NON-THEMATIC REVIEW

Of vascular defense, hemostasis, cancer, and platelet biology: an evolutionary perspective

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Abstract

We have established considerable expertise in studying the role of platelets in cancer biology. From this expertise, we were keen to recognize the numerous venous-, arterial-, microvascular-, and macrovascular thrombotic events and immunologic disorders are caused by severe, acute-respiratory-syndrome coronavirus 2 (SARS-CoV-2) infections. With this offering, we explore the evolutionary connections that place platelets at the center of hemostasis, immunity, and adaptive phylogeny. Coevolutionary changes have also occurred in vertebrate viruses and their vertebrate hosts that reflect their respective evolutionary interactions. As mammals adapted from aquatic to terrestrial life and the heavy blood loss associated with placentalization-based live birth, platelets evolved phylogenetically from thrombocytes toward higher megakaryocyte-blebbing-based production rates and the lack of nuclei. With no nuclei and robust RNA synthesis, this adaptation may have influenced viral replication to become less efficient after virus particles are engulfed. Human platelets express numerous receptors that bind viral particles, which developed from archetypal origins to initiate aggregation and exocytic-release of thrombo-, immuno-, angiogenic-, growth-, and repair-stimulatory granule contents. Whether by direct, evolutionary, selective pressure, or not, these responses may help to contain virus spread, attract immune cells for eradication, and stimulate angiogenesis, growth, and wound repair after viral damage. Because mammalian and marsupial platelets became smaller and more plate-like their biophysical properties improved in function, which facilitated distribution near vessel walls in fluid-shear fields. This adaptation increased the probability that platelets could then interact with and engulf shedding virus particles. Platelets also generate circulating microvesicles that increase membrane surface-area encounters and mark viral targets. In order to match virus-production rates, billions of platelets are generated and turned over per day to continually provide active defenses and adaptation to suppress the spectrum of evolving threats like SARS-CoV-2.

Keywords Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) · Corona virus disease 2019 (COVID-19) · Platelet · Coagulation · Toll-like receptor (TLR) · C–C chemokine receptors (CCR 1,3And 4)

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1 Offerings from cancer expertise to understanding platelet evolution

We have acquired an informed perspective and extensive expertise in the field investigating the role of platelets in cancer biology [1–10]. One of the key discoveries that led to a better understanding of the links between coagulation and cancer was that of Trousseau's syndrome, which is defined as a migratory thrombophlebitis found typically in patients with an underlying malignancy. Among other discoveries throughout the years, one of the key discoveries linking platelets to tumor cell interactions was made by Gasic et al. [11]. Our efforts in this field greatly expanded the knowledge base regarding platelet-tumor cell interactions and the role of prostaglandins in particular during cancer metastasis [2, 12]. Fast forward, this study is for expanding our current knowledge base in identifying unique aspects of platelet function and platelet biology in the growth and progression of ovarian cancer [4, 10]. It is from this unique cancer-centric perspective that we recognized that the numerous venous-, arterial-, microvascular-, and macrovascular thrombotic events and immunologic disorders are caused by severe, acute-respiratory syndrome coronavirus 2 (SARS-CoV-2) infections. This perspective led us to examine the evolutionary connections placing platelets at the epicenter of hemostasis, immunity, and adaptive phylogeny. All of these novel perspectives may provide new leads to better understand not only the role of platelets in vascular protection and immune function but also a keener insight into the role of platelets in cancer and metastasis.

2 Viral and platelet evolution

2.1 Single-stranded RNA virus evolution

Positive sense, single-stranded RNA viruses are thought to be among the earliest forms of life; lineages have been traced through the conservation of RNA-dependent RNA polymerases within the picornavirus super-group [13–16]. Over the past century, multiple single-stranded RNA viruses, including human immunodeficiency virus-1, influenza A, and severe, acute-respiratory-syndrome coronavirus 2 (SARS-CoV-2), have emerged to infect humans on a large scale—a modern consequence of ancient virus evolution [17, 18]. Endogenous retroviruses help to record past RNA retroviral infections and are ubiquitous in vertebrate genomes [19]. Coronaviruses are among the class of positive-strand RNA viruses that infect mammals and birds and can achieve zoonosis [20–22]. Evidence of a

SARS-like coronavirus arising in bats shows zoonotic implications of a direct ancestor of SARS coronavirus [23, 24]. Bats can carry viruses that are deadly to other mammals without having serious symptoms, possibly involving unique immune- and rapid cellular-spreading properties [25]. During the current SARS-CoV-2 pandemic, key viral mutations may have also occurred via person-to-person transfer complicated by zoonotic passage, highlighting the rapid evolution of this virus [26–32]. Overall, the phylogeny of vertebrate RNA viruses reflects that of their vertebrate hosts coevolving with a transition from ocean-to-land and exhibits origins that date back to the time of early terrestrial animals [18, 33, 34].

2.2 Phylogenetic co-evolution of platelets in adapting to viral pathogens

Many aspects of platelet biology and evolution remain unrecognized, especially regarding their rapid responsiveness to viruses [35–37]. Platelets may have coevolved with viruses to provide speedy responses but this possibility remains unexplored. However, platelets have been shown to endocytose viral particles and are activated via toll-like receptor signaling [38]. The severity of low-platelet count (thrombocytopenia), a common complication of influenza-virus infection, predicts the clinical outcome of critically ill patients [39]. These platelet responses are biochemically and biologically rapid and may also involve integrin receptors [40]. In the case of viral diseases like COVID-19, the responses may remain unnoticed during asymptomatic and early phases [41, 42]. As there is an expression gradient of entry factors for SARS-CoV-2 along the airways, these are the likely sites of initial viral infection, spread, and clearance [43]. General symptoms can consist of cough, myalgia, loss of appetite, and gastrointestinal discomfort. Olfactory and gastrointestinal disorders are prevalent with sudden anosmia (loss of smell), ageusia (loss of taste), or dysgeusia (metallic taste), but not always fever, as informative symptoms of the COVID-19 infection [44–48]. Given the one-to-two, cell-layer separation between many airway passages and the microcirculation coupled with the evolutionary characteristics of platelets, this suggests that they are the first thrombocyte/immunocyte that virions such as SARS-CoV-2 may encounter and thereby rapidly respond to in the bloodstream [38, 49]. For example, with the human immunodeficiency virus, platelets have been shown to reduce viral load [50] and harbor viral particles [51].

## 2.3 Early evolutionary ties between innate immunity and coagulation

Coincident activation of innate immunity and the coagulation system after an injury is a phylogenetically ancient,

adaptive response that can be traced back to the early stages of eukaryotic and chordate evolution [52–57]. Most invertebrate species like the horseshoe crab (*Limulus polyphemus*) lack differentiated phagocytic cells and platelets, but they do have large nucleated amoeboid granular hemocytes [58–60] (Fig. 1). Once their open circulatory system is breached, they respond to microbial threats via a common amoebocyte- and humoral pathway of inflammation and clotting [58–60]. Lysates prepared from the amebocytes of *Limulus* have long been known to undergo coagulation upon exposure to endotoxin and have been used to detect that endotoxin [61]. Archetypal functions of *Limulus* amebocytes are found in human platelets, including aggregation, adhesion, spreading, and granule-based release of coagulation factors [62–64]. These properties are found throughout phylogenetic evolution as common antimicrobial and proinflammatory responses to stimuli that activate both the clotting cascade and the phagocytic effector cells. Non-mammalian vertebrates—that include early chordates, fish, birds, amphibians, and reptiles—have large, nucleated,

Fig. 1 Platelet evolution. Thrombocyte and platelet evolution remain at the center of both hemostasis and immunity. Depicted are species and thrombocyte/platelet reproductions where transmission electron micrography-, morphological-, and functional data were available. Invertebrate thrombocytes of the horseshoe crab *(Limulus polyphemus)* are typically large amoeboid cells. Thrombocytes gradually became reduced in size, more elongated, and retained nuclei throughout the evolution of (1) the chordate and aquatic vertebrates such as agnatha or jawless fishes like the hagfish (*Myxine glutinosa*), (2) the cartilaginous or Chondrichthyes fish such as the dogfish shark (*Squalus acanthias*), and (3) the boney or teleost fish such as zebrafish (*Danio rerio*). As vertebrates adapted to terrestrial life, these trends continued in amphibians such as the green frog (*Rana clamitans*), reptiles like crocodiles (*Crocodylus porosus*), and even avian forms such as the chicken (*Gallus gallus*). Unique to mammals and marsupials, platelets dramatically decreased in size and developed improved biophysical properties, including the elimination of nuclei
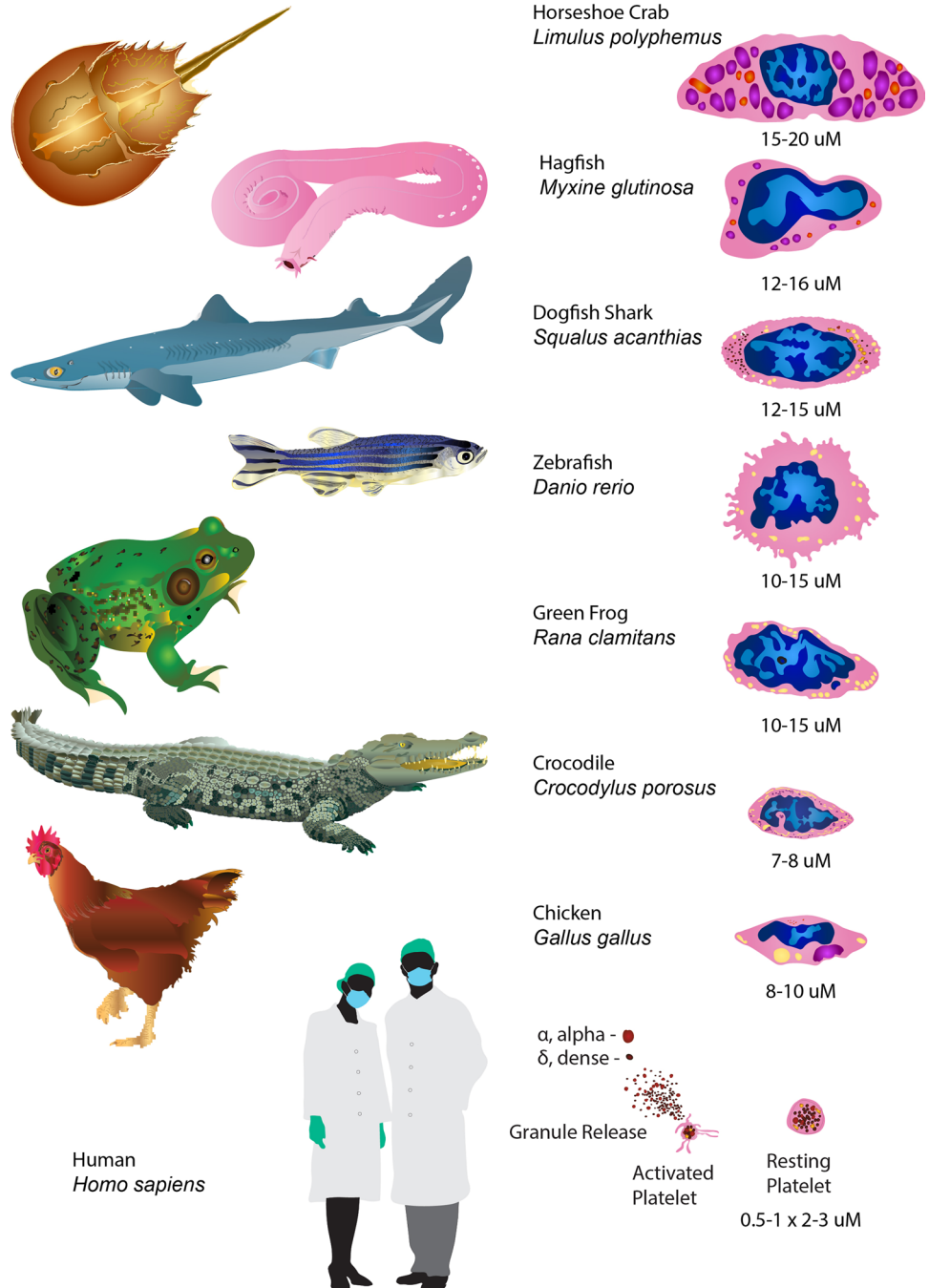
often spindle-shaped thrombocytes that mediate thrombo-cytic activity [36, 54–57, 65].

2.4 Platelet adaptation through decreasing size and losing nuclei

Throughout evolution, the cell size and dimensions of thrombocyte nuclei have gradually decreased; this process accelerated as species became more terrestrial and began to thermoregulate (Fig. 1). In the jawless fish-like Hagfish (*Myxine glutinosa*) [66, 67]*,* cartilaginous fish-like sharks *(Squalus acanthias)* [68, 69], boney fishes like Zebrafish (*Danio rerio*)[70], and other fish species, circulating nucle-ated thrombocytes have some phenotypic features and func-tional characteristics similar to those of mammalian platelets [71, 72]. As aquatic animals like the lungfish (*Neoceratodus forsteri*, *Lepidosiren paradoxa*) adapted to terrestrial life, thrombocytes remained large and retained large nuclei, while developing a sophisticated granule system to effectively regulate and maintain coagulation and immune functions, particularly during the dramatic changes associated with dry-season-based estivation or dormancy [73, 74]. Similar morphological associations found in thrombocytes of other non-mammalian vertebrates were retained in amphibians such as the green frog (*Rana clamitans)* [75], reptiles such as crocodiles (*Crocodylus porosus*) [75, 76], and birds such as the chicken (*Gallus gallus)* [76, 77]*.* In contrast, mammals [78] and marsupials have developed various essential evolu-tionary changes during the processes of erythroid and throm-bocytic development and differentiation. Examples include megakaryocyte endoreduplication and platelet enucleation, each involving a reduction in size and improvements in func-tional biophysical morphology [36, 76, 79]. Mammals have also developed more intricate associations between platelets and other immune cells (neutrophils, monocytes, and mac-rophages) to coordinate innate immunity and the coagula-tion system [53]. From an evolutionary perspective directed at defending against viral threats, platelet adaptations may be an effective way to improve host responses. Platelets are important anucleate elements of the immune and hemostatic systems that have minimal nucleotide- or protein synthesis machinery to indefinitely make new gene products [80–82]; their ability to reproduce viral particles is limited or has been shown for only a few single-stranded-RNA viruses like Den-gue virus and potentially SARS-CoV-2 [83–85]. Some viral replication may be excluded by restricting gene expression to a pre-existing, limited subset of ribosome-bound mes-senger RNAs that engage the ribosome rescue-factor pelota (PELO) in regulating messenger-RNA decay [86]. The pos-sibility also exists that viral replication may occur in mega-karyocytes within the bone marrow prior to their budding from parent cells, but this has not been fully explored [87, 88]. Although unrecognized as part of platelet evolutionary

biology to date [36, 37], a more important function of plate-lets in mammals may be the lack of nuclei and limited rep-lication machinery to support long-term viral replication, providing a more highly evolved defense and, potentially, a sink against these infections.

The vertebrate transition from aquatic to terrestrial envi-ronments applied significant selective pressure to the co-evolution of viruses and animals. This was accompanied by multiple geophysical, external, selective pressures, which include changes in luminosity, oxygen, carbon dioxide, and asteroid-based impacts (Fig. 2). Co-evolution is a complex interaction of co-divergence between virus and host over an extended time and includes frequent cross-species transmis-sions coupled with external survival pressures severe enough to elicit the change [18, 33]. In this manner, SARS-CoV-2 evolution has accelerated in conjunction with zoonotic exchanges with humans over the past 100 years (on the time scale in Fig. 2, this would be approximately the size of a period).

3 Adaptive characteristics

The evolution of platelets includes multiple adaptations to deal with viral infections. As one evolutionary mecha-nism for dealing with viral pathogens, large, multinucleated megakaryocytes evolved in the bone marrow to protect and enable the production of high numbers of platelets [89–91]. These mechanisms have avian roots and enabled euthe-rian placentalization [92, 93]. There is another significant advantage over the 2-N thrombocytes of lower vertebrates found in mammalian megakaryocytes. Significantly enlarged megakaryocytes provide a major amplification response to bleeding or viral immune threats incurred by increasing DNA content up to 128 N [93] No studies have yet deter-mined whether these megakaryocytes serve and monoclonal source of targeted platelets responding to a specific threat. The adaptation of increasing DNA content significantly increases the capacity to produce even more platelets with increased receptor density; more organelles per unit cellular volume; and more prothrombotic proteins to reduce bleed-ing time or adapt to viral threats. This process culminates in mammalian platelet evolution and hemochorial placenta-tion because mammals are the only vertebrate group that has evolved with a highly effective and unique system of hemostasis [93]. This hemostasis effectiveness is essential at parturition where even minimally invasive placentae can hemorrhage [93]. Platelet evolution has enabled the preven-tion of rapid blood loss and damage from massive injury or microinjury, which is particularly important when the brain is more advanced. Because microbes and viruses have a short ten-day life span, platelets must have co-evolved to cre-ate survival advantages with adaptive mechanisms to meet
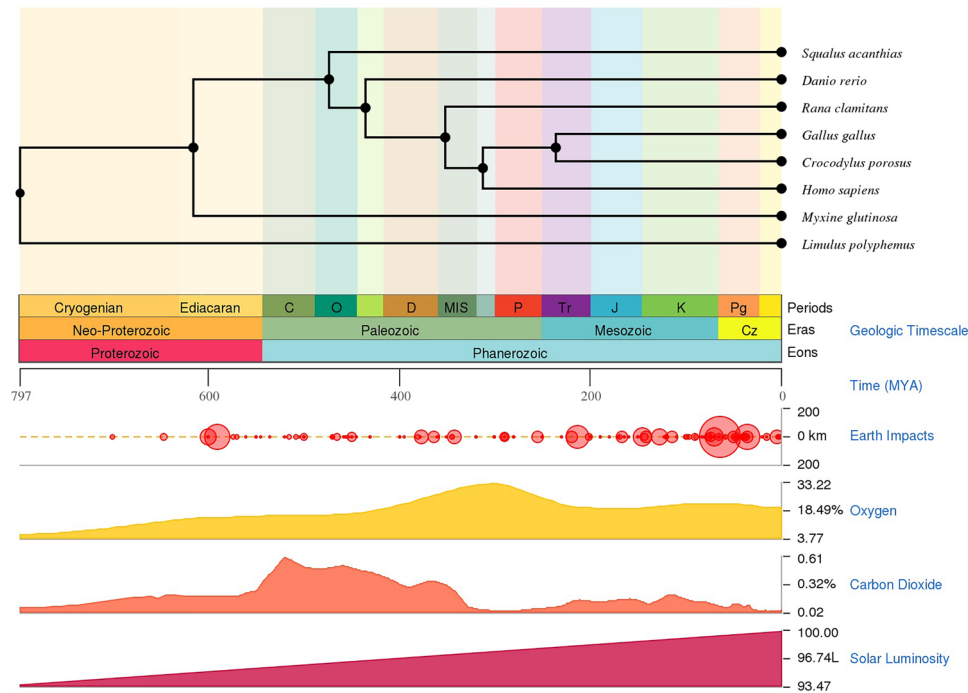
Fig. 2 Evolutionary timeline. Using available transmission electron micrography- and morphological data from the literature, a nodal evolutionary tree for the species listed in Fig. 1 was constructed using the Time Tree Website, http://www.timetree.org. A species list was generated as a text file list for the following: *Limulus polyphemus*, *Myxine glutinosa*, *Squalus acanthias*, *Danio rerio*, *Rana clamitans*, *Crocodylus porosus*, *Gallus gallus domesticus*, and Mammals/*Homo sapiens*. Egg-laying mammalian evolution began 220 MYA, pla-cental-Eutherian evolution occurred 125 MYA and human evolu-tion began 2.5 MYA. This file was then uploaded as a list file. *Time*: million years ago, MYA *Periods*: Cambrian, C:542.0–488.3; Ordo-

vician, O: 488.3–443.7; Silurian, S:443.70–416.0; Devonian, D: 416.0–359.2; Mississippian, MIS: 359.2–318.1; Pennsylvanian, PEN: 318.10–299.0; Permian, P: 299.0–251.0; Triassic, Tr: 251.0–199.6; Jurassic, J:199.6–145.5; Cretaceous, K:145.50–65.50; Paleogene, Pg:65.50–23.03; Neogene, N:23.03–0.0. *Eras:* Neo-Proterozoic: 1000.0–542.0; Paleozoic: 542.0–251.0; Mesozoic: 251.0–65.5; Ceno-zoic, Cz**:** 65.50–0.0–542.0. *Eons*: Proterozoic: 2500.0–542.0; Phan-erozoic: 542.0–0.0. *Earth impacts:* Sphere size equals the diameter of the impact (e.g., Chicxulub, location: Yucatan, Mexico, coordinates: 21.333, −89.50, diameter: 150.0 km, age: 65 MYA)

and sequester rapidly cycled microbial- and viral threats and pathogen response-based turnover.

The sheer number and biophysical properties of megakary-ocyte-derived mammalian platelets make them more likely to be the first blood component to encounter virus particles and limit spread. Human platelet genesis is well studied and primarily occurs by membrane-bound, organelle-containing cytoplasmic extrusion into the blood stream of numerous small size- and volume blebs ranging between 9.7 and 12.8 femtoliters or in plate-like structures of 2.6 to 2.9 µm in diameter [90]. This blebbing, subcellular, genesis process occurs primarily in the bone marrow from surfaces of mega-karyocytes—the largest cell in the body (ranging between 40 and 100 µm in diameter). Normal human-platelet concentra-tions range between 150,000 and 400,000 per microliter. The roughly 10^{11} platelets produced each day are responsible for coagulation—specifically for creating a fibrin plug at the site of blood vessel injury. However, emerging data sug-gest a greater impact on viral interdiction, pathogen surveil-lance, cancer biology, and immune function. As part of the

anti-viral response, platelets are known to actively engage and directly phagocytose viral pathogens [94–106]. Note that this ability of nucleated thrombocytes to phagocytose pathogens is also present in lower vertebrates [107], which also exhibit an extensive open-canalicular system [72]. Platelets have been shown to endocytose viral particles and become activated via toll-like receptor (TLR) signaling [38]. Mammalian virus uptake may also involve the platelet open-canalicular system that exchanges factors with the surround-ing microenvironment [95, 97, 108–111]. Once platelets take in virus particles, they may then undergo phagocytosis by other immune cells[106]. Platelet surface changes that occur after taking in viral particles can also mark the platelets for clearance by other organs including the liver and spleen.

3.1 Platelet formation of plate-like structures and wall shear biophysics

Other key aspects of adaptive evolution in the mammalian platelet are size decreases and improvements in biophysical

shape properties to enhance encounters with virus-infected vascular surfaces. In lower vertebrates, nucleated thrombocytes are less plate-like and10 to 20 times larger than platelets causing them to primarily distribute in the center of laminar shear fields [36, 70, 72] (Fig. 1). In humans, resting platelets are plate-like discs designed to maximize planar-surface interactions[112–114] that, due to their small size and shape, biophysically concentrate toward the outer fluid-shear fields of flowing blood [115–122]. Taken together, these properties enhance encounters and recognition of any vascular-wall lesions, wounds, or tumors. Should platelets encounter basement membranes or their underlying matrix, the platelets undergo receptor-mediated activation [2, 123–127]. This activation is connected to rapid cytoskeletal- and membrane changes to form filopodia leading to adhesion [128–135]. This is a process that occurs within seconds along with a shape change from exocytic degranulation. Degranulation, in turn, encompasses the release of proteins, growth factors, cytokines, and lysozymes along with a variety of bioactive lipids, small molecules, and other factors. Successful sequential recruitment of additional platelets and immune cells coupled with thrombogenesis ultimately seals any tissue gaps and sterilizes the lesion. Since platelets segregate within shear fields near the endothelial cell surfaces, they have a high probability of encountering viral particles that enter the bloodstream. This behavior also affords platelet endothelial-cell interactions that can occur with an aggressive, influenza-like cytokine storm that triggers cell damage in lung capillaries [136].

3.2 Platelet microvesicle production and increased membrane surface area

Compared to any other form of circulating microvesicle, exocytic platelets generate the majority of microparticles and exosomes in circulation [137–142]—possibly another form of platelet evolution to deal with viral threats. In lower vertebrates, microparticle generation by thrombocytes plays a key role in thrombocyte function [70]. During laser-injury experiments in zebrafish, thrombocyte microparticles were the first cell-based entities to arrive at the injury site, even before the young thrombocytes [143, 144]. In the case of viral infections like SARS-CoV-2, platelet microparticle and exosome shedding would significantly increase the platelet-membrane surface area and possibly mitigate the threat potential through target decoration and further immune-system stimulation[145].

3.3 Tissue migration

A phylogenetic adaptive loss of platelet nuclei may also enable rapid endothelial transmigration into perivascular spaces. Platelets readily undergo tissue migration because

of their small size, minimal displacement volume, and highly active cytoskeletal responses linked to activation, adhesion, and aggregation [146–148]. Even greater is the vascular-transmigration advantage of being unencumbered by the presence of nuclei, which limit the migration of other immune cells to interdict viral threats [146–150]. This nuclei absence may also limit the distance that platelets can move into tissue, which limits nucleotide and protein-synthesis capabilities. Due to limited nucleotide and protein-synthesis capabilities, platelets cannot indefinitely maintain protein replacement [80, 151]. These immune-surveillance and rapid viral-response properties facilitate speedy sterilization and quickly initiate the repair process during a virus-induced, tissue-injury response. With viral infections, platelets have been shown to influence viral invasion of the central nervous system in canine distemper-virus infection [152, 153]; however, few studies exist that examine platelet invasion or extravasation as part of a viral immune response. Alternatively, because viral infection may lead to endothelial damage and platelet extravasation, activation and granule release may promote the attraction of other immune cells that produce inflammation in the affected tissues.

Various factors in response to various stimuli can contribute to platelet transmigration across leaky or inflamed vessel walls to aid in wound sterilization and tissue regeneration [154–160]. Platelet inflammatory responses can also cause them to undergo vascular transmigration and granule release that engages various additional immune cells [161–163]. Within the extravascular microenvironment, the release of the stromal cell-derived factor-1 named C-X-C chemokine-ligand 12 (CXCL12), along with other cytokines, can also provide a potent stimulus for platelet migration into extravascular spaces [10, 150, 164–167] [168–171]. Among the many response factors expressed by platelets are C-X-C chemokine-receptors 4 and 7 (CXCR-4, CXCR7), which are the cognate receptors for CXCL12. These platelet receptors may be involved in inflammatory- or allergic responses or in platelet activation in human immunodeficiency virus and other viral infections [172]. Along with those involving lymphatic biology, these thrombo-immune responses and wound healing characteristics were conserved from lower vertebrates [107, 173–177] [178].

4 Virus-induced platelet activation and thrombotic complications

Cyclooxygenase and prostaglandin production, associated with gene duplications and losses, have been retained throughout metazoan and vertebrate evolution [179, 180] that began in teleosts and resulted in a divergence between cyclooxygenase-1 and cyclooxygenase cyclooxygenase-2 (COX-1 and COX-2) [180]. A release of the

COX-2-associated prostacyclin PGI_2 from vascular endothelial cells helps to maintain the resting state of circulating platelets through G-protein-coupled receptors (GPCR) [181–185] (Fig. 3). Should platelets become activated during the virus uptake, responses are rapidly amplified by activating molecules such as thrombin or adenosine diphosphate (ADP). These molecules are released by platelets and trigger their cognate GPCRs at the cell surface or as a result of the release reaction. Similarly, COX-1-associated and endogenously synthesized thromboxane A_2 (TXA_2) amplifies the local platelet response to recruit additional platelets through TXA_2-GPCRs that accelerate the thrombogenesis/clotting process (Fig. 4). Platelet TXA_2 levels increase following virus infections and can be attenuated by aspirin treatment [186–190]. The production of TXA_2 and other lipids initiates vasoconstriction [191, 192]. 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 rapid (< 30 s) hydrolysis [193, 194]. Because these rapid changes accelerate over a matter of minutes, a fibrin network is generated to trap and activate more platelets within the forming clot in a cyclic fashion to limit blood loss. This amplification process occurs over 20 min or less, while clot maturation and solidification continue for about an hour to initiate—over days to weeks—prompting immune-cell recruitment and inflammation. Recruitment of fibroblasts and immune cells through platelet-initiated, angiogenic repair mechanisms stimulates further wound healing and resolution [195].

4.1 Granule release

The release of dense, δ-granule components influences the vascular microenvironment of the platelet (Fig. 3). The release of calcium and magnesium ions promotes platelet activation and aggregation. The release of nucleotides such
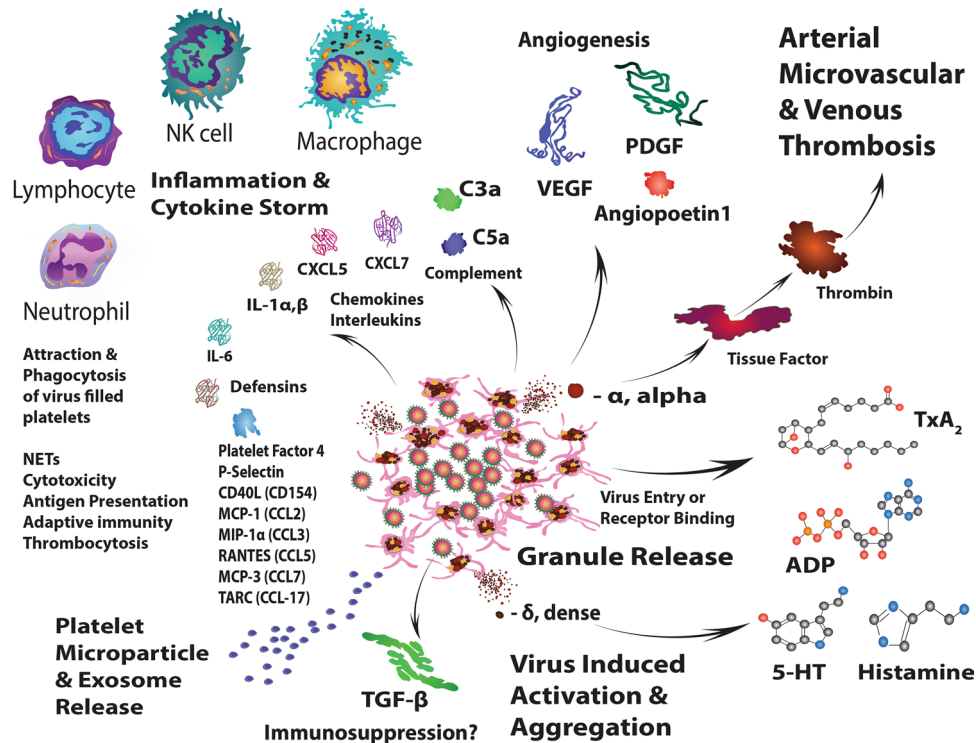

Fig. 3 Platelet responses to SARS-CoV-2. Platelet responses to viruses include activation, aggregation, and granule release. Dense δ-granules contain bioactive small molecules including thromboxane A_2 (TxA_2), adenosine diphosphate (ADP), serotonin (5-hydroxytryptamine [5HT]), and histamine. The α-granule contains numerous bioactive proteins involved in thrombus formation, coagulation, and aggregation including tissue factor and thrombin. It also contains numerous bioactive molecules involved in immune regulation and inflammation including Cys-X-Cys (C-X-C) motif chemokines such as CXCL1 (GRO1 oncogene [GRO-α]), CXCL4 (platelet factor 4 [PF4]), CXCL5 (ENA-78), CXCL7 (β-thromboglobulin [β-TG], platelet binding protein [PBP], CTAP-III, and NAP-2), CXCL8 (interleukin-8 [IL-8]), and CXCL12 (stromal cell-derived factor-α [SDF-1α]). Platelet α-granules also contain Cys-Cys (C–C) motif chemokines that include CCL2 (monocyte chemoattractant protein 1 [MCP-1]), CCL3 (macrophage inflammatory protein [MIP-1α]), CCL5 (regulated on activation, normal T-cell expressed and secreted [RANTES]), CCL7 (MCP-3), and CCL17 (thymus and activation regulated chemokine [TARC]), along with interleukins IL1-β and IL-6, platelet-activating factor [PAF], defensins, and complement factors C3a and C5a. Alpha-granule release factors also include growth factors such as vascular endothelial-cell growth factor (VEGF), platelet-derived growth factor (PDGF), and angiopoietin
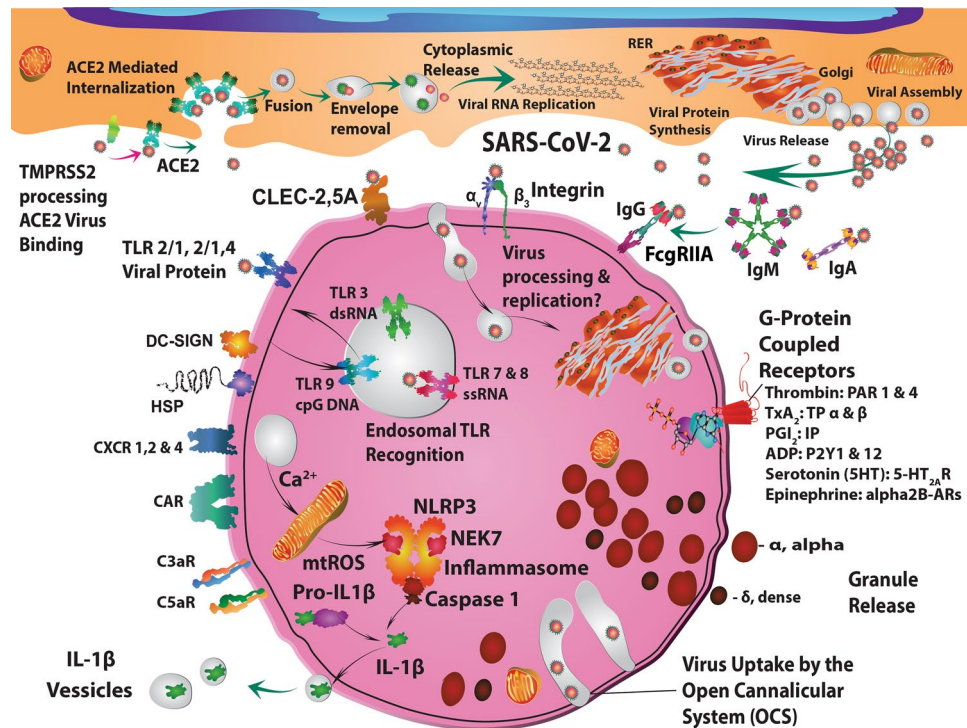
Fig. 4 SARS-CoV-2 replication and platelet receptor interactions. At the top, virus replication within vascular endothelial cells is initiated by *SARS-CoV-2 spike-protein binding* to angiotensin-converting enzyme (ACE) and enzymatic processing by transmembrane protease, serine 2 (TMPRSS2). Viral uptake results in viral-particle uncoating, viral reverse transcriptase activity of the positive single-stranded (+ssRNA) genome, and replication. The endoplasmic reticulum of the host cell supports protein synthesis, assembly in the Golgi apparatus, and delivery to the exterior by exosomal transport or host-cell disruption, death, and retraction. The platelet depicted at the center illustrates the numerous receptors that bind to various virus types. Those that bind coronavirus species are indicated by larger-font text and include (alphabetically) coxsackie-adenovirus receptor (CAR), CCL chemokine Cys-Cys (C–C motif) ligand, cluster of

differentiation (CD), C-type lectin domain family 2 and 5 (CLEC-2 and CLEC-5), complement receptor (CR 3a and CR 5a), Cys-X-Cys (C-X-C) motif chemokine receptor type (CXCR1, CXCR1-2, and CXCR1-4), dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN), Fc gamma receptor II (FcγRII), heparan sulfate proteoglycan (HSP), integrin ($\alpha_v\beta_3$), and toll-like receptor (TLR). Also depicted are the phosphate-transferring nucleotide-binding domain-like receptor protein 3 (NRLP3), the inflammasome-response switch serine/threonine-protein kinase (NEK7), and the pro-inflammatory cytokine caspase 1 that mediates the enzymatic processing of interleukin-1β (IL-1β) prior to microvesicle release. Also shown are the large numbers of G-protein-coupled receptors involved in platelet signal transduction, activation, and granule release

as ADP activates platelets through $P2Y_1$ and $P2Y_{12}$ receptors [196, 197] and stimulates vasoconstriction [198] (Fig. 4). ADP can accumulate in the ischemic vascular microenvironment as a consequence of circulatory stasis or thrombus formation. The release of neurotransmitters such as serotonin (5-hydroxytryptamine), epinephrine, and histamine can potentiate ADP-induced platelet activation and aggregation [196, 197, 199, 200]. Platelets may serve as neuronal and innate immune cells to help mediate T cells during tissue inflammation [201]. Epinephrine is also likely to worsen COVID-19-induced stress-related effects on platelets and platelet-mediated cytokine responses [202]. By contrast, lower-vertebrate thrombocytes do not aggregate in response to ADP or epinephrine; neither do they accumulate or produce serotonin [65, 203].

Conversely, platelet release of alpha (α)-granules in serum results in substantial increases in multiple proteins

responsible for most of the coagulation, growth stimulation, angiogenesis, immune function, and wound-repair factors. Adhesion molecules released from α-granules help to stimulate the rapid arrest of platelets in circulation. This is a process that is mediated by adhesion factors such as the von Willebrand factor (vWF), fibrinogen, thrombospondin, and fibronectin as well as integrins and other adhesion receptors αIIbβ3, αvβ3, and P selectin. These adhesion proteins regulate platelet interactions with other platelets, and with endothelial cells, exposed basement-membrane extracellular matrix, leukocytes, neutrophils, monocytes, and tumor cells. These same storage α-granules release the prothrombin, fibrinogen, factor V, and factor VIII that stimulate and promote coagulation and fibrin formation [3, 9, 204–212].

4.2 Viral infection of endothelial cells

Endothelial cells express angiotensin-converting enzyme (ACE) and transmembrane protease, serine 2 (TMPRSS2) that are involved in the SARS-CoV-2 invasion via its spike-surface protein binding and processing [213–218] (Fig. 4). After uptake, SARS-CoV-2 undergoes uncoating and viral-RNA reverse transcription and replication in the rough endoplasmic reticulum followed by new SARS-CoV-2 assembly and release (Fig. 4). Should the virus infect endothelial cells, endotheliitis, complement activation, and endothelial-cell death can occur [219–224]. Endothelial-cell retraction, whether virus- or inflammation-induced, can lead to matrix exposure that triggers platelet activation and granule release. Blood-vessel injury can amplify platelet responses and may help trigger heightened immune responses during the second phases of COVID-19 infection [219, 222, 225].

Analysis of megakaryocytes in bone marrow data from the Human Cell Atlas did not identify expression of these receptors [226, 227]; however, the detection of ACE2- and TMPRSS2 receptors in platelets requires direct protein-characterization technology, not RNA sequencing, because the platelets lack nuclei and the sequencing technique does not provide adequate sensitivity. As part of their immune-surveillance properties, platelets can recognize foreign bodies or invading pathogens [9, 228–230]. Along with other platelet receptors, the toll-like receptors expressed by megakaryocytes [231] may be involved in innate immune responses to viruses, may take part in endocytosis of a variety of pathogens by platelets [38, 232–234], and may release factors that can influence antiviral responses [157, 235–246] (Fig. 4).

4.3 SARS-CoV-2 infection and platelet recognition

Normally, platelets serve to rapidly respond during the wounding process and hemostasis. When virally damaged, blood-vessel endothelial cells die, are lost, or retract; this exposes platelets to subendothelial elements that initiate receptor-based recognition of the extracellular matrix. These interactions are driven by a variety of platelet glycoprotein receptors that bind to endothelial cells and extracellular matrix factors including proteoglycans, laminin, fibronectin, vitronectin, and various isoforms of collagen. vWF binds to exposed collagen I, collagen III, and collagen VI fibers. vWF is also recruited into matrix networks by forming tethering fiber strands [247–251]. Many vWF characteristics of hemostatic proteins are conserved during ancestral vertebrate evolution, but the hagfish (*Myxine glutinosa*) jawless vertebrate (a cyclostome) lacks functional domains required for primary hemostasis under high flow [66]. Many of the typical platelet-surface receptors also bind to viruses [34] but the role of platelet binding that may sequester viral particles in the vasculature has not been studied in detail.

Platelets contextually encounter numerous bloodstream-circulating ligands, cells, pathogens, and extracellular-matrix ligands. Immediate platelet responses are governed by a variety of integrin receptors through transmembrane glycoprotein-α and glycoprotein-β heterodimers once ligands are engaged (Fig. 4). Resting platelets express low-affinity conformation integrins that are bent to protect binding sites and to form high-affinity- or open-binding states that, once activated, efficiently interact with ligands. Rolling platelet behavior is initiated by surface-level, multimeric GPIb-complex interactions with vWF that activate a key stabilization integrin $\alpha_{IIb}\beta_3$ [252–255] to bind a variety of RGD (arginine-glycine-aspartic acid)-containing ligands [252–255] including fibrin, fibrinogen, fibronectin, vitronectin, thrombospondin, or vWF complexes. Platelets also interact with hanta- and adenoviruses through $\alpha_{IIb}\beta_3$ receptors [94, 98, 256–260]. Certain integrins bind to echo- and rotaviruses[261] while vitronectin is engaged by platelet $\alpha_v\beta_3$ integrin heterodimers that also bind to echovirus9; coxsackieviruses A9 and -A16; and hanta-, parecho-, and coronaviruses [98, 256, 257].

Platelet C-type lectin-like receptors CLEC-2 and CLEC-5A initiate platelet activation and trigger signal transduction through molecular multimerization [262–266]. CLEC-2 binds to the transmembrane sialomucin-glycoprotein podoplanin among other molecules [267–269]. Podoplanin is expressed on cells of the lymphatic endothelia, type I lung epithelia, choroid plexus epithelia, kidney podocytes, and lymph-node stroma to potentiate migration and invasion [267–270]. CLEC-2 expression is maintained on activated platelets and on platelet microparticles to substantially increase the probability of platelet-mediated interactions with virus particles [271]. Platelet CLEC-2 and CLEC-5A receptors bind to the human immunodeficiency- and coronaviruses [271–273].

Platelet P-selectin, also known as membrane glycoprotein GMP-140 [274, 275], binds to P-selectin glycoprotein ligand 1 (PSGL-1) [276], neutrophil leukocyte-endothelial cell-adhesion molecule 1 (LECAM-1) [277], endothelial cell-leukocyte adhesion-molecule 1 (ELAM-1) [278], and Sialyl Lewis (x) oligosaccharide [279]. Along with a variety of immune cells and endothelial cells, P-selectin interaction is important in mediating inflammation, auto-immunity, and wound healing, and plays a role in coxsackievirus-induced myocarditis [280–284]. P-, L-, and E-selectins help with the tethering and rolling of cells that flow past the vascular luminal surfaces during the initial phases of intravascular, adhesive interactions. These processes are stabilized by other receptors [285–291] and may contribute to interactions with virus-laden platelets.

4.4 Thrombus initiation

Platelets often serve as foci for coordinating thrombus initiation and formation. Tissue factor initiates platelet activation and aggregation [292] and may be linked to some virus-induced prothrombotic states associated with septic shock, myocarditis, and respiratory viral infections[293–296]. Thromboemboli and thrombocytopenia can also lead to COVID-19-related complications as reported in a number of publications [297–306]. In vivo, the viral threat mitigation process is likely to be rapid, as platelets aggregate in response to circulating threats. In the case of platelet interactions with virions such as SARS-CoV-2, intravital observations are unlikely due to the small, average-viral-particle size. Histologically, these changes are difficult to track microscopically due to the lack of nuclei as platelet reference points; the post-activation, morphological platelet changes; and dramatic, aggregation-related shape changes that create an amorphous mass. Rapid thrombocyte/platelet responses have been conserved phylogenetically in vertebrates[307]. Depending on the agonist, the initiation of zebrafish thrombocyte/platelet aggregation occurs within 20 s, plateaus over 1–3 min, and involves conserved α_{IIb} receptor subunits[307]. Thrombotic plug formation is stabilized and counterbalanced by the disaggregation of platelets and fibrinolysis. Platelets migrate and help to initiate immune sterilization, tissue repair, and scar formation [195, 308–311]. In critically ill patients with a significant viral load, these platelet-mediated immune responses may be more rapid and severe.

5 Consequences of platelet-viral responses

Major and life-threatening events associated with SARS-CoV-2 infections are common. A number of coagulation/thrombotic disorders are linked to COVID-19 infections including stroke, disseminated intravascular coagulation, pulmonary embolisms, acute respiratory distress syndrome (ARDS), sepsis-induced coagulopathy, local microthrombi, venous thromboembolism, arterial thrombotic complications, and thrombo-inflammation connected to disease progress, severity, or mortality[312–315]. One tragic example in the young is the association between COVID-19-related strokes and amputations [316–326]. Platelets can play an integral role at any stage of coagulation/thrombotic disorders.

Like other viral infections, asymptomatic disease is present in a significant but hard-to-identify fraction of affected individuals. In most symptomatic patients, a 1-week, self-limiting, viral respiratory disease often occurs [221, 327–333]. This phase of disease may end when neutralizing-, anti-viral-, T-cell-, and antibody immunity is engaged. If cross-reactivity occurs with other serum-based coronavirus antigens, immunoglobulin (Ig)M-, IgA-, and IgG-type virus-specific antibody levels can be important indicators of population immunity against this disease. In the case of extreme viral load during the first infection course or repeated exposure to virus that can occur in healthcare workers, the rate and extent of this response can be an important factor for severity and localization of disease[221, 327–332]. These stage- and extent-of-disease responses will influence the development of any high-specificity and a high-accuracy serological assay that is easy to use, reliable, reproducible, and critical to the successful measurement of COVID-19 immunity in our global population [334–353].

5.1 Platelet FcγRIIA (CD32a) receptors

As COVID-19 progression becomes more severe, antibodies that platelet FcγRIIA (CD32a) receptors can recognize may be generated [259, 354] (Fig. 4). FcγRIIA—known to recognize aggregated IgG complexes [355]—can contribute to $\alpha_{IIb}\beta_3$ activation and aggregation [356]. Aggregated IgG complexes can trigger the release of microvesicles, as can happen with H1N1-virus (swine flu) exposure [354, 356]. FcγRIIA receptors contribute to the production of COVID-19-related autoantigens also amplified by platelet microparticle release. This may underlie the formation of potent inflammatory components: the microparticle-associated immune complexes [357]. Similarly, the complexes appear to play a role in heparin-induced thrombocytopenia, a prothrombotic disorder mediated by complexes between platelet factor 4 (PF4) and heparin or other polyanions [358]. This risk of thrombosis may extend beyond exposure to heparin implicating other PF4 partners as well [358]. Platelet FcγRIIA receptors are capable of recognizing multiple antibody subclasses that include IgM, IgA, and IgG [359–364]—all produced by patients with COVID-19 [221, 327, 339, 342, 365].

5.2 Thrombocytopenia

Thrombocytopenia initially has been associated with severe COVID-19 adverse outcomes and mortality [297, 300, 304–306, 366]—possibly due, in part, to the consumption of platelets during the ongoing platelet-virus interaction process. *However, others have not found thrombocytopenia to be an infallible predictor of disease progression or adverse outcome* [367]. Decreases in platelet numbers have been associated with poor outcomes in multiple studies [306, 368–374]. Platelet changes can be associated with neutrophil extracellular traps—extracellular webs of chromatin, microbicidal proteins, and oxidant enzymes that are released by neutrophils to contain infections[242, 375, 376]. Some of these conserved higher-orders in response to microorganisms can lead to clustering around pathogens

that encapsulates them, properties which are also observed in thrombocytes of lower vertebrates [377–379].

5.3 Thrombocytosis

Using ultrasound-guided, minimally invasive autopsy to assess COVID-19 pulmonary involvement revealed the presence of fibrinous thrombi in alveolar arterioles along with a high density of alveolar megakaryocytes that likely contribute to thrombocytosis [222] [380]. With accompanying elevations in interleukin (IL)-1 and IL-6 in patients with COVID-19 [297, 370, 381–393], this may lead to thrombocytosis due to inflammation-induced platelet activation, inflammasome formation, and IL-1-laden microvesicle release (Fig. 4), all of which are processes that associate with consumption-based feedback. IL-6 elevates platelet production in the metastatic ovarian-cancer setting when generated by tumors that stimulate liver-based thrombopoietin production [4, 10]. Thrombopoietin, in turn, stimulates megakaryocyte/platelet thrombocytosis in the bone marrow [4, 10]. By contrast with COVID-19, pathogenic T cells and inflammatory monocytes associated with large amounts of IL-6 secretion can incite an inflammatory (cytokine) storm, which may be curbed through treatment with tocilizumab, a monoclonal antibody treatment that targets IL-6 pathways [380].

5.4 Aspirin

Controversy exists over the use of aspirin in patients with COVID-19 particularly in those who are pregnant and display skin reactions [394–396]. In other studies, aspirin has shown benefit when combined with rivaroxaban (dual pathway inhibition) for the prevention of ischemic events in patients with cardiovascular- and peripheral-artery disease [397] [398]. Whether platelet consumption is the body's way of isolating these diseases or immediately mitigating the spread of COVID-19 remains to be determined. In other studies, anti-coagulation effects were associated with improved COVID-19 survival after adjusting for mechanical ventilation.

5.5 Role of platelets in complications of viral infection

ARDS is among the most worrisome of all responses to SARS-CoV-2 infections [220, 221] (Fig. 5). Platelets can promote or contribute to all stages of ARDS development and progression, including thrombosis, inflammation, angiogenesis, and fibrosis [219–221, 223, 313, 366, 399–402]. Platelets can also help initiate many of the inflammatory responses in the lung. Endothelial-cell death and retraction can trigger platelet activation and granule release [219–221,

403], the latter of which includes many of the proinflammatory molecules that contribute to immune-cell infiltration and cytokine storming [27, 404–412].

Autopsies of COVID-19 patients have been difficult to achieve but they reveal many details of ARDS [220–222, 224, 413–418]. Certain reports suggest that in severe COVID-19 cases, platelets are centered within thrombotic responses with an absence of protective immune states [403, 419, 420]. As ARDS progresses, exudative, diffuse alveolar damage (DAD) occurs and can intensify the release of alveolar exudates to stimulate hyaline membranes, septal edema, and mild/moderate lymphocytic infiltration. This can lead to pleomorphic, alveolar, epithelial-cell alterations resulting from SARS-CoV-2 cytopathic effects, which then can cause diffuse epithelial desquamation. Epithelial cells can also develop distorted cytoplasm, large nuclei, eosinophilic nucleoli, giant cells, and squamous alveolar metaplasia. The release of platelet α-granule proteins can stimulate epithelial-cell- and endothelial proliferation and fibroblast invasion. Proliferative DAD has been characterized by disorganized fibrous tissue within alveolar septa while alveolar lumens can become severe with fibrinous thrombi[222]. These pulmonary changes are the result of severe epithelial injury and microthrombotic vascular phenomena[222].

5.6 Platelet contributions to cytokine storms

In patients with COVID-19, platelets can associate with SARS-CoV-2 RNA to become hyperactivated and can contribute to an eicosanoid storm [421] [422]. Hyperactivated platelets are characterized by proinflammatory granule release which includes C-X-C motif chemokines such as CXCL1 (GRO-α), CXCL4 (PF4), CXCL5 (ENA-78), CXCL7 (PBP, β-TG, CTAP-III, and NAP-2), CXCL8 (IL-8), and CXCL12 (also called stromal cell–derived factor-α) [171] (Fig. 4). Platelet α-granules that are C–C motif chemokines include CCL2 (MCP-1), CCL3 (MIP-1α), CCL5 (RANTES), CCL7 (MCP-3), and CCL17 (TARC); along with IL1-β, the platelet-activating factor acetylhydrolase, and lysophosphatidic acid [423]. In some cases, SARS-CoV-2-infected lung tissue may not be heavily infiltrated by CD20 + B cells, CD57 + NK cells, or lymphoid aggregates. By contrast, the number of CD4 + and CD8 + T cells may be few-to-moderate and may form small aggregates in patients with fibroproliferative DAD [222]. CD68 + macrophages populate alveolar spaces and sites of tissue remodeling in fibroproliferative areas. Some multinucleated, atypical giant-cells (CD68 + alveolar macrophages) [222] can amplify the production and release of factors that contribute to a cytokine storm [424–427]. In SARS-CoV-2-infected lung tissue ex vivo, platelets combined with resident and infiltrating immune cells led to the increased production of interferons IFNβ, IFNγ, IFNλ1, IFNλ2, and IFNλ3 as well as
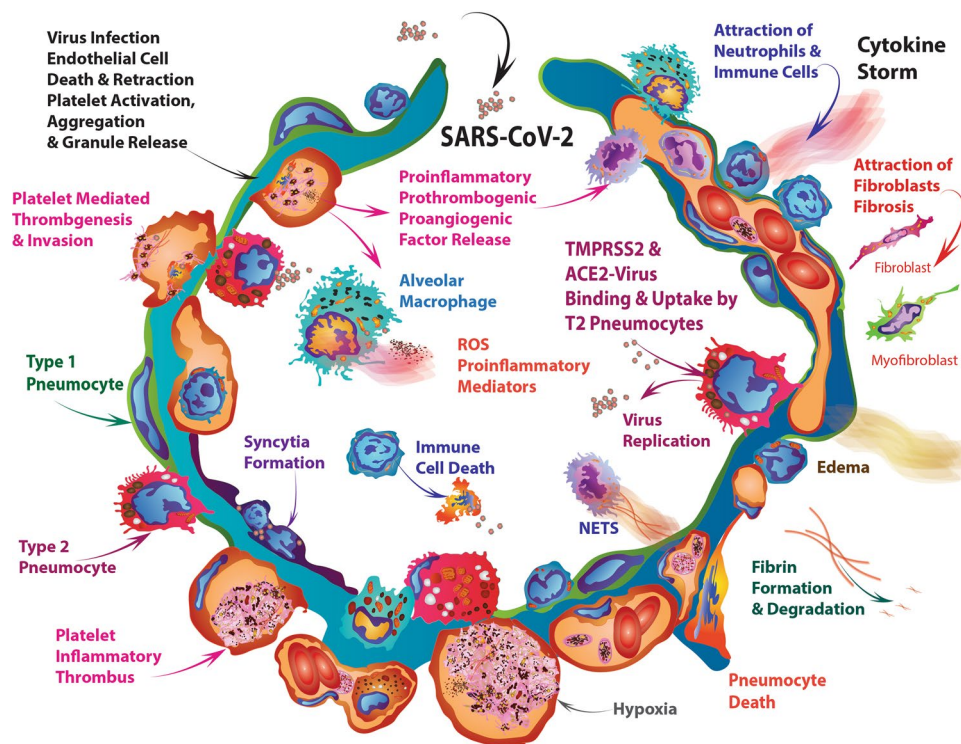
Fig. 5 SARS-CoV-2 in acute respiratory distress syndrome (ARDS). In contrast to type 1 pneumocytes, type 2 pneumocytes contain high levels of angiotensin-converting enzyme (ACE) and highly expressed transmembrane protease, serine 2 (TMPRSS2) –key targets for SARS-CoV-2 infection. The ensuing viral replication and vascular spread can trigger both vascular endothelial- and pneumocyte-cell death and matrix exposure that activates platelets. Pulmonary injury in SARS-CoV-2-induced COVID-19 can be amplified by many platelet-derived factors and bioactive processes[440]. Complete occlusion of blood vessels leads to hypoxia and additional damage. Acute respiratory distress and diffuse alveolar damage (DAD) can be induced by platelet factors and amplified by residential macrophages, neutrophils, and lymphocyte apoptosis. Platelets release cytokines and chemokines that also stimulate the production of residential, alveolar immune cells; recruitment of additional macrophages and neutro-phils; lymphocyte apoptosis; formation of reactive oxygen species (ROS); and increased inflammation. Vascular endothelial-cell damage resulting from viral damage and complement activation amplifies the platelet activation and increases permeability and inflammatory thrombus formation. Fibrin formation and fibrinolysis can also be activated, releasing fibrin degradation fragments. Blood-vessel changes can dominate while damage in the alveolar space remains relatively mild. Platelet-neutrophil extracellular traps (NETs) may also play a role in severe disease [441]. Damage that accelerates to the alveolar space becomes more severe with additional immune-cell-death-related NET formation. Platelets, along with increased permeability and edema, can contribute to any cytokine storm that ensues. Platelets can also contribute to recruitment and activation of fibroblasts and myofibroblasts, formation of fibrous tissue, and scarring

interleukins IL-1β, IL-6, IL-8, MCP1, MIP1α, RANTES, CXCL1, CXCL2, and CXCL5 [427].

5.7 Extrapulmonary disease

Platelets can also contribute to many of the extrapulmonary comorbidities related to ARDS [220–222, 402, 413–417]. In many cases, the extrapulmonary disease attributed to thrombotic axis comorbidities (such as hypertension and diabetes mellitus) often shows renal arteriolosclerosis, cardiomyocytes hypertrophy, myocardial fibrosis, focal glomerular sclerosis, liver steatosis, and cerebral microvascular disease [222]. COVID-19-induced shock and thrombotic lesion formation may also be associated with liver-based centrilobular congestion and acute kidney-tubular lesions. Syndromes secondary to SARS-COV-2 infection include systemic inflammation or shock linked to platelet activity associated with myositis, orchitis, lymphomononuclear myocarditis, and superficial perivascular mononuclear infiltrates in the skin.

Secondary platelet endothelial-cell-mediated changes in small vessels can include cell tumefaction, vessel wall edema, and fibrinoid alteration. Other secondary changes include fibrin microthrombi in the glomeruli, skin, testis, liver sinusoids, and heart; mesangial glomerulopathy; liver-based hyper-reactive Kupffer cells; spleen-based lymphoid hypoplasia; and brain-based reactive gliosis.

6 Summary and future directions

This paper describes the importance of platelet evolution and responses secondary to SARS-CoV-2 infection along with their likely role in the thrombotic and immune function of patients with COVID-19. As primordial life forms, viruses (particularly single-stranded-RNA viruses such as SARS-CoV-2) coevolved and diverged as did vertebrates as they adapted to major environmental selective pressures while emerging from an aquatic to a terrestrial environment. Invertebrate and vertebrate thrombocytes and immunocytes retained aggregation capabilities, coagulation enzymes, and phagocytic properties involved in virus immobilization and uptake; these evolved into an active open-canalicular system. Retention of a highly active and responsive cytoskeletal system of granule release and rapid migratory capacity sustained cellular responsiveness to microbial threats. Thrombocyte/platelet evolution developed and maintained receptor-based, pathogen-directed, recognition capabilities to identify viruses. This evolution was coupled with active, membranous vesicle production to increase surface contacts and the probability of interacting with virus particles. As receptor-based response times decreased significantly and diverged over time, a finely regulated balance between endothelial COX2/PGI$_2$- and platelet COX1/TxA$_2$ pathway enzymes emerged. Targeting platelet adenosine receptors may also have an impact on the COVID disease state [428]. Selective serotonin reuptake inhibitors (SSRIs) are also candidates for potential intervention [429]. As vertebrates coevolved with viruses, their platelets typically remained elongated and retained morphological support by a circular ring of microtubules that ultimately formed the mammalian platelet. As they gradually became smaller and evolved into plate-like discs, this maximized planar-surface interactions and provided a biophysical advantage by concentrating the numerous platelets produced each day toward the outer fluid-shear fields of flowing blood. Management of severe COVID-19 is likely to require case-specific considerations depending on viral-load exposure, clinical presentation, and assessment of circulating platelets, megakaryocytes, cytokines, immune cells, and antibodies [430–439]. Much remains to be discovered regarding the evolution and biological function of platelets including a consideration of the many emerging selective pressures involved with SARS-CoV-2- and other viral infections. We continue to evolve in a globally connected world of rapid transit and exchange, which allows for the rapid dissemination of diseases that can outpace our ability to quickly respond with therapeutic interventions. Having learned so much from our experience studying the role of platelets in cancer and metastasis, we have tried to bring new insights into their role in immune defense mechanisms. From this perspective, we recognize that a better understanding of the platelet biology involved in the viral immune response is critical to being prepared for the rapid development of lethal viral threats such as SARS-CoV-2—and those yet to evolve.

Declarations

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