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REVIEW

Platelet life cycle during aging: function, production and clearance

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Abstract

Platelets are important players in hemostasis. Alterations in platelet number and/or function lead to life-threatening conditions like thrombosis, myocardial infarction and stroke. During aging, changes at the cellular, organ and systemic level occur that affect platelet counts, platelet functionality, the expression of platelet surface receptors, clearance markers as well as their interactions with immune cells. Understanding how these changes influence platelets can help to prevent the alterations of hemostasis and thrombosis we observe in the elderly. In this review, we highlight the respective changes at important sites of the platelet life cycle: bone marrow, liver and spleen, but also show how alterations in immunity contribute. We point out the necessity for further research on age-related systemic alterations in these systems and their interplay with platelets to better understand the complex processes that cause alterations in the platelet life cycle during aging.

Plain Language Summary

Platelets are small cells without a nucleus that play significant roles in hemostasis and immunity. Alterations in platelet life span might contribute to cardiovascular diseases frequently observed in the elderly that could lead to bleeding or thrombotic complications. In this review, we introduce the checkpoints of platelet life cycle where the platelets might be affected by changes in an aging organism. We describe alterations in platelet progenitors called megakaryocytes and changes in the bone marrow microenvironment. We discuss the chronic inflammation observed in elderly and how this "inflamm-aging" potentially influences platelet function and count. Major organs responsible for platelet clearance are the spleen and liver which both undergo changes in structure and function during aging. In this review, we highlight how these affect clearance of platelets at the end of their lifespan. A better understanding of how aging affects platelet clearance and function might help to identify potential targets for the development of novel therapeutic approaches for prevention of acquired hemostatic complications in aged individuals and improve their quality of life.

Keywords
Aging, inflamm-aging, macrophages, megakaryocytes, platelets

History
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Introduction

Platelets are small anucleated cells responsible for maintenance of vascular integrity, modulation of immune response and tissue remodeling.[1] Platelets play a significant role in the progression of cardiovascular diseases, especially atherothrombosis and, consequently, ischemic heart disease (IHD) and ischemic stroke.[2] Antiplatelet therapy (acetylsalicylic acid, P2Y receptors inhibitors) is commonly used in elderly people for the prevention of thrombosis. On the other hand, bleedings also occur frequently in aged individuals, from petechiae and epistaxis to intracranial bleeding during hemorrhagic stroke.[3] During aging, alterations in the coagulation cascade or platelet function and/or count may lead to either bleeding or thrombosis.

The platelet lifecycle begins in the bone marrow where mature megakaryocytes (MKs) produce platelets and release them into circulation.[4] Platelets circulate in the bloodstream for 7–10 days in healthy humans to maintain hemostasis. Aging of platelets is characterized by the loss of sialic acid moieties from the glycans on membrane glycoproteins. This leads to the exposure of several sugar residues that can be recognized by macrophages in the liver and spleen.[4] At least three different receptors on immune cells in several organs take part in the elimination of platelets from the bloodstream: CD11b (Mac-1),[5] macrophage galactose-type lectin (MGL)[6,7] and Ashwell-Morell receptor.[6] In this review, we will describe the age-related changes in all parts of the platelet circle of life to understand the causes of altered platelet count and function observed during aging (Figure 1).

Age-related changes in platelet function

Platelet function changes from neonatal to elderly age. In the first days after birth, the blood cell counts fluctuate frequently due to the

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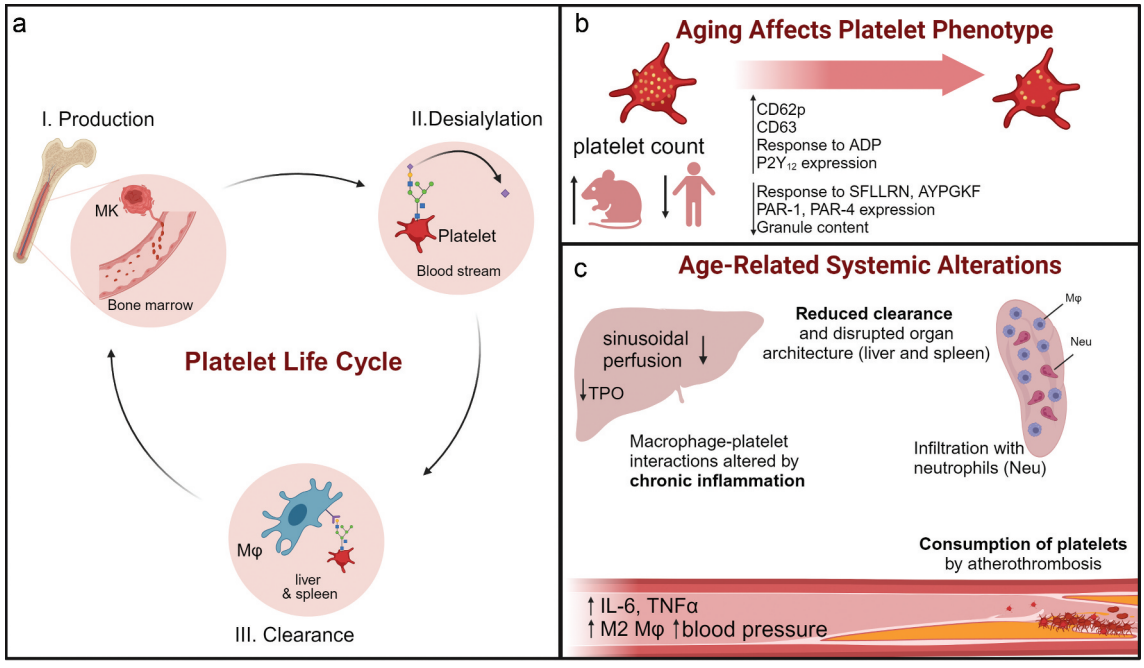

Figure 1. Alterations of the platelet life cycle in aging. (a). The platelet life cycle starts in the bone marrow (I) where platelets are produced by megakaryocytes (MK). II. Newly generated platelets enter the blood stream where they circulate and age and become desialylated. III. Aged platelets with exposed sugar residues are recognized by tissue macrophages (Mφ) in liver and spleen. Hepatocytes produce thrombopoietin that stimulates proliferation of bone marrow megakaryocytes. (b). Platelets in elderly individuals show an altered phenotype. The platelet count is increased in old mice but decreased in older humans. Platelets of aged individuals show a pre-activated phenotype (increased expression of CD62p, CD63 in resting state) and higher response to ADP due to increased expression of $P2Y_{12}$ receptor. On the other hand, PAR-driven activation is reduced. Also, platelets of elderly individuals have reduced granule cargo. (c). Immune system of elderly individuals shows characteristics of chronic inflammation: levels of pro-inflammatory cytokines are elevated, and spleen is infiltrated with neutrophils. Spleen and liver – the main organs for platelet clearance – have disorganized architecture which leads to diminished clearance capacity. Atherothrombosis drives consumption of platelets by a thrombus forming on a ruptured atherosclerotic plaque.

replacement of fetal red blood cells with normocytes and start of active development of the immune system.[8] The counts differ from the mean platelet count typically observed in adults but remain in ranges of healthy adults. However, the platelet count decreases with age in humans, especially in males.[9,10] On the other hand, mice, which are an important tool for basic research show an increase in platelet counts with age which suggests aging might have a different impact on mice compared to humans.[11] One can argue that humans age differently from mice gaining plethora of pathologies, including hypertension, diabetes and other conditions leading to excessive inflammation and consequent recruitment of platelets. However, it was shown that aged mice also show a similar phenotype of aging including renal dysfunction, neoplasm formation and chronic inflammation.[12] Neonatal platelets show reduced responses to stimulation via all major platelet receptors, but the responsiveness increases with adolescence. Compared to healthy adults, platelets of neonates upon activation show less integrin activation, decreased extent of degranulation and higher sensitivity to natural activators such as epinephrine, thrombin, ADP, collagen but reduced expression of major receptors ($P2Y_{12}$, GPVI, PAR-1, PAR-4).[13,14] In the elderly, platelets become hyperresponsive to ADP stimulation but not to PAR-1 and PAR-4 activation with agonists SFLLRN and AYPGKF, respectively (measured by aggregometry, flow cytometry of α- and dense granules release and integrin activation).[15,16] This was explained by increased expression of the $P2Y_{12}$ receptor on platelets in elderly individuals and more active cleavage of PARs by thrombin. Interestingly, platelets of elderly individuals showed a significant increase in the number of unstable interactions with von Willebrand factor. In females, these changes were even more pronounced suggesting that alterations in the adhesive properties of platelets during aging is also sex-dependent.[17] D'Aurelio et al. also described decreased mitochondrial function of platelets of aged individuals.[18] Altogether, these studies show that not only platelet count but also platelet signaling is affected by aging, starting from reduced responses to physiological stimuli in neonates and changing toward hypersensitivity upon aging. Further confirmation comes from a proteomic assay that showed significant enrichment of proteins related to platelet activation, confirming the tendency for hyperreactivity of platelets in the elderly.[19,20] One explanation for platelet hyperreactivity and reduced platelet counts in elderly might be the interaction of platelets with ruptured atherosclerotic plaques. Atherosclerotic lesions form in the vessel wall because of endothelial dysfunction occurring with aging.[21,22] Circulating monocytes are recruited to the lesion and become so-called foam cells that store oxidized lipids. Later, these lesions can rupture and expose their content to the bloodstream. This leads to thrombus formation via activation of platelets and the coagulation system.[23] Circulating platelets that pass a forming thrombus become pre-activated – expose increased P-selectin levels on the outer membrane[16] - and more responsive to further stimuli.

Alterations in the immune system during aging

The immune system is highly affected by the age of an individual. The term "inflamm-aging" (low-grade chronic inflammation) describes the changes taking place during aging. This state is characterized by increased levels of inflammatory cytokines, like TNFα, IL-6 and decreased responses from B- and T-cells.[24,25] Thus, the adaptive immune response is altered. Besides adaptive immunity, macrophages as members of the innate immune system are also affected. Macrophages are phagocytic cells responsible for consumption of apoptotic bodies and

pathogens.[26] They are roughly divided into two subtypes: M1 that are pro-inflammatory and M2 macrophages with an anti-inflammatory and pro-angiogenic phenotype.[25] Each subtype has its own markers that are indicative of their respective functions. Certain stimuli promote monocytes to become M1 or M2 macrophages. Macrophages are found in almost all tissues, including bone marrow, liver and spleen. Tissue macrophages interact with cells via ligand-receptor contact to eliminate pathogens, senescent cells and apoptotic bodies.[1] How aging affects macrophages and monocytes has been reviewed elsewhere.[24,25,27] Here, we focus on the changes in macrophage phenotype that could affect platelet lifecycle.

Macrophages/monocytes can interact with platelets through several receptors.[28] CD11b (also known as Mac-1 and integrin $\alpha_M\beta_2$) is abundant on all subtypes of macrophages.[29] The recognition site for CD11b is N-acetylglucosamine which is exposed upon platelet desialylation – removal of sialic acid from platelet glycans during aging of platelets.[5] It was demonstrated that expression of CD11b on monocytes is elevated in aged individuals[30] which could facilitate more frequent interactions between them and platelets.

CD206 (mannose receptor) belongs to the C-type lectin (CLEC) family of receptors and is exclusively expressed by M2 macrophages.[31] Members of the CLEC receptor family are able to recognize different carbohydrate residues, e.g. CD206 recognizes mannose, N-acetylglucosamine and fucose.[32] Jackaman et al. described an elevated number of M2 macrophages in aged organisms under naïve conditions *in vivo*.[33] Furthermore, bone marrow-derived macrophages from old animals produce more M2 markers upon stimulation with LPS compared to young mice *in vitro*.[34,35]

Liver tissue macrophages are called Kupffer cells. Kupffer cells and hepatocytes express the Ashwell-Morell receptor which also belongs to the CLEC receptor family and recognizes β-galactose residues.[36] In addition, Kupffer cells express MGL and C-type Lectin Domain Family 4 Member F (CLEC4F) that recognize β-galactose. CLEC4F additionally binds fucose and N-acetylglucosamine.[6,37,38] MGL is also expressed by splenic macrophages.[7,37]

The receptors described above contribute to the clearance of aged desialylated platelets that present galactose, N-acetylglucosamine and fucose on their surface glycoproteins.[4] In addition, macrophage toll-like receptors and STAT1 signaling in older animals are in general less responsive to conventional stimulations with LPS or IFNγ,[31] hinting toward reduced recognition of desialylated, aged platelets. They secrete less cytokines and express less CD40 and activated MAPK (mitogen-activated proteinkinase) that indicate alterations in signaling pathways. Altogether, these findings demonstrate that even though the number of M2 macrophages is elevated, their functionality is reduced.[33] Therefore, changes in macrophage function might be responsible for changes in platelet counts and function in aged individuals.

Age-related changes in the spleen

The spleen is a secondary lymphoid organ responsible mainly for blood filtration, clearance of old blood cells and antigen-presentation.[39] It consists of the red and white pulp that are separated by the marginal zone (perifollicular zone in humans). Contrary to the human system, in rodents the red pulp is also a site of extramedullary hematopoiesis under steady state conditions.[40] In the red pulp the clearance of red blood cells, platelets and apoptotic bodies takes place via macrophages. In contrast, the white pulp is responsible for antigen-presentation to lymphocytes. Age-related changes of the spleen are well described.[41] The functional changes of spleen macrophages are similar to the changes observed in macrophages from other tissues including elevated CD11b expression and increased secretion of inflammatory cytokines like IL-6 and TNFα.[42] In rodents, the microanatomical structure of the spleen becomes less uniform with age, leading to a disrupted marginal zone. This results in a disseminated location of macrophages in the spleen tissue in older mice and rats. Similarly, dislocation of lymphocytes of the white pulp into the red pulp occurs. This reorganization leads to a reduced immune response due to missing lymphocyte priming: antigen-presentation is diminished, the consumption of senescent cells is lower and overall phagocytosis is decreased.[42,43] A study by Alex et al.[44] showed the atrophy of splenic tissue in humans and reduced number of B-cell follicles. This suggests a functional decline of the human spleen with age, but a detailed description of all age-related changes is lacking. Upon aging, neutrophils infiltrate the spleen tissue at a higher extent compared to young mice.[45] In summary aging is accompanied by a decreased clearance function in both human and mice and leads not only to poor pathogen response but also to reduced clearance of senescent cells. This could contribute to an increased platelet count in mice due to reduced clearance. However, the reduced immune cell function in spleen tissue does not explain diminished platelet counts in humans.

How aging affects liver function

The liver is a key organ in understanding the physiological changes associated with aging because of its intricate role in hemostasis and the control of platelet count, which is closely linked to its larger functions. The liver plays a major role in the generation of thrombopoietin (TPO), a cytokine promoting MK maturation and enhancing platelet reactivity, and coagulation factors; hence, its age-related decline has a substantial impact on systemic health.[46,47] Notably, liver-resident Kupffer cells promote the clearance of desialylated, aged platelets.[6] A detailed consideration of these physiological connections is important in order to completely comprehend how aging affects platelet clearance.

There is substantial proof that aging causes a reduction in liver volume and blood flow; research on individuals dating back to the 1990s first reported on these effects.[48] A subsequent study by Moon et al. further strengthened the validity of these discoveries by using cutting-edge imaging techniques like 4D flow MRI to verify these alterations.[49] Studies on rodents show that aging causes a decline in sinusoidal perfusion and a loss of liver mass.[50] The functionality of several cell types, such as Kupffer cells, liver sinusoidal endothelial cells (LSECs), and hepatocytes is directly impacted by the decrease in hepatic perfusion.

One of the key differences observed between young and old mice is a reduced plasma level of TPO.[51] Interestingly, the bone marrow concentration of TPO is higher compared to its plasma levels; however, upon aging a systemic decrease in TPO levels occurs, a phenomenon that also occurs in the bone marrow cavity.[50–53] This points to a dysregulation of the typical feedback loops controlling the synthesis and release of TPO, mediated through sequestration via the c-Mpl receptor on the surface of platelets.[54] The glycan-dependent clearance of platelets by Kupffer cells in young, healthy livers is hypothesized to regulate the synthesis of TPO by hepatocytes, which produce TPO in order to maintain steady-state platelet levels.[55] Despite platelet desialylation as the initiator of TPO generation, Kaser et al. demonstrated that recombinant IL-6 therapy raises TPO plasma levels.[56] Moreover, it was shown in 2021 that the IL-6 R pathway in mice directly affects TPO regulation.[57] The liver's ability to detect and react to desialylated platelets could decrease with age. Since abnormalities in the hepatic microenvironment, such

as altered Kupffer cell activity, decreased blood flow, and deteriorated endothelial cell behavior, may interfere with basal regulatory processes.[24,25] Furthermore, circulating and tissue levels of IL-6 gradually rise with age,[58] possibly influencing TPO gene expression. Thus, altered TPO sequestration by platelets could further explain the observed drop in systemic TPO levels.

Kupffer cells also undergo significant changes upon aging as already described for macrophages in general. This includes alterations in their number, morphology and phagocytic activity.[59] Older people had higher Kupffer cell counts and activity, according to two early human studies.[60,61] Some reports indicate a decrease in density in rats, while others show an increase in their numbers.[62,63] Age related changes of Kupffer cells include diminished development of pseudopodia and cytoskeletal components, indicating a decline in movement and function.[64] Simultaneously, an increased lysosome count could suggest a less responsive, more degradative phenotype.[65] These alterations probably worsen the dysregulation of TPO synthesis by decreasing the ability of Kupffer cells to remove old or desialylated platelets.

As already described, aging causes reduced liver perfusion which is a critical factor regulating cellular interactions. The expression of receptors for cell–cell interactions, e.g., ICAM or VCAM, is highly regulated and responds to inflammatory stimuli.[66] However, upon aging the trafficking of different immune cell types such as monocytes neutrophils and lymphocytes is dysregulated,[67] in part probably due to decreased perfusion and altered mechanical forces within the hepatic vasculature. These altered mechanical forces also directly influence platelets. Shear stress specifically affects the glycoprotein (GP) Ib on the surface of platelets, which is a component of the von Willebrand factor receptor complex.[68] Additionally, it is hypothesized that this receptor carries 60% of the platelet glycan mass, which is crucial for platelet clearance.[69,70] Ion channels, like the recently identified Piezo1 are important for mechanosensitive regulation of the ion-flux in platelets, promoting platelet hyperreactivity and subsequent thrombosis.[71]

In general, age-related changes in liver perfusion could alter cellular interactions of platelets within the liver vasculature, which could affect the number of circulating platelets. On the one hand, platelet clearance might be reduced due to reduced cell interaction. Platelet retention as a result of platelet-endothelial cell interactions is diminished accompanied by fewer platelet-Kupffer cell interactions causing reduced TPO synthesis. While on the other hand, platelet consumption might be mitigated by Kupffer cell-independent mechanisms, as platelets become hyperreactive.

Megakaryocytes in the aging organism

In both humans and rodents, aging significantly alters the phenotype of MKs. Age-related increases in bone marrow MKs size and ploidy, a general marker for pro-platelet forming MKs, have been demonstrated in several studies.[53,72,73] This increase is often accompanied by higher platelet production in mice, while on the other hand in humans the platelet count seems to be reduced with age.[10,74] Interestingly, MKs can also be found outside the bone marrow, e.g. in the spleen and lung. In 2017, Lefrançais et al. identified the lung as a site of extramedullary megakaryopoiesis using intravital microscopy in mice.[75] However, it remains unclear to which extent lung and splenic MKs contribute to age-related changes in platelet count. The functional differences between human and rodent bone marrow environment and extramedullary megakaryopoiesis needs to be further addressed in upcoming studies since we can only speculate on cross species differences yet. However, while inflamm-aging causes an increase in pro-inflammatory cytokines such as IL-6 in humans and mice, the efficiency of platelet generation may be impaired due to age-related alterations in the bone marrow microenvironment.[76]

The synthesis of platelets and the regulation of MK function depend on the level of TPO in the bone marrow cavity. The liver is the primary producer of TPO.[77] According to a study by Decker et al. bone marrow hematopoietic stem cells (HSCs) are depleted after targeted deletion of TPO from hepatocytes, suggesting that TPO produced by hepatocytes is the primary source for bone marrow HSC maintenance at steady-state.[78] However, bone marrow stromal cells, specifically mesenchymal stromal cells (MSCs) and osteoblasts, also synthesize TPO in smaller amounts.[79] The bone marrow niche is impacted by aging, which results in alterations to cellular composition and function that affect TPO availability. For example, the total number of MSCs declines which lowers the local production of TPO.[80] Furthermore, the myeloid output from the HSC compartment increases upon aging.[73,81] Under inflamm-aging conditions the increasing levels of inflammatory cytokines, like IL-6, can also affect TPO levels. It has been demonstrated that hyperinflammation increases TPO synthesis in the liver tissue in a model of premature aging by constitutive gp130 signaling in T-cells, causing massive thrombocytosis and increased MK numbers in both, spleen and bone marrow.[82] Alternatively, aging-related chronic inflammation may cause dysregulated TPO signaling. The observed alterations in MK phenotype and function may be partially attributed to this dysregulation, which may also lead to irregular platelet formation.

The function of CD48, a member of the signaling lymphocyte activation molecule (SLAM) family, is highlighted in recent studies. CD48 is expressed on hematopoietic stem cells (HSC) and important for MK development. While CD48 is widely expressed on hematopoietic cells, quiescent long-term HSCs do not express it. Marcos et al. reported a stepwise maturation from HSCs to MKs that depends on high CD48 expression, in parallel to a direct differentiation to mature MKs.[83] CD48 surface expression is altered in an age-dependent manner, which may have an impact on the development and functionality of MKs. Poscablo et al. discovered a distinct one-step differentiation pathway from HSCs to MKs that gets more pronounced during aging, which is consistent with Marcos et al. Interestingly, they discovered that MK progenitors from aged animals are more likely to replenish platelet numbers following thrombocytopenia.[84] Alterations in CD48 expression could be a factor in the dysregulation of megakaryopoiesis due to inflamm-aging. Poscablo et al. could show that LPS injection into mice, promoted CD48 expression and a stepwise MK maturation. Even though it is unclear how CD48 directly affects generation of pro-platelet forming MKs, its expression is linked to aging and affects bone marrow homeostasis and platelet formation. Four different subpopulations of mature MKs have been described in the literature: niche-supporting, pro-platelet forming, cycling, and inflammatory MKs.[85] However, it remains unclear whether an altered maturation process during aging causes a shift in these subpopulations. Although increased ploidy is suggested as a marker for MK maturation and platelet production, more research is required to understand how ploidy is altered during aging.[86]

A crucial part of MK maturation and pro-platelet formation is cytoskeletal reorganization. The process of pro-platelet formation is directly linked to the formation of pro-platelet branches into the bone marrow vasculature.[87] The cytoskeleton is made up of actin filaments, microtubules, and intermediate filaments and is reportedly negatively affected upon aging.[88] Hence, altered MK cytoskeletal dynamics could result in irregular pro-platelet formation. The endothelium of the bone marrow microenvironment also changes with age.[89] Together with a reduced blood flow in the bones,[90] both

factors might affect the shear force on pro-platelet branches and therefore have an impact on their capacity to form platelets. Indeed, the shear forces in the bone marrow vasculature play a key role in regulating the generation of new platelets.[91] However, how exactly the structural alterations of an aged bone marrow affect the MKs niche and pro-platelet formation is still unknown.

Conclusion

In conclusion, the aging process has a major impact on the lifecycle and functionality of platelets, which are critical for maintaining hemostasis. MKs undergo significant changes during aging as part of the generally altered bone marrow environment. Thus, platelet production is naturally affected. Changes in ploidy, size, and cytoskeletal organization together result in an altered phenotype of platelets that are released into the blood. Furthermore, the clearance of aged, desialylated platelets might be abrogated or reorganized due to a hyperreactive platelet phenotype.

The spleen and liver are important sites for platelet clearance. Both organs not only undergo tissue-specific changes upon aging, but also immune functions in these tissues are changing. As a consequence of inflamm-aging upon aging, chronic activation of the immune system occurs, also affecting platelet function and the interaction of platelets with other immune cells. Not only thrombo-inflammatory events might increase due to an imbalance in platelet reactivity and limited immune cell function, but also general immune cell activation. Altogether, these alterations directly affect the phagocytotic capacity of immune cells like macrophages, causing a reduced filtration of senescent platelets. Therefore, a detailed understanding of the communication between platelet and immune cells upon aging is needed.

By expanding our knowledge of the complex interplay between platelet biology and aging, we may be able to design customized medications that improve clinical outcome and the quality of life for the aging population. Future treatments for cardiovascular disorders like ischemic heart disease and stroke could benefit from a better understanding of how aging effects specific pathways that control platelet count and function. For example, the age-related decrease in platelet count that goes together with platelet hyperreactivity highlights the necessity of balancing antiplatelet therapies to lower the risk of bleeding while at the same time reducing thrombotic events. Antiplatelet treatment customized to the platelet biology of the aging individual may target hyperactive integrin signaling pathways or enhanced platelet desialylation. Furthermore, by comprehending how platelet-immune cell interactions are altered by chronic inflammation, new therapeutic targets to modulate these pathways and stop excessive platelet activation or clearance may become apparent. On the one hand, the suppression of chronic inflammation might help to reduce the overreaction of the immune system and its influence on the bone marrow and hemostasis. On the other hand, the elderly are more predisposed to infections due to reduced antigen-presentation and thus anti-inflammatory treatment might lead to the development of life-threatening conditions. The importance of further research into the age-related dynamics of platelet function and its broader consequences for health and disease is highlighted by this review.

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