matrix networks by forming tethering fiber strands [33–37].

Platelet surface GPIb forms multimeric complexes that initiate catch bond interactions with exposed tethering fiber strands [33–37]. Catch-slip-tethering bonds cause platelets to begin rolling within blood fluid shear stress fields [33–37]. Four transmembrane proteins contribute to functional GPIb complexes including two 20-kDa GPIX subunits, two 26-kDa GPIbβ subunits, two 135-kDa GPIbα subunits, and one central 82-kDa GPV subunit [38, 39]. GPIb receptors belong to the LRR receptor family of proteins that are uniquely expressed by platelets [38, 39]. Genetic loss of GPIb expression leads to Bernard-Soulier syndrome bleeding disorders [40]. GPIb-IX-V glycosphingolipid domain multimeric complexes interact with VWF multimers [41]. Tethering can also occur with ultralarge von Willebrand factor (ULVWF) and endothelial cells to attract platelets to these protein strands along with other cells such as leukocytes and potentially tumor cells [42–44]

Platelets contextually encounter numerous circulating ligands, cells, pathogens, and extracellular matrix ligands in the bloodstream. Immediate responses are mediated by a variety of integrin receptors through transmembrane glycoprotein α and β heterodimers once ligands are engaged. Resting platelets express low-affinity conformation integrins that are bent over protecting binding sites. Once activated, α and β subunits protrude forming high affinity or open binding state that efficiently interact with ligands. Rolling platelet behavior is initiated by multimeric GPIb-complex interactions with VWF, which activates a key stabilization integrin $\alpha_{IIb}\beta_3$ [45–48] shifting them from a closed to an open state. In the open state, transmembrane $\alpha_{IIb}\beta_3$ heterodimers that are very promiscuous and bind multiple RGD-ligand containing proteins [45–48]. These RGD-ligand containing proteins include: fibrin, fibrinogen, fibronectin, vitronectin, thrombospondin or VWF complexes. Abnormal $\alpha_{IIb}\beta_3$ integrin receptor expression is involved in Glanzmann's thrombasthenia [49–51].

More selective ligand binding integrins also stabilize interactions with the vascular microenvironment. For example, the collagen receptor $\alpha_2\beta_1$ is a key matrix-stabilizing integrin [52, 53]. Once activated, $\alpha_2\beta_1$ stabilizes adhesive contacts and initiates lamellipodia formation and platelet spreading. In contrast, circulating or extracellular matrix fibronectin is engaged by platelet $\alpha_5\beta_1$ integrin heterodimers [54]. The $\alpha_5\beta_1$ integrin binding is activation state dependent, binding more selectively to fibronectin RGD peptide sites under static conditions. Tyrosine phosphorylation and changes in calcium levels can also facilitate filopodia formation [55]. Platelets also express $\alpha_6\beta_1$ integrin receptors that selectively bind to laminin in the basement membrane and induce filopodia formation [56, 57]. The activation of $\alpha_6\beta_1$ integrin

receptors typically involves crosstalk with platelet collagen receptor glycoprotein VI (GPVI) to achieve stable adhesion.

Additional receptors are involved in biologic responses of platelets such as GPVI, which belongs to the Ig receptor superfamily and is found exclusively in platelets [58, 59]. GPVI is a major collagen receptor that recognizes the quaternary structure of collagen, and activates platelets [60, 61]. Platelet GPVI monomers shift from low affinity and signal transduction potential to multimers that gain high affinity collagen periodic structure [41, 62–65].

Platelet C-type LECtin-like receptor (CLEC-2/aggrus) is another platelet receptor that initiates platelet activation through molecular multimerization [41, 62, 66–68]. CLEC-2 binds to mucin glycoprotein podoplanin [69–71]. Podoplanin is expressed on cells of the lymphatic endothelia, type I lung epithelia, choroid plexus epithelia, kidney podocytes, lymph node stroma along with cancer cells and potentiates migration and invasion [69–72]. Podoplanin is a transmembrane sialomucin glycoprotein [41, 69, 73, 74], which interacts with platelet CLEC-2 receptors triggering signal transduction [41, 67, 68, 75].

Platelet P-selectin is also known as membrane glycoprotein GMP-140 [76, 77]. P-selectin binds to P-selectin glycoprotein ligand (PSGL)-1 [78], neutrophil leukocyte-endothelial cell adhesion molecule 1 (LECAM-1) [79], endothelial cell-leukocyte adhesion molecule 1 (ELAM-1) [80], and sialyl Lewis(x) oligosaccharide [81]. P-selectin interaction with a variety of immune cells and endothelial cells is important in mediating inflammation, autoimmunity, and wound healing [82–84]. P-selectins along with L- and E-selectins help tethering and rolling of cells flowing past the vascular luminal surfaces during the initial phases of intravascular adhesive interactions that are stabilized by other receptors [85–91].

Thrombus formation relies on platelet "first responder" mediated rolling, adherence, spreading, migration, aggregation, and stabilization. Nitric oxide, prostacyclin (PGI_2), and CD39-mediated reduction of local purine nucleotides help maintain the resting state of circulating platelets [92–96]. Injury-induced exposure of subendothelial matrix occurs transient tethering bonds are made between matrix-bound VWF and platelet GPIb-IX-V receptor complexes [33–37, 39]. Transient tethers support rolling and slow platelet movement. Slower movement permits more intimate interactions between collagen fibers and platelet GPVI surface receptors shift integrins from a closed to an open state [58, 59]. Activated $\alpha_2\beta_1$ binding with collagen and $\alpha_{IIb}\beta_3$ binding to fibrinogen stimulate platelet shape change and degranulation [45–48]. Release of α-granules and dense granules amplifies secondary platelet responses and initiates tissue repair. Activation forms platelets prothrombotic nucleation centers for tissue factor initiated coagulation [97]. Platelets interact with nearby platelets through $\alpha_{IIb}\beta_3$ receptors and bind fibrinogen and fibrin fibers [45–48]. Progressive cycles of platelet activation, adherence, spreading, migration, aggregation, and stabilization form a thrombus that builds a fibrin network and entraps other blood cells. Thrombotic plug formation is stabilized and counterbalanced by the disaggregation of platelets and fibrinolysis. Platelets migrate and initiate tissue repair [98–102].

First responder reactions are rapidly enhanced by activating molecules such as thrombin or ADP that are triggered at the cell surface or as a result of the release reaction. Activation results in release of granular contents or molecular export, which include proteins and molecules such as thromboxane A_2 (TXA_2) that amplify the local platelet response to recruit additional platelets to the forming clot and accelerate the thrombogenesis/clotting process [103, 104]. The production of TXA_2 along with other lipids initiates vasoconstriction [105, 106]. As a primary stimulant of platelet recruitment and aggregation, TXA_2 is among the shorter-lived prostaglandins due to molecular epoxide bond strain in the active part of the molecule that is prone to hydrolysis in <30 s [107, 108]. These rapid changes accelerate over a matter of minutes and generate a fibrin network that traps and activates more platelets within the forming clot in a cyclic fashion and limits blood loss. This first responder amplification process occurs over approximately a 20-minute time frame or less and clot maturation and solidification continues for an hour or so and initiates immune cell recruitment and inflammation over the next few days to weeks. Recruitment of fibroblasts and immune cells through platelet-initiated angiogenic repair mechanisms stimulates wound healing and resolution [99]. Proliferation, tissue remodeling, and wound repair that resolves normally over a month to a year timeline.

The release of platelet dense granule components influences the vascular microenvironment. The release of calcium and magnesium ions promotes platelet activation and aggregation. The release of nucleotides such as ADP activates platelets through $P2Y_1$ and $P2Y_{12}$ receptors [109, 110] and stimulates vasoconstriction [111]. The dense granule release or engagement of membrane tetraspanins, CD9, CD63, CD151, Tspan9, and Tspan32, regulates cell surface interactions [112, 113]. CD9 is the most abundant platelet tetraspanin and engages Fc RIIA, a low-affinity receptor for IgG or GPVI collagen receptors during platelet interactions [112–114]. Platelet dense granule membranes also contain lysosomal associated membrane proteins (LAMPs), which aid in the breakdown cellular debris [115, 116]. The release of neurotransmitters serotonin (5-hydroxytryptamine; 5-HT), epinephrine, and histamine can potentiate ADP-induced platelet activation and aggregation [109, 110, 117].

3 "Threat response and damage control"

Also, as part of their first responder characteristics, platelets actively transmigrate across any leaky or inflamed vessel wall in response to a variety of stimuli to aid in wound sterilization and tissue regeneration [118–124]. Stromal cell-derived factor-1 (SDF1 or C-X-C chemokine ligand 12:CXCL12) acts as a very potent stimulus that triggers platelet migration into extravascular spaces [125–130]. In addition to CXCL12, platelets release many

transmigration stimulating chemokines and cytokines, CXCL1 (GRO-α), CXCL4 (platelet factor 4, PF4), CXCL5 (epithelial-derived neutrophil-activating peptide-78; ENA-78), CXCL7 (pro-platelet basic protein, PPBP; β-thromboglobulin, βTG), and CXCL8 (interleukin-8; IL8) among numerous others from storage granules. Once released from platelets, these factors can initiate the migration and invasion of additional platelets, immune cells (neutrophils macrophages and leukocytes), as well as bone marrow progenitor and endothelial progenitor cells or tumor cells [131–134]. The notion of "first responders" is further strengthened by the discovery of C-X-C chemokine receptor 4 and 7 (CXCR-4, CXCR7) the cognate receptors for SDF1: CXCL12 on platelets.

As part of their immune surveillance properties, platelets can recognize foreign bodies or invading pathogens [1, 135–137]. Additional inflammation and pathogen defense mediating receptors on platelets and pathogen signals, include toll-like receptors (TLRs), sialic acid-binding immunoglobulin-type lectins (Siglecs), damage-associated molecular patterns (DAMPs, e.g., alarmins), infectious pathogens harboring pathogen-associated molecular patterns (PAMPs), platelet C-type lectin-like type II transmembrane receptor (CLEC-2), complement receptor type 2 (CR-2), C–C chemokine receptors (CCR 1,3 and 4), dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN), and coxsackie adenovirus receptor (CAR) [121, 138–149]. Self-associated molecular patterns (SAMPs) that can be mimicked by pathogens have also been proposed but their disposition and influence on platelets remains to be fully determined [150].

Platelets exhibit optimal tissue migration properties. Utilizing these immediate-threat sensing receptors to rapidly initiate migration during potential first responses, platelets are ideally suited for movement because of the highly active cytoskeletal responses linked to activation, adhesion, and aggregation [1, 18, 36, 151–153]. Platelets are more streamlined and suited for vascular transmigration, not only because they are small in size and minimal displacement volume coupled with their highly active cytoskeleton [154–156]. An even greater vascular transmigration advantage may arise from being unencumbered by the presence of nuclei, which limits the migration of other immune cells [127, 154–157]. The absence of nuclei may also limit the distance that platelets can move into tissue. Due to limited protein synthesis capabilities, they cannot indefinitely maintain the replacement of proteins [158, 159]. All of these immune surveillance and rapid response properties facilitate speedy sterilization along with the ability to quickly initiate the repair process during the wound response.

4 Platelet mediated thrombogenesis, inflammatory, and resolution responses

Platelets release membrane fragments with bioactive molecules in the form of platelet microparticles (PMPs) on activation, permitting distant effects [160–164]. Platelet cytoskeletal rearrangement results in budding of PMPs, which exposes phosphatidylserine (PS), membrane antigens (Ag), and cytoplasm components. The exposure PS-Ag-Cyto complexes on the outer leaflet of PMP creates surface for assembly of a factor V and factor Xa catalytic complexes that generate thrombin. Thrombin-mediated cleavage of fibrinogen leads to fibrin clot formation and entrapment of additional platelets at wound sites [165–168]. Fibrinolysis then ensues to control clot growth [165, 166]. PMPs also interact with immune cells via adhesion molecules such as selectins that selectively bind carbohydrate molecules associated with immune function [121, 142, 144, 169]. Aggregates can have additional immune functions such as neutrophil-ensnared traps (NETs), which are collections of DNA and anti-microbial biomolecules [145, 170].

Platelets help initiate or coordinate the immune responses as key subcomponents of systemic biology [121, 144–147, 169]. They initiate inflammation by releasing a heterogeneous mix of protein molecules that include, transforming growth factor beta (TGF-β), P-selectin, CD40L, and RANTES [121, 171–173]. These molecules include an assortment of cytokines and adhesion molecules that directly bind or activate or elicit homing responses for monocytes, neutrophils, and even T-lymphocytes as chemoattractants to the endothelium; inhibit apoptotic signals; and promotes extravasation into affected sites [121, 142, 144, 169]. Platelets can also activate the complement system of which C3a and C5a are potent anaphylatoxins that amplify inflammatory responses.

The first responder role to threats is thought to be the reason why platelets evolved to have both hemostatic and immune properties [2, 163, 174–176]. This is best highlighted in the wound response model whereby platelets have a unique role in recognizing tissue damage and stimulating more specialized immune cells to infiltrate and initiate the sterilization of the area, particularly where a pathogen may have been introduced past physical barriers. In studies of skin injury, these phases have been described crudely into hemostasis, inflammation, proliferation, and resolution. Platelets with a primary role in hemostasis are uniquely poised to initiate inflammation synergistically with resident cells within damaged tissues such as macrophages. Other non-immune resident cells that platelets stimulate include fibroblasts. These evolve into myofibroblasts as they enter the granulomatous tissue that leads to resolution and retraction [177–179]. Platelet release of TGF-β coordinates with extracellular matrix (ECM) tension help drive fibroblasts to transition into a myofibroblast phenotype that help with repair [180, 181]. TGF-β systemic release also enhances mesenchymal stem cells (MSCs) differentiation and functions as a mechano-stimulatory factor to improve wound closure [182]. Platelet TGF-β also helps neutrophils infiltrate into wounds that are replaced by macrophages. These immune cells initially to acquire a pro-inflammatory phenotype during wound inflammation and proliferation phases and then facilitate myeloid

polarization of macrophages and neutrophils toward immunosuppressive phenotypes during tissue repair and resolution phases [183–186]. Platelets are thereby intrinsically linked to the immune and wound repair system.

5 Platelet "first response" facilitated cancer progression

Cancer is generally considered as a chronic or non-healing wound [187–189] that can continuously engage platelets any time exposure to tumor components occurs. As a part of the metastatic process, platelet receptors recognize complexes of tumor cell receptors surface bound matrix proteins or cellular products as they invade blood vessels due to platelet-tumor cell first response interactions [2, 130, 190]. Extensive membrane changes occur at bilayer interfaces between platelets and tumor cells [1, 2, 191, 192]. Tumor cells form extensive membrane/cytoskeletal processes that heavily interdigitate with a central platelet aggregate and involves the uptake of platelet fragments and mitochondria [1, 2, 191, 192]. These interactions are thought to result in the suppression of immune recognition/cytotoxicity or the promotion of cell arrest at the endothelium, or entrapment in the microvasculature. These responses all support survival and spread of cancer cells and the establishment of secondary lesions. Additional mechanisms of the platelet-metastasis relationship may include the production of platelet exosomes or extravascular migratory behavior of platelets helping to drive cancer progression or preconditioning of secondary metastatic sites [1, 2, 191, 192]. In contrast to the many mechanisms involved in platelet-metastasis relationships, little is known about the role of platelets in precancerous lesion development. This paucity of knowledge exists despite numerous large randomized clinical trials illustrating the cancer preventive effects of nonsteroidal anti-inflammatory drugs (NSAIDs), particularly aspirin in reducing the cancer incidence, mortality, and metastasis [193–195]. Additional aspirin studies also reduced cancer incidence and all-cause mortality [196–199]. In the case of prior colorectal cancer [200] or colorectal adenomas [201], those taking aspirin showed fewer new adenomas compared to controls. In The Colorectal Adenoma/Carcinoma Prevention Programme (CAPP) trial, aspirin reduced adenomas in Lynch syndrome patients [202]. In the ASPirin Intervention for the REDuction of colorectal cancer risk (ASPIRED) trial, the effects of aspirin will also be examined using various biomarker endpoints [203]. The ASPIRED study will determine how aspirin influences adenoma biology.

Aspirin covalently acetylates and inactivates platelet cyclooxygenase 1 and thereby eliminates all downstream prostaglandin production from arachidonic acid (AA) by platelets [193]. This includes the key bioactive lipid involved in platelet activation, TxA_2, which can be counterbalanced by PGI_2 and its analogs that inhibit platelet activation [192, 204, 205]. Metabolically, the genesis of TxA_2 and other bioactive lipids are also impacted by ω-3 polyunsaturated fatty acid substrate substitution for AA [193]. Although not well studied, this places platelets not only at the center of the metastasis discussion but also the progression of pre-malignancies. Since neoangiogenesis produces leaky blood vessels during early cancer progression, it stands to reason that platelets are the "first responders" to extravasate, activate, and release their stroma stimulating, proangiogenic, chemoattractive, and immunomodulatory contents [1, 2]. These normal platelet functions and products undoubtedly promote precancerous lesion progression as a series of cyclic amplification events. Platelets are suspected to have a key role within the full spectrum of the cancer progression continuum, which makes limiting their first response an important target for both prevention and therapy.

6 Platelets as "first responders" in cancer metastasis

"First responders" describes platelets as active participants in metastatic processes [1]. Platelets are thought to facilitate cancer and metastasis by various mechanisms [1, 192, 206, 207]. Due to these combined properties, during metastasis, circulating platelets can also elicit a first response to the exposure, sloughing or active invasion of tumor cells into the blood stream at primary tumor sites. Obstruction of blood flow and angiogenesis associated with primary tumor growth is likely to further enhance the probability of platelet/tumor cell encounters through membrane interactions [208–210]. The net result is likely to be platelet activation either to subdue cells at the primary site or generate tumor cell-platelet emboli in circulation [1, 19, 191]. Based on such significant numbers in circulation, small size, biophysical shear properties, adhesion, aggregation, and streamline migration properties, platelets are well suited to serve as "first responders" to a variety of pathologic stimuli, including metastasis.

7 Tumor cell migration, invasion, and intravasation

The proliferation and migration of cancer cells within primary tumors drives a number of events that can impact metastasis [211–215]. Direct impact can occur by shedding, sloughing, or active entry of tumor cells into the blood vessels. Based on single cell profiling of circulating tumor cells (CTCs), there is a large diversity of cells found in the circulation that reflect tumor heterogeneity [216, 217]. Within the diversity spectrum, CTCs also frequently exhibit stem cell properties [218]. A variety of triggers can initiate entry of CTCs into the circulation. For example, decreased availability of blood vessels can increase the induction of hypoxia as tumors

outgrow their blood supply and release of angiogenesis or wounding related factors [219–221]. These factors stimulate the formation of new blood vessels that are typically abnormal and leaky, enabling entry of tumor cells into the blood stream [222–224]. Although not extensively studied, there is also potential for leakage or migration of platelets into the tumor that may further enhance the angiogenesis/leaky blood vessel genesis cycle [125, 225–227]. More aggressive tumor cells that enter the circulation often undergo epithelial-mesenchymal transition EMT [228]. In fact, direct signaling between platelets and cancer cells induces an EMT and promotes metastasis *in vitro* and *in vivo* [229–231]. Cells with EMT characteristics are more fibroblastic in morphology and are typically much more motile and invasive as a result [229, 230]. These EMT cells are prone to actively invade blood vessels by using matrix metalloproteinase (MMP) to digest the extracellular matrix and basement membrane of blood vessels [232, 233]. As a part of the invasion process interactions between platelets and tumor cells increase the production of MMP-9 [230]. This tumor cell invasive process is termed intravasation and is considered an early dissemination step of the hematogenous metastatic cascade [234].

8 Hematogenous spread, extravasation, and secondary site metastasis

Billroth in 1878 was the first to identify cancer-cell-containing thrombi with the spread of tumors [235]. Wood first observed real-time arrest and formation of platelet thrombi along with tumor cell migration into the perivascular spaces [207, 236]. Baserga and Safi-Otti observed the intravascular arrest and proliferation of anaplastic carcinoma (T1SO) cells prior to extravasation. Both studies identified thrombus formation and tumor cell arrest in small arterioles [207, 236, 237]. When tumor growth occurred intravasculary, it resulted in the destruction of the vessel then tumor cell extravasation. Jones et al. observed the formation of tumor cell-platelet emboli and fibrin using electron microscopy and immunofluorescence after tail vein injection in rats [238]. Early stage emboli formation revealed neutrophils and lymphocytes followed by fibrin formation even after the disappearance of platelets [239] confirmed by others [240]. The release of platelet vesicles and adhesion to vessel walls was observed *in vitro* [241] along with tumor cell migration through the endothelial layer from the adherent embolus [242]. Rat AH-130 ascites hepatoma cells also revealed tumor cell-platelet emboli in microvessels of the lung [243]. Gastpar also performed intravital capillary microscopy in the mesentery of rats to test sulfinpyrazone inhibition of lethal pulmonary tumor cell emboli [244].

Advancements in time-lapse, deep-tissue imaging using intravital microscopy have demonstrated the importance of tumor cell migration *in vivo* [245]. Invasion through the genesis of invadopodia illustrate a dependence on prostaglandin signaling [246]. Intravital fluorescence microscopy has also revealed dynamic platelet-melanoma cell interactions in mice [247]. Platelet depletion significantly reduced melanoma cell adhesion to the injured vascular wall *in vivo* [247]. Platelet interactions and metastasis of B16 melanoma cells to the lungs were decreased after treatment with mAb blocking the $\alpha_{IIb}\beta_3$ or $\alpha_v\beta_3$ integrin [247]. Platelets from the perivascular space can also migrate into extravascular tissues in support of tumor cell invasion and formation of metastases [1, 125–129, 230]. Nonetheless platelet migration may exhibit certain constraints, the lack of nuclei and protein synthesis may limit the distance that platelets migrate because they cannot indefinitely sustain the replacement of proteins [158, 159]. Thus, platelets may potentially prepare or enable extravasation at secondary metastatic sites [2, 67, 130, 248–251]. The use of intravital microscopy coupled with fluorescent platelets is expected to reveal even more details of this rapidly occurring process.

Enzymatic digestion of minced tumor fragments using collagenase, and trypsin inhibitors followed by counterflow centrifugal retained the representative receptor expression profile and other intrinsic properties that are closer to the native tumor state. Tail vein injections of these pure tumor cell preparations into syngeneic mice enabled accurate characterization of the resulting intravascular biology *in vivo* [191, 252]. In these experiments, platelet-aggregating activities of Lewis lung carcinoma, B16 amelanotic melanoma and 16C mammary adenocarcinoma resulted in tumor cell-platelet emboli formation in the lungs [191]. Platelets aggregated with tumor cells as early as 2 min followed by biphasic association with arrested tumor cells that peaked at 10–30 min and 4–24 h [191]. Ultrastructurally, tumor cells formed processes that extended into the platelet aggregate. At early time intervals (2–10 min), intravascular platelet degranulation in association with tumor cell processes. Tumor cells also engulfed platelet fragments *in vivo* [191]. Follow-up studies using the same models focused on tumor cell interactions with endothelial cells and the subendothelial matrix [19]. Mitoses were observed after 24 h with cell division and the development of intravascular tumor nodules. The final step in the extravasation sequence was dissolution of the basement membrane by the attached tumor cells [19]. In other mouse studies, platelet adhesive glycoprotein receptors and their counterparts expressed by tumor cells participated in tumor cell induced platelet aggregation (TCIPA) as an early step in the development of metastatic lesions [253].

9 Thrombocytosis

Cancer induces thrombocytosis resulting in elevated circulating platelets linked to Trousseau's syndrome [254–256]. A multicenter study of epithelial ovarian cancer revealed

mechanistic associations between platelet counts and disease outcome [130]. Thrombocytosis associated with tumor interleukin-6 (IL-6) and liver generated thrombopoietin has been associated with shortened survival in ovarian cancer patients [130]. Orthotopic ovarian mouse models revealed tumor-derived IL-6 stimulated hepatic thrombopoietin synthesis and paraneoplastic induction of thrombocytosis [130]. These studies showed a paracrine link between cancer and thrombocytosis. More CD63-positive platelet microparticles were also found in the circulation of ovarian cancer patients compared to those with benign tumors [257]. Procoagulant microparticles were found along with venous thromboemboli in cancer patients [258, 259]. The impact of IL6 on thrombocytosis has been observed elsewhere and in other cancers [260, 261].

10 Next response?

This overview illustrates the importance of platelet "first responder" characteristics to hemostasis wound repair, cancer immune function, and cancer biology. Thrombocytosis and thrombogenesis remain key areas of interest for biologic and prognostic characteristics of cancer. The critical nature of platelets to carcinogenesis as well as platelet-tumor cell heterotypic emboli to metastasis will continue to advance. Advancements in intravital microscopy coupled with fluorescent platelets are expected to facilitate elucidation of the rapid process of platelet-tumor cell invasion. The impact of platelets on tumor immunity is an exciting new field of interest with a bright rapidly responding future.

Acknowledgements

Grant and other support Boone Pickens Distinguished Chair for Early Prevention of Cancer, Duncan Family Institute, Colorectal Cancer Moon Shot, P30CA016672-41, 1R01CA187238-01, 5R01CA172670-03, and 1R01CA184843-01A1, CA177909, and the American Cancer Society Research Professor Award.

Compliance with ethical standards

Conflict of interests The authors declare that they have no conflicts of interest.

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