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Review

Platelet Immune Interactions, Lifespan, and Senescence

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Abstract

In addition to their hemostatic functions, platelets play an essential role in immunologic interactions, which is confirmed by the observation of an increase in platelet counts in patients with immune-related thrombocytopenia and other autoimmune diseases after immunomodulatory treatment with intravenous human immunoglobulin concentrate. The mechanisms of action of this biological therapeutic option induce the development of therapeutic monoclonal antibodies, agonists, and antagonists that target the complex pathophysiology of the innate and adaptive immune systems. Platelets play an essential role in severe adenovirus infection and adenovirus-based vaccination. Activated platelets have a shorter lifespan and early senescence in many diseases. Laboratory findings, such as senescence-associated secretory phenotypes, may lead to new biologic options for developing remedies for particles of platelets, named senolytics. The causative factors influencing platelet lifespan were also discussed.

Keywords

Platelets; senescence; SASP; thrombin; immunoglobulin

1. Introduction

At the end of the 19th century, “small shapes” between red and white blood cells were observed by microscopy [1] and are now known as nonnucleated, multifunctional platelets and stem from nucleated bone marrow megakaryocytes. In the sixties of the 20th century, platelet senescence was discussed. Baldini demonstrated a twofold higher uptake of protein labeled by valine-C^{14} in 1–3 days by young platelets versus 3–6 days by old platelets [2]. McDonald observed that larger platelets were younger than smaller ones by comparing platelets from individuals with normal platelet counts and patients with low platelet counts induced by antiplatelet antibodies [3]. Shulman et al. reported that only young platelets were hemostatically effective [4]. Additionally, Karpatkin explained the removal of platelets from circulation by biochemical and functional heterogeneities with progression from young to old platelets [5]. In 1971, Karpatkin reported more megakaryocytes in patients with chronic idiopathic thrombocytopenia (ITP), systemic lupus erythematosus, or intravascular coagulation [6]. In 1972, he reviewed the findings titled “Human platelet senescence” [7]. Recently, platelet volumes have been reported to be smaller in patients recovering from ischemic stroke than in individuals suffering from stroke with poor outcomes [8]. These observations suggest different aging of platelets during their lifespan/senescence based on their functions in health and diseases.

The seminal clinical observation in two boys with thrombocytopenia, one with congenital immune deficiency Wiskott–Aldrich syndrome with hypogammaglobulinemia and thrombocytopenia and the other with an acquired severe treatment-refractory ITP and secondary hypogammaglobulinemia due to long-term immunosuppressive treatments, revealed that the boy with Wiskott–Aldrich syndrome exhibited a minimal increase in his platelet counts after each substitution of the human-derived immunoglobulin concentrate (IVIG) from thousands of healthy blood or plasma donors, which led to the idea to administer the same IVIG to the other boy with chronic refractory ITP, who exhibited a dramatic increase in platelet counts immediately after the administration of IVIG. This new phenomenon was confirmed in 13 consecutive children with ITP (Figure 1) [9], followed by clinical phase 1–3 studies in children and adults with ITP [10]. Similar beneficial effects of IVIG administration were observed in patients with other autoimmune disorders, such as dermatomyositis, Kawasaki syndrome, remitting-relapsing multiple sclerosis, systemic lupus erythematosus, intravascular coagulation, and Guillain–Barré syndrome [11]. Laboratory studies showed that the mechanisms of action of IVIG indicated the synergistic immunomodulation of the innate and adaptive immune systems [12, 13]. Additionally, the mechanisms of action of IVIG on the different components of the immune system led to the development of targeted monoclonal antibody therapies and other targeted cellular and humoral therapeutics. Biologically targeted immunotherapies progressively complement or replace classic immunosuppressive therapies for autoimmune and oncologic diseases. However, immunosuppression is still vital for attenuating the inflammatory side effects of new immunotherapies (i.e., cytokine storm).

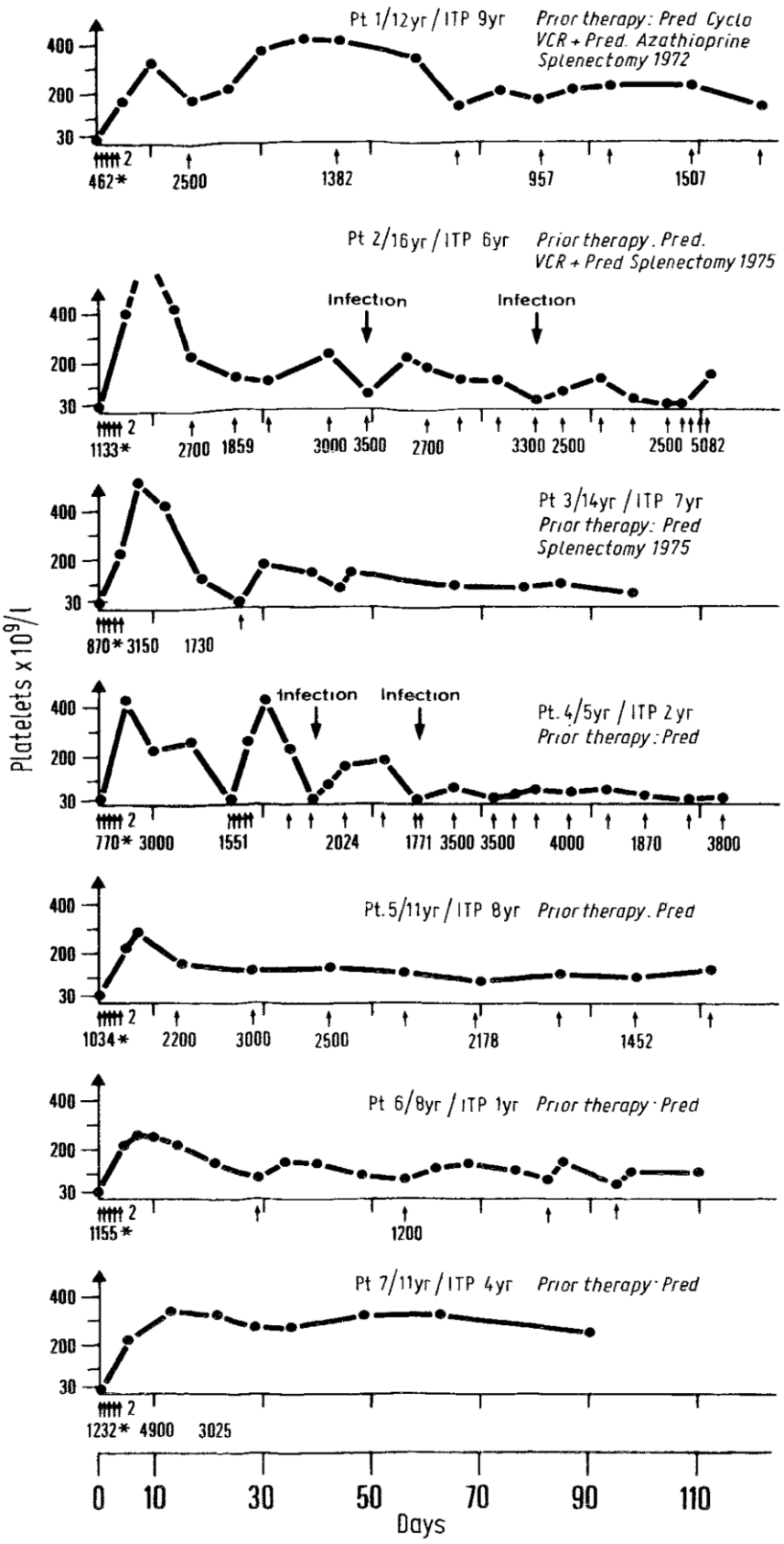

Figure 1 The Doors opener for IVIG Therapy.

The follow-up of 7 children suffering from idiopathic thrombocytopenic purpura, ITP, is taken from a Lancet 1981 paper (9). From a total of 13 consecutive children (six with newly diagnosed ITP

not shown) the seven children suffering from chronic intermittent ITP, three were splenectomized in order to remove part of the reticuloendothelial system, which would remove platelets. Patients 1 and 2 had bleeding episodes despite conventional, i.e. at time usual, immunosuppressive treatment. Of the four non-splenectomized children, prednisone resistance was present with platelet counts. 5-97 × 10^9/L for 6 months prior to IVIG transfusion (patient 4), two patients were prednisone dependent (patients 5 and 6), and one, patient 7, was healed during the protracted observation of several months. This observation did not retard to become confirmed by both pediatricians and docs caring for adults around the globe, and it made whole blood and blood plasma donation, on a voluntary base, an indispensable source for the much-needed stable blood product to purify IVIG. All consecutive patients with primary ITP demonstrated increases in platelet counts after IVIG administrations: Arrows indicate IVIG 0.4 g/kg body weight/day.

Platelet pathophysiology and ITP became models for biological interventions through IVIG and targeted treatments. The increased number of young platelets and their extended lifespan help protect patients from thrombocytopenic bleeding.

2. Hemostatic and Immunologic Components of Platelets and Their Interactions (Figure 2)

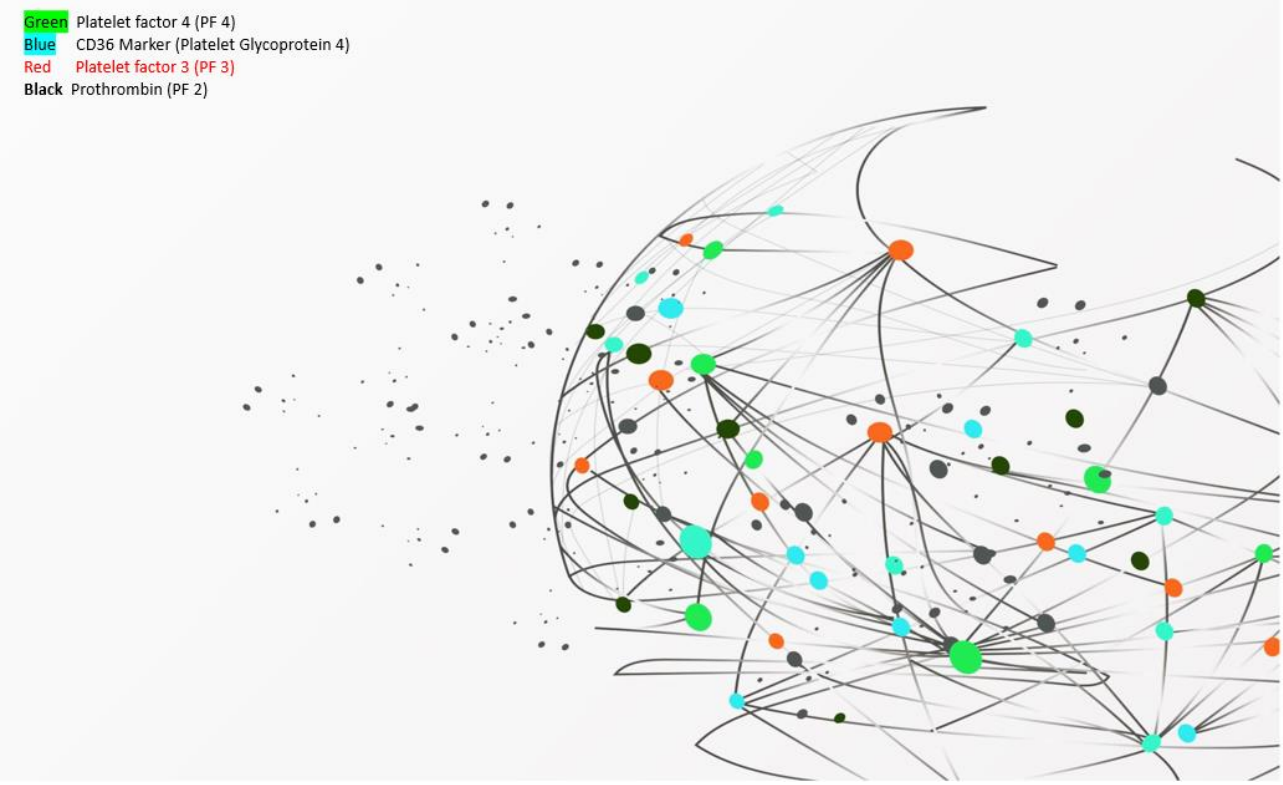

Figure 2 The Galaxy of Platelet Receptors.

The platelet surface with its receptors impinges on the suspending proteome, influencing our blood's hemostatic function.

Iatrogenic measures or viral infections must be scrutinized on their impact on one or the other platelet surface characteristics; anti-PF 4 antibodies are a hallmark of patients with heparin-induced thrombocytopenia. As a thrombospondin receptor, CD36 relays apoptotic signals in cancer metastasis. CD36, thus, is widely distributed in different cell types, and platelets join in the network,

kind of like a scavenger surface. Production of proinflammatory cytokines by inducing reactive oxygen species (ROS) – would platelets help shovel their graveyard or accelerate their senescence?

Since platelets have no nucleus (i.e., no nuclear DNA), it was supposed that no intracellular component of the platelet could receive information about the receptor-ligand interaction. This feature resembles immune complexes lodging outside the cell membrane [14]. However, three known thrombin receptors are detected in the coagulation functions of platelets: protease-activated receptor 1 (PAR1), PAR3, and PAR4. PARs are activated by proteolysis. Thrombin is an allosteric serine protease that is an essential effector of coagulation. It is produced at vascular injury sites and plays a critical role in the cellular response to blood-related diseases [15]. It binds to and cleaves the extracellular N-terminal domain of its cognate receptors.

Besides the platelet functions of hemostasis and tissue remodeling, immunomodulation by human immunoglobulin G (IgG) concentrate administration evoked new interactions and tasks of platelets synergistically [12, 13] within the whole complex network of the innate and adaptive immune systems. Platelets acquire their immune properties via transfer from megakaryocytes [16]. They interact with leukocytes, monocytes, phagocytes, and the complement cascade, activating adaptive T and B cells and their compounds [17]. Fc receptors of platelets [18] form immune complexes and platelet-leukocyte aggregates, immobilizing pathogens [19]. Different platelet receptors bind to many viruses, such as rotavirus via GP1a/11a, adenovirus via GP IIb/IIIa, CMV via TLR2, and EBV via CR2. Toll-like receptors (TLR) recognize and present bacteria to neutrophils [20], thereby inhibiting bacterial growth, activating bacteria via chemokines from platelet granules, and promoting phagocytosis by macrophages. Platelet TLR7 senses RNA influenza viruses, leading them to a neutrophile extracellular trap (NETosis) [21, 22].

Platelets store many chemokines and cytokines in their granules [23], which bind to cognate receptors at sites of inflammation, activate neutrophils, and increase adhesion by antibacterial proteins. The number of microvesicles may correlate with disease severity. Additionally, “stored” IgG in platelet vesicles neutralizes viruses [24]. Antimicrobial peptides and chemokines in platelets inhibit bacterial and fungal growth. Cytokine interleukin (IL)-1β from platelets can increase IL-1β production of macrophages, resulting in the opsonization and phagocytosis of pathogens [25]. Platelets contain RNA species in microvesicles, which induce immunomodulation. They have a pool of intact functional major histocompatibility complex (MHC) class 1 molecules for antigen presentation to CD8 T cytotoxic cells, which enables distinguishing young from old platelets as they lose their MCH-1 over time. MHC class 1 molecules on platelets and natural killer cells provide cytotoxicity toward virus-infected cells and tumor cells, forming coats around tumor cells, which protects them from destruction and drives the tumor toward a more migratory evasion (metastasis spreading). Therapeutic antibodies diminish antitumor activity [26, 27].

As an example of interactions, CD 40L/CD42 present on megakaryocytes and platelets amplifies the immune response. Ligation stimulates the secretion of IL-12 from antigen-presenting cells (dendritic cells), which process antigen presentation via neonatal Fc receptors. IL-12 activates CD4Th1, CD8, natural killer cells, T regulatory cells, and indirectly B cells. Adaptive T or B cells, the former with the learning ability to conserve memory to instruct the B memory cells for antibody production, exhibit an extensive range of survival times by preserving memory.

The highly cationic platelet factor 4 (PF4) is an additional platelet-associated receptor. As number 4 indicates, PF4 is a tetramer [28]. PF4 is a target in the shooting path of autoimmune disease, mediated explicitly by platelet-activating anti-PF4 antibodies. They form IgG-PF4 immune

complexes predominantly on the platelet surface, spilling over to monocytes and neutrophils [29]. Monocytes and neutrophils often exchange surface properties with platelets [30].

Based on these findings, medicine has more recently begun to understand vaccine-induced immune thrombocytopenia and thrombosis, an untoward effect of vaccination, mainly when achieved with the help of adenovirus. Chemokine PF4 (CXCL4-PF4) is essential in triggering NETosis in patients with severe COVID-19. Platelet hyperactivity in SARS-CoV-2 contributes to immune thrombosis and thrombocytopenia via TLR7, TLR9, and cross-reacting antibodies. In some patients with vaccine-induced immune thrombocytopenia and thrombosis, platelet-activating anti-PF4 antibodies remain active for over a year [31].

3. Platelet Lifespan and Aging in Balanced and Imbalanced Immune Responses

Under physiological conditions, shape change is the first sign of platelet aging [32]. According to Karpatkin, the linear curve may represent the balanced lifespan in healthy individuals, and the exponential curve may relate to the high rate of activated platelets in patients with an imbalanced immune response and early elimination, which is responsible for immune thrombocytopenic purpura [7]. Thus, thrombocytopenia reflects a model disorder for many other immune and autoimmune diseases.

Recent studies have aimed to understand age-related changes within platelets as they circulate from the bone marrow to the bloodstream [32, 33]. Platelets typically survive for 10 days. However, the lifespan of platelets can be reduced in some disorders. During their lifespan, platelets lose sialic acid from their glycans. As a marker of the aging of platelets, lifespan is mainly determined by platelet membrane surface sialic acid [34], the sugar residues of glycoproteins desialylated by the enzyme neuraminidase [35] released from platelet mitochondria and granules. This may make them vulnerable to complement, as known by neuraminidase-treated red blood cells [36]. Additionally, neuraminidase is involved in TLRs and matrix metalloproteinase 7 signaling [37, 38], which plays an important role in thrombotic thrombocytopenic purpura as an adjuvant therapeutic substitution, as known from the inborn deficiency of ADAMTS 13.

Another marker of platelet aging is the reduction of RNA and protein levels. This appears to be a property of platelet aging. Additionally, surface HLALAHLH-1 loss over time distinguishes young from old platelets [39]. However, specific biomarkers that can be used to explore these aging reactions and their loss of function are not yet available.

4. Clearance of Platelets

Clearance of desialylated platelets from the circulation is mediated by blood macrophage receptors [40, 41]. They are recognized by liver cells, such as Ashwell-Morell receptors in hepatocytes and Kupffer cells. In healthy humans, spleen macrophages are less active in platelet elimination. However, more active clearance is observed in opsonized platelets with glycoprotein antibodies in patients with ITP. Reduced platelet lifespan is observed in patients with primary or secondary immune deficiency, acquired disorders and imbalanced immune response (autoimmune and cancer diseases), viral or bacterial infection, sepsis with platelet aggregation (thrombosis), endothelial injury, and other inflammation causes.

Early activation of young platelets may lead to thrombocytopenia, known as “suicidal” platelet elimination. The pathophysiology as mentioned earlier leads to biologic therapeutic approaches,

such as polyclonal human-derived IgG concentrate, the multitude of monoclonal antibodies, immunologic agonists, or antagonists [11], and stimulation of megakaryocyte growth factors (thrombopoietin receptor agonists) [42].

5. Beneficial and Harmful Senescent Cells, Senescence-Associated Secretory Phenotypes (SASP), and the Development of Biologic Remedies and Vaccines Against Early Aging (Senolytics)

Senescent cells exist in an irreversible replication arrest, are metabolically active (Figure 3) and resistant to apoptosis [43] (Figure 4), and express SASP, including chemokines and other factors [44, 45]. In young and healthy individuals with an intact immune system, SASP may promote tissue remodeling against inflammation and tumor suppression. Conversely, in older individuals with immune dysfunction (autoimmunity and cancer), the persistence of senescent cells is harmful, leading to chronic inflammation and tumor progression. The recent development of aging cells and their SASP is a fascinating area of research.

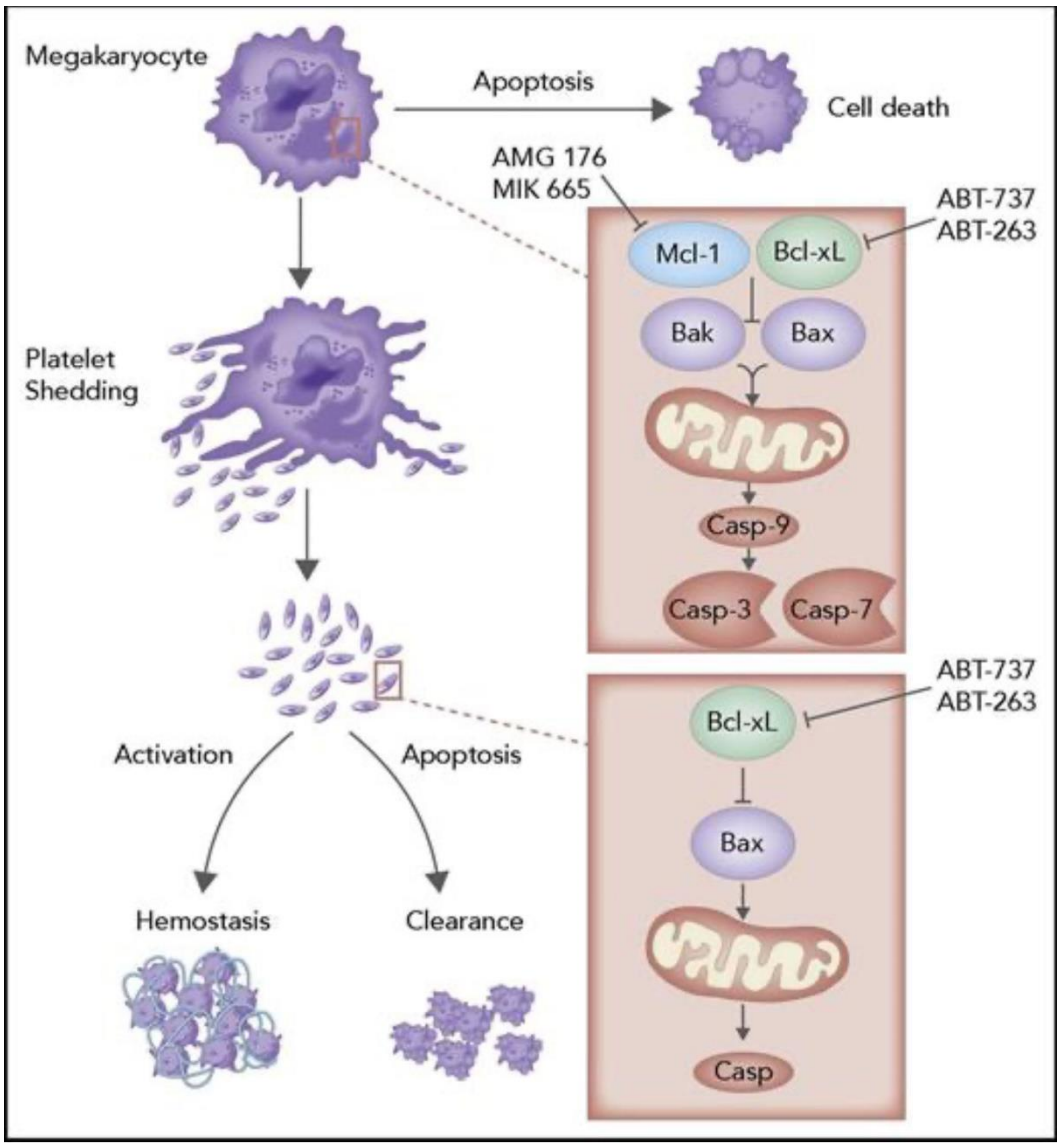

Figure 3 Platelets Survive the Laws of Apoptosis.

This drawing is from a publication in a BLOOD Spotlight from February 2018 (McArthur, K., Chappaz S, Kile, BT: Apoptosis in Megakaryocytes and Platelets: the life and death of a lineage https://doi.org/10.1182/blood-2017-11-742684) on apoptosis, a question which burned us under the nails became finally clear:

Megakaryocytes and platelets both depend on the mitochondrial apoptosis pathway governed by the BCL-2 family of caspases. (BCL-2, BCL-XL, MCL-1, BCL-W, and A1). Activation of the pathway induces clearance of megakaryocytes followed by platelet shedding (right portion of figure). Important questions remain as to how apoptosis is initiated in these cells at a steady state and in response to pathophysiological insults.

On the left half, the authors depict the healthy life course of platelets, and on the right portion, many biologicals impacting apoptosis (is this a complete set, or are there more?) are listed. We assume that apoptosis is not a vital cell death factor for platelets, given their relatively short survival (see also Figure 4).

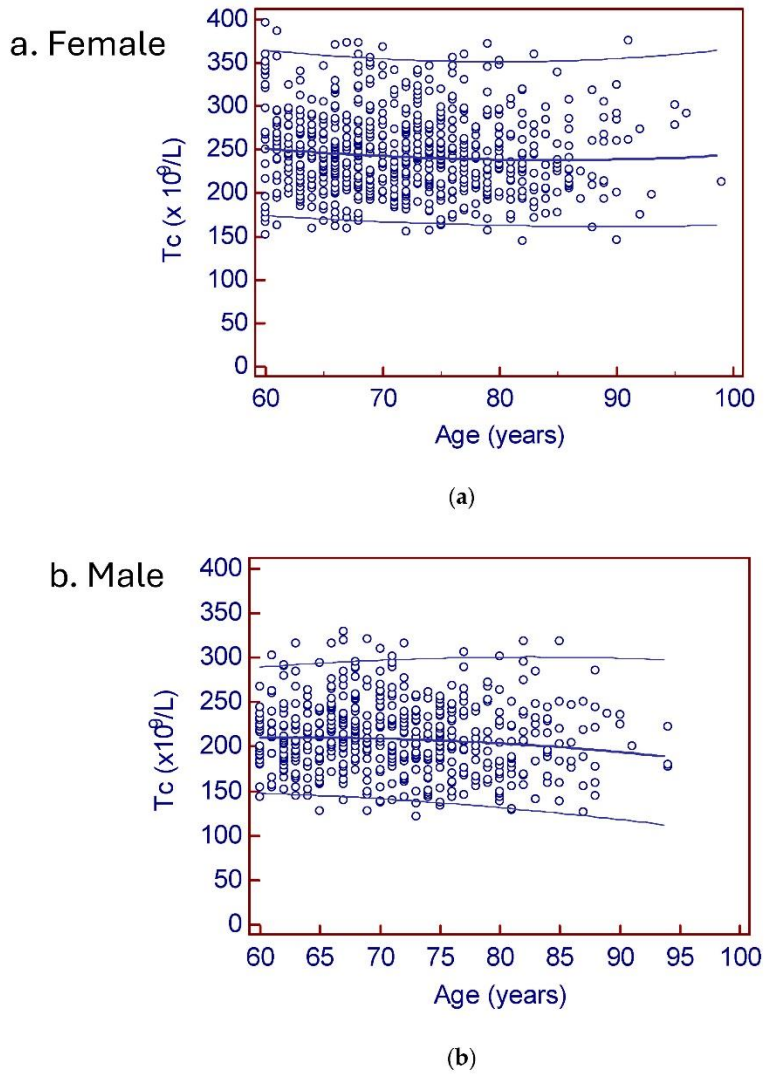

Figure 4 Platelet Reference Intervals Escape Senescence. Figure 4 is a copy/paste from the article of Wolfgang Hermann et al.

Platelet counts with age-stratified values drawn from the SENIORLABOR Study conducted on 1447 senior citizens in the Bern, Switzerland region. The regression analysis shows that as we age, we maintain our platelet pool: the 2.5th to 97.5 percentiles and the medians (thicker lines) bend only slightly in >90-year-old males. Longevity escape velocity at its best.

The deceleration and acceleration of cellular and tissue senescence are the aims of developing therapeutic senolytics and respective vaccines [46]. Eliminating senescent cells/SASP is demonstrated by immune suppression and chemotherapy (i.e., rapamycin) and is a feasible therapeutic option for developing senolytic drugs. Additionally, efforts have been made to engineer targeted vaccines against the senescence of cells/tissues for age-related diseases, inflammation (autoimmunity), and cancer (neoantigens). Using proteomic and bioinformatic methods to define selectively killing subsets of senescent cells/SASP leads to such senolytic products [47]. Genomic instabilities and epigenetic alterations in disease development are key mediators targeting disease-related senescence associations (i.e., senescent cell and humoral antigen). One major hindrance is that the targets may involve healthy components, cells, and tissues essential for survival. For prevention and therapy, the targets of senolytics and vaccines must express high antigen immunogenicity in senescent cells and tissues, which activate the innate and adaptive immune systems to achieve healthy aging.

In the direction of senolytics, published examples in health or disease are the elimination of senescent cells, which are emerging targets for diseases of aging [48, 49], inhibition of IL-1β (i.e., in lung cancer) [50], and targeting T cell aging [51] and CAR-T cells, which reverse senescence-associated pathologies [52, 53]. Platelet-derived SASP may play an interactive role as therapeutics (senolytics) in health [54, 55] and disease [56].

One of the first therapeutics redirected to senolytic drugs is the inhibitor of degranulation of neuraminidase (the antiviral drug oseltamivir, Tamiflu®) or canakinumab, an IL-1b inhibitor. A biologic monoclonal antibody may efficiently treat chronic inflammatory and autoimmune diseases associated with immune senescence by genetic, environmental, and immunological factors, such as diabetes type 2 with transformed transforming growth factor-beta [57]. However, the exact causative events of distinct genomic backgrounds are not well known.

6. Discussion

Platelets are characterized by elimination when activated. This review summarizes some platelet components and their functions (Figure 5). In addition to the hemostatic function, platelets interact with the immune system. In the future, the immune response, together with the interactions and short life of platelets, might play an important role in the ongoing discussion of living factors, such as climate change, neurologic steering related to platelet senescence, human activity-related exerkines, foreign environmental factors, and transplantation.

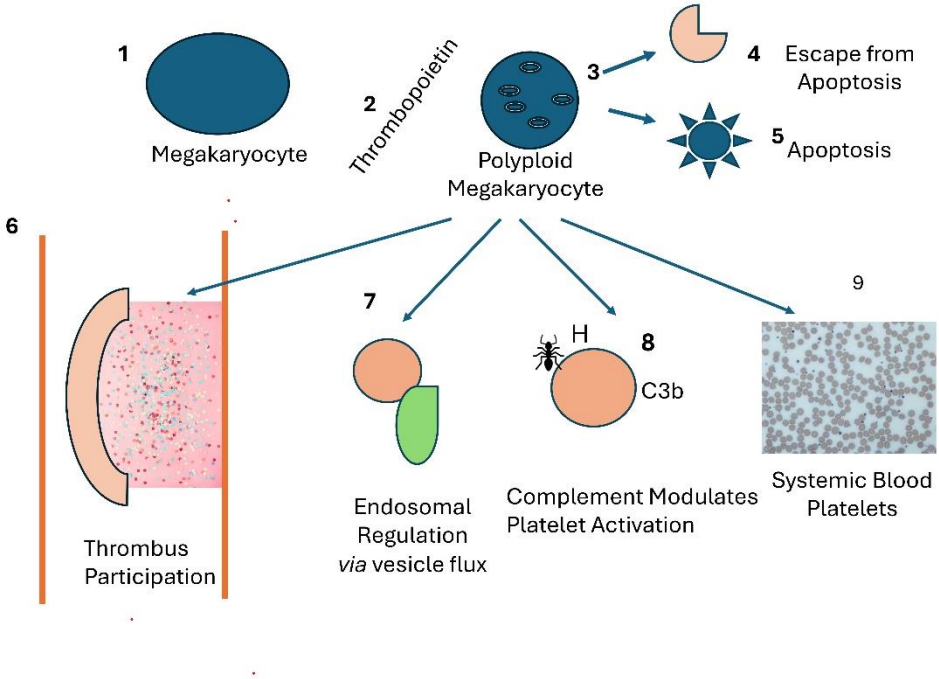

Figure 5 Bone Marrows' Megakaryopoiesis and further platelet fate.

The nine stages of the life cycle of a blood platelet. In **1,** the bone marrow platelet progenitor called megakaryocyte with its single nucleus shows up in a bone marrow smear. Under the action of **2** thrombopoietin, endomitosis announces the release of platelets: a single megakaryocyte sets thousands of platelets free upon a still intra-medullary series of remodeling phenomena (**3** and **4**). Apoptotic Escape, as shown in **5**, may happen at this stage, but further studies are needed (see also Figure 2). **6** Released platelets going immediately at work, here sketched by their participation in thrombus formation – in health, platelets may cooperate with endothelial cells sealing blood vessels. **7** Transmembrane proteins, as the recently identified CD36 is, are localized on platelets as well and make them part of the reactive oxidative stress (ROS) injury and inflammatory signaling systems (see also Figure 5). **8** Quite recently, and symbolized here by an ant, one needs to see platelets as participants in the complement system, be it by activating, regulating or downplaying activity; complement factor H regulates platelet activation via its C-terminal moiety. **9** Blood platelets in a blood smear of platelet concentrates destined for transfusion – a therapeutic powerhouse.

A reference interval of platelet survival in days or lymphocyte survival in weeks is unnecessary because individual cell clones may be subject to epigenetic control or recruitment to combat infectious agents. Flow cytometry analyses have revealed that platelets sense immune cues from the organism and act as regulators of the body's inflammatory response [58, 59].

6.1 Climate Change

The effects of climate change on human platelets are still unexplored. Still, we must remember that the Urban Heat Island Index in metropolitan areas invites the urban climatology community not to forget the well-being of blood cells, including platelets. The Global Historical Climatology Network provides an understanding of platelet senescence [60].

Some natural phenomena have turned out to be wrong. Recent studies on apoptosis (programmed cell death to eliminate unwanted cells) from Santa Barbara, CA, USA, have shown that platelets do not comply with cell death through apoptosis [61]. Feedback, propagation, and noise in apoptotic signaling suggest that some cells—platelets excluded—could escape self-amplifying death as apoptosis is defined.

6.2 Steering of the Central Nervous System (Figure 6)

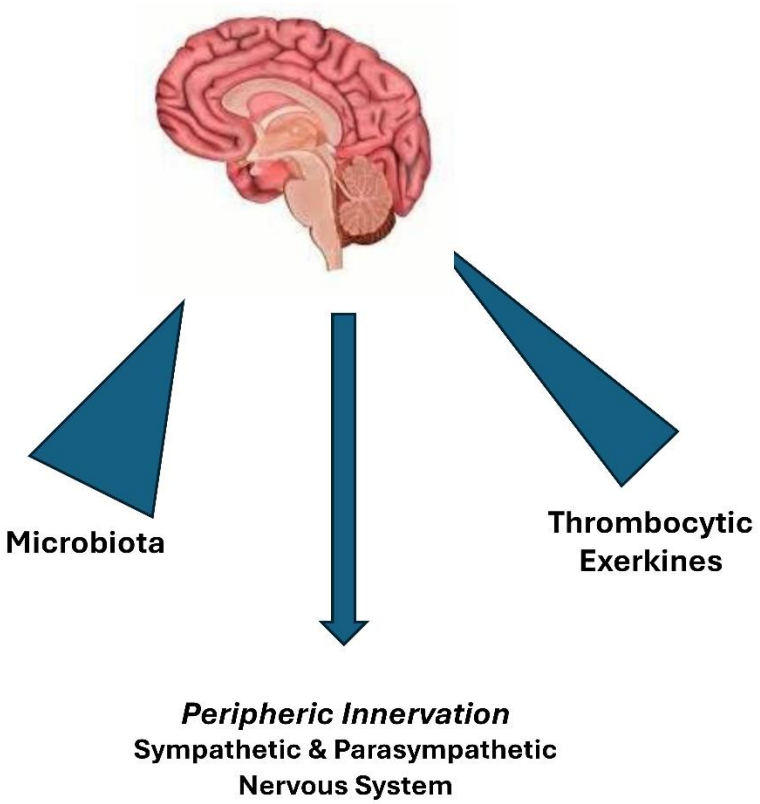

Figure 6 Platelet Biologicals Send Messages to the Brain: SASP at the Doorstep of Science.

Since the brain as a communicator with microbiota became in the limelight, research began to scan around the body to find other communicators. While writing this report, we found evidence in the literature that the platelet pool is also connected to the brain, and the authors termed the biologicals to become involved EXERKINES. We ignore why a putative nomenclature community chose this name, but for now, we use 'exerkine' to designate the cytokine produced by platelets to target the brain. A response of the brain to the peripheral nervous system seems mandatory.

Recently, neurologic steering of the immune response has been discovered. Two groups of neurons in the vagus nerve respond to proinflammatory and anti-inflammatory immune signals, each endowed with different degrees of immunosenescence. These neurons send messages to the brain, allowing it to monitor and modify the immune response. However, what the brain sends back to the immune system remains to be elucidated [62, 63]. The experiments, which were conducted in laboratory mice, require confirmation but remain spectacular.

6.3 Exerkines

Factors secreted upon exercise (jogging, intense physiotherapy, tennis, and rowing) into the circulation emerge as possible mediators of the beneficial effects of physical activity on brain aging. Over the past decades, hundreds of exerkines released from the skeletal muscle, heart, liver, adipose tissue, brain, and gut have been identified, and some exerkines, such as FGF21, IL-6, and adiponectin, are now being exploited as potential drugs in clinical studies. However, the source and identity of exerkines remain unclear. Recently, evidence has shown that an antigenic exercise is secreted by platelets [64]. Platelets are activated by exercise and are required for the exercise-induced increase in hippocampal precursor cell proliferation in aged mice. Furthermore, increasing the systemic levels of the platelet-derived exerkine CXCL4/PF4 reduces age-related regenerative and cognitive impairment in a hippocampal neurogenesis-dependent manner. These findings highlight the role of platelets in mediating the rejuvenating effects of exercise during physiological brain aging.

6.4 Foreign Materials Impinging on Platelets

Another aspect is the impact of plastics, rubber, and other environmental materials. Platelet participation in thrombus formation, when microplastics are engaged, is an upcoming concern in healthcare [65]. The foresight of scientists interested in meteorology [66] put evidence-based policy at the top of working group activities mandated by the Intergovernmental Panel of Climate Change (www.ipcc.ch). Histological microscopic findings revealed that some thrombi become entangled with pollutive or amorphous materials, such as polyvinyl chloride (C_2H_3Cl) (www.plasticsrecycling.com), microplastics [67], and polyethylene. Polyvinyl chloride is usually used in construction, whereas polyethylene is used in bottles and shopping bags. Polyamide 66 is used in textiles and other fabrics. Not surprisingly, D-dimer levels become elevated in subjects with plastics in their thrombi.

6.5 Solid Organ Transplantation and Platelets

The rapid immunological progress of knowledge and contributions of platelets to organ recipients' welfare cannot be overlooked. Successful CRISPR-conditioned pig organ transplants that offer hope to human patients (i.e., xenotransplantation) are currently in the limelight of medicine. Gene editing holds immense promise for more efficient and affordable techniques. CRISPR-Cas9 is a gene-editing technology that is in the process of being approved by health authorities. Gene-edited pigs are making significant progress toward becoming sources of kidneys or livers for human transplantation (Powell Alvin, April 16, 2024, in The Harvard Gazette). In March 2024, a genetically modified pig kidney was transplanted into a 62-year-old male in Boston, marking the first in a long-struggling field, with surgeons at the Massachusetts General Hospital (USA) succeeding in applying the CRISPR genome edition. The pig genome contained as many as 69 gene edits that were chosen to avoid rejection of the xenograft by the human recipient. Nanoparticle delivery systems will serve as a solid pillar, and target cells will be injected into the organism subjected to gene editing. The pig von Willebrand factor can aggregate human platelets spontaneously by binding to the GP1b receptor, leading to postreperfusion thrombocytopenia [68]. Unexpected challenges lie ahead when using this technique, similar to when using drugs such as senolytics. So far, human results with

pig xenotransplantation have provided a bright future. However, we must remain aware of the complexities of balancing scientific progress, including immune responses.

In conclusion, platelets are part of the SASP senescent cell family in addition to their known functions.

Author Contributions

Urs Nydegger suggested this review, mainly wrote the texts 6. Discussion and created/chosed the Figures 2-6. Paul Imbach mainly wrote the title, the abstract and the texts of chapters 1–5. Both authors discussed all aspects of the article.

Competing Interests

The authors have declared that no competing interests exist.

References

1. Hayem G. Du purpura. Presse Med. 1895; 233-235.
2. Baldini M, Costea N, Dameshek W. The viability of stored human platelets. Blood. 1960; 16: 1669-1692.
3. McDonald TP, Odell Jr TT, Gosslee DG. Platelet size in relation to platelet age. Proc Soc Exp Biol Med. 1964; 115: 684-689.
4. Shulman NR, Watkins Jr SP, Itscoitz SB, Students AB. Evidence that the spleen retains the youngest and hemostatically most effective platelets. Trans Assoc Am Physicians. 1968; 81: 302-313.
5. Karpatkin S. Heterogeneity of human platelets. Metabolic and kinetic evidence suggestive of young and old platelets. J Clin Investig. 1969; 48: 1073-1082.
6. Karpatkin S, Garg SK, Siskind GW. Autoimmune thrombocytopenic purpura and the compensated thrombocytolytic state. Am J Med. 1971; 51: 1-4.
7. Karpatkin S. Human platelet senescence. Annu Rev Med. 1972; 23: 101-128.
8. Zheng YY, Wang L, Shi Q. Mean platelet volume (MPV) and platelet distribution width (PDW) predict clinical outcome of acute ischemic stroke: A systematic review and meta-analysis. J Clin Neurosci. 2022; 101: 221-227.
9. Imbach P, Barandun S, D'Apuzzo V, Baumgartner C, Hirt A, Morell A, et al. High-dose intravenous gammaglobulin for idiopathic thrombocytopenic purpura in childhood. Lancet. 1981; 1: 1228-1231.
10. Imbach P. Antibody therapy: The clinical translation of intravenous Immunoglobulins from Substitution—immunomodulation—monoclonal immunotherapy. Berlin, Heidelberg, London, New York: Springer Verlag; 2019. pp. 1-11.
11. Imbach P. Chapter 4: Manual of Intravenous and Subcutaneous IgG: Indications in Autoimmune Diseases in Antibody therapy. In: Substitution—immunomodulation—monoclonal immunotherapy. Berlin, Heidelberg, London, New York: Springer Verlag; 2019. pp. 35-60.
12. Imbach P, Lazarus AH, Kühne T. Intravenous immunoglobulins induce potentially synergistic immunomodulations in autoimmune disorders. Vox Sang. 2010; 98: 385-394.

13. Lazarus AH. Chapter 6: Mechanisms of Action and Immunomodulation by IVIg in Substitution—immunomodulation—monoclonal immunotherapy. Berlin, Heidelberg, London, New York: Springer Verlag; 2019. pp. 73-82.
14. Spycher MO, Nydegger UE, Luescher EF. The calcium-dependent neutral protease of human blood platelets: A comparison of its effects on the receptors for von Willebrand factor and for the Fc-fragment derived from IgG. Adv Exp Med Biol. 1984; 167: 241-251.
15. Heuberger DM, Schuepbach RA. Correction to: Protease-activated receptors (PARs): Mechanisms of action and potential therapeutic modulators in PAR-driven inflammatory diseases. Thromb J. 2019; 17: 22.
16. Levin J. The evolution of mammalian platelets. In: Platelets. London, UK: Academic Press; 2019. pp. 1-23.
17. Maouia A, Rebetz J, Kapur R, Semple JW. The immune nature of platelets revisited. Transfus Med Rev. 2020; 34: 209-220.
18. King M, McDermott P, Schreiber AD. Characterization of the Fc γ receptor on human platelets. Cell Immunol. 1990; 128: 462-479.
19. McKenzie SE, Taylor SM, Malladi P, Yuhan H, Cassel DL, Chien P, et al. The role of the human Fc receptor Fc γ RIIA in the immune clearance of platelets: A transgenic mouse model. J Immunol. 1999; 162: 4311-4318.
20. Levi M. Platelets in critical illness. Semin Thromb Hemost. 2016; 42: 252-257.
21. Koupenova M, Corkrey HA, Vitseva O, Manni G, Pang CJ, Clancy L, et al. The role of platelets in mediating a response to human influenza infection. Nat Commun. 2019; 10: 1780.
22. Koupenova M, Vitseva O, MacKay CR, Beaulieu LM, Benjamin EJ, Mick E, et al. Platelet-TLR7 mediates host survival and platelet count during viral infection in the absence of platelet-dependent thrombosis. Blood. 2014; 124: 791-802.
23. Bakogiannis C, Sachse M, Stamatelopoulos K, Stellos K. Platelet-derived chemokines in inflammation and atherosclerosis. Cytokine. 2019; 122: 154157.
24. Schrottmaier WC, Salzmann M, Badrnya S, Morava S, Luik AL, Kral-Pointner JB, et al. Platelet-stored antibodies potently diminish viral infection in vitro and in vivo. Acta Physiol. 2019; 227: 187.
25. Kraemer BF, Campbell RA, Schwertz H, Cody MJ, Franks Z, Tolley ND, et al. Novel anti-bacterial activities of β-defensin 1 in human platelets: Suppression of pathogen growth and signaling of neutrophil extracellular trap formation. PLoS Pathog. 2011; 7: e1002355.
26. Placke T, Kopp HG, Salih HR. Modulation of natural killer cell anti-tumor reactivity by platelets. J Innate Immun. 2011; 3: 374-382.
27. Gasic GJ, Gasic TB, Stewart CC. Antimetastatic effects associated with platelet reduction. Proc Natl Acad Sci U S A. 1968; 61: 46-52.
28. Warkentin TE. Platelet-activating anti-PF4 disorders: An overview. Semin Hematol. 2022; 59: 59-71.
29. Jungi TW, Spycher MO, Nydegger UE, Barandun S. Platelet-leukocyte interaction: Selective binding of thrombin-stimulated platelets to human monocytes, polymorphonuclear leukocytes, and related cell lines. Blood. 1986; 67: 629-636.
30. Middleton EA, He XY, Denorme F, Campbell RA, Ng D, Salvatore SP, et al. Neutrophil extracellular traps contribute to immunothrombosis in COVID-19 acute respiratory distress syndrome. Blood. 2020; 136: 1169-1179.

31. Schönborn L, Seck SE, Thiele T, Kaderali L, Hoffmann T, Hlinka A, et al. Long-term outcome in vaccine-induced immune thrombocytopenia and thrombosis. J Thromb Haemost. 2023; 21: 2519-2527.
32. Aslan JE, Itakura A, Gertz JM, McCarty OJT. Platelet shape change and spreading. Methods Mol Biol. 2012; 788: 91-100.
33. An O, Deppermann C. Platelet lifespan and mechanisms for clearance. Curr Opin Hematol. 2024; 31: 6-15.
34. Goswami K, Koner BC. Level of sialic acid residues in platelet proteins in diabetes, aging, and Hodgkin's lymphoma: A potential role of free radicals in desialylation. Biochem Biophys Res Commun. 2002; 297: 502-505.
35. van der Wal DE, Davis AM, Mach M, Marks DC. The role of neuraminidase 1 and 2 in glycoprotein Ibα-mediated integrin αIIbβ3 activation. Haematologica. 2020; 105: 1081-1094.
36. Nydegger UE, Fearon DT, Austen KF. Autosomal locus regulates inverse relationship between sialic acid content and capacity of mouse erythrocytes to activate human alternative complement pathway. Proc Natl Acad Sci U S A. 1978; 75: 6078-6082.
37. Abdulkhalek S, Amith SR, Franchuk SL, Jayanth P, Guo M, Finlay T, et al. Neu1 sialidase and matrix metalloproteinase-9 cross-talk is essential for toll-like receptor activation and cellular signaling. J Biol Chem. 2011; 286: 36532-36549.
38. Amith SR, Jayanth P, Franchuk S, Siddiqui S, Seyrantepe V, Gee K, et al. Dependence of pathogen molecule-induced toll-like receptor activation and cell function on Neu1 sialidase. Glycoconj J. 2009; 26: 1197-1212.
39. Angénieux C, Dupuis A, Gachet C, de la Salle H, Maître B. Cell surface expression of HLA I molecules as a marker of young platelets. J Thromb Haemost. 2019; 17: 1511-1521.
40. Hoffmeister KM, Felbinger TW, Falet H, Denis CV, Bergmeier W, Mayadas TN, et al. The clearance mechanism of chilled blood platelets. Cell. 2003; 112: 87-97.
41. Mortensen RF, Duszkiewicz JA. Mediation of CRP-dependent phagocytosis through mouse macrophage Fc-receptors. J Immunol. 1977; 119: 1611-1616.
42. Imbach P, Crowther M. Thrombopoietin-receptor agonists for primary immune thrombocytopenia. N Engl J Med. 2011; 365: 734-741.
43. Chaib S, Tchkonia T, Kirkland JL. Cellular senescence and senolytics: The path to the clinic. Nat Med. 2022; 28: 1556-1568.
44. Langhi Prata LGP, Tchkonia T, Kirkland JL. Cell senescence, the senescence-associated secretory phenotype, and cancers. PLoS Biol. 2023; 21: e3002326.
45. Coppé JP, Patil CK, Rodier F, Sun Y, Muñoz DP, Goldstein J, et al. Senescence-associated secretory phenotypes reveal cell-nonautonomous functions of oncogenic RAS and the p53 tumor suppressor. PLoS Biol. 2008; 6: e301.
46. Wu R, Sun F, Zhang W, Ren J, Liu GH. Targeting aging and age-related diseases with vaccines. Nat Aging. 2024; 4: 464-482.
47. Chang J, Wang Y, Shao L, Laberge RM, Demaria M, Campisi J, et al. Clearance of senescent cells by ABT263 rejuvenates aged hematopoietic stem cells in mice. Nat Med. 2016; 22: 78-83.
48. Baker DJ, Childs BG, Durik M, Wijers ME, Sieben CJ, Zhong J, et al. Naturally occurring p16(Ink4a)-positive cells shorten healthy lifespan. Nature. 2016; 530: 184-189.
49. Childs BG, Gluscevic M, Baker DJ, Laberge RM, Marquess D, Dananberg J, et al. Senescent cells: An emerging target for diseases of ageing. Nat Rev Drug Discov. 2017; 16: 718-735.

50. Ridker PM, MacFadyen JG, Thuren T, Everett BM, Libby P, Glynn RJ, et al. Effect of interleukin-1beta inhibition with canakinumab on incident lung cancer in patients with atherosclerosis: Exploratory results from a randomised, double-blind, placebo-controlled trial. Lancet. 2017; 390: 1833-1842.
51. Mittelbrunn M, Kroemer G. Hallmarks of T cell aging. Nat Immunol. 2021; 22: 687-698.
52. Amor C, Feucht J, Leibold J, Ho YJ, Zhu C, Alonso-Curbelo D, et al. Senolytic CAR T cells reverse senescence-associated pathologies. Nature. 2020; 583: 127-132.
53. Amor C, Fernández-Maestre I, Chowdhury S, Ho YJ, Nadella S, Graham C, et al. Prophylactic and long-lasting efficacy of senolytic CAR T cells against age-related metabolic dysfunction. Nat Aging. 2024; 4: 336-349.
54. Lu K, Han Q, Ma Z, Yan Q, Pei Y, Shi P, et al. Injectable platelet rich fibrin facilitates hair follicle regeneration by promoting human dermal papilla cell proliferation, migration, and trichogenic inductivity. Exp Cell Res. 2021; 409: 112888.
55. Wyles SP, Yu GT, Gold M, Behfar A. Topical platelet exosomes reduce senescence signaling in human skin: An exploratory prospective trial. Dermatol Surg. 2024; 50: S160-S165.
56. Liu Y, Wang Y, Yang Y, Weng L, Wu Q, Zhang J, et al. Emerging phagocytosis checkpoints in cancer immunotherapy. Signal Transduct Target Ther. 2023; 8: 104.
57. Voelker J, Berg PH, Sheetz M, Duffin K, Shen T, Moser B, et al. Anti-TGF-beta1 antibody therapy in patients with diabetic nephropathy. J Am Soc Nephrol. 2017; 28: 953-962.
58. Shen CL, Wu TF. Flow cytometry for evaluating platelet immunophenotyping and function in patients with thrombocytopenia. Tzu Chi Med J. 2022; 34: 381-387.
59. Frelinger AL, Spurgeon BE. Clinical cytometry for platelets and platelet disorders. Clin Lab Med. 2023; 43: 445-454.
60. Kline MC, Malits JR, Baker N, Shirley H, Grobman B, Callison WÉ, et al. Climate change, environment, and health: The implementation and initial evaluation of a longitudinal, integrated curricular theme and novel competency framework at Harvard Medical School. PLoS Clim. 2024; 3: e000042.
61. Nano M, Montell DJ. Apoptotic signaling: Beyond cell death. Semin Cell Dev Biol. 2024; 156: 22-34.
62. Medzhitov R. The spectrum of inflammatory responses. Science. 2021; 374: 1070-1075.
63. Guglielmi GG. Found: The dial in the brain that controls the immune system. Nature. 2024. doi: 10.1038/d41586-024-01259-2.
64. Leiter O, Brici D, Fletcher SJ, Yong XL, Widagdo J, Matigian N, et al. Platelet-derived exerkine CXCL4/platelet factor 4 rejuvenates hippocampal neurogenesis and restores cognitive function in aged mice. Nat Commun. 2023; 14: 4375.
65. Wang T, Yi Z, Liu X, Cai Y, Huang X, Fang J, et al. Multimodal detection and analysis of microplastics in human thrombi from multiple anatomically distinct sites. EBioMedicine. 2024; 103: 105118.
66. Lindzen RS. Can increasing carbon dioxide cause climate change? Proc Natl Acad Sci USA. 1997; 94: 8335-8342.
67. Wu D, Feng Y, Wang R, Jiang J, Guan Q, Yang X, et al. Pigment microparticles and microplastics found in human thrombi based on Raman spectral evidence. J Adv Res. 2023; 49: 141-150.
68. dos Santos N. Kidney xenotransplantation: Are we ready for prime time? Curr Urol Rep. 2023; 24: 287-297.