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Aging and Mammalian Platelet Biomarker

Soumyabrata Banerjee and Mrinal K Poddar*
Department of Pharmaceutical Technology, Jadavpur University, India

***Corresponding author:** Mrinal K Poddar, Department of Pharmaceutical Technology, Jadavpur University, 188, Raja S. C. Mallick Road, Kolkata 700032, India

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Abstract

Platelet is one of the crucial cellular blood component containing different organelles inside along with different enzymes. The number of platelet changes in an individual than normal healthy condition conveys the development of different pathological conditions like aging, aging-induced proteinopathies, thrombocytopenia, cancer etc. During aging the platelet MAO-A, MAO-B, cyclooxygenase, phospholipase enzymes are changed their activities. The platelet count and its MAO-A, and serotonin are known to be interlinked. They have the potency to be used as biomarker(s) in many pathological conditions. Platelet Aβ1-40 may also be used as an index of development of aging-induced proteinopathies. The deterioration in neurotransmitter systems of brain, and proteinopathies reflect to the peripheral circulatory system, especially in platelet counts, its mitochondrial enzyme activities, stored proteins and neurotransmitters as well. These footprints will lead us to find out biomarker(s) of aging and aging-induced neurodegenerative pathological conditions in the near future.

Keywords: Aging; Platelet count; Platelet MAO-A; Platelet MAO-B; Platelet amyloid-beta

Introduction

In the circulatory system, blood contains different cellular components like Red Blood Cells (RBC), White Blood Cells (WBC), and platelets. The WBCs are the only nucleated blood cells and are responsible for the immunity of our system. RBCs and WBCs are well-studied blood components and have identified their important roles for the survival of living creatures; whereas, the less explored blood component is platelet.

George Gulliver in 1841 first time ever drew the picture of observed blood components including platelet (it was not named platelet at that time) when he was working with a newly made compound microscope with twin lens [1]. Platelet was identified for the first time by Giulio Bizzozero at the end of the 19th century [2]. Blood platelet in its form is found in mammals, but in other vertebrates like birds and amphibians, it is present in circulation as intact mononuclear thrombocytes [3]. Platelets are not true cells, and it is classified as cell fragments having no nucleus and nuclear DNA (deoxyribonucleic acid). The platelet count only uses in particular few pathological purposes, but other parameters are also there which may be considered as a biomarker of different diagnostic purposes. It (platelet) is an important component like other components of blood in the circulatory system. It forms from the megakaryocyte in mature bone marrow. Its average lifespan is 7-10 days in circulation. Circulating inactivated platelets have the biconvex discoid structure with a maximum diameter of 2-3 μm [4]. During haemostasis, tethering platelets adhere to the vascular injury through the interaction between their Glycoprotein (GP) Ib/V/IX receptor complex and GP VI/GP Ia with the von Willebrand factor (vWF) and collagen provided by the lesioned environment, respectively. Adherent platelets aggregate and secrete platelet activation mediators, such as Thromboxane A2 (TXA2) and Adenosine Diphosphate (ADP). It is well known that platelets help to form blood clots and prevents bleeding. The activated platelet membrane surface becomes procoagulant enhancing the coagulation cascade ending in the formation and stabilization of the haemostatic plug and arresting blood leakage [5]. Platelets also act as storehouse of different neurotransmitters in circulation. It has several organelles inside like dense granules, lysosomes, cytoplasm including mitochondria. Platelet mitochondria contain many enzymes in its outer and inner membrane [4]. During different clinical conditions these platelet mitochondrial enzyme activities, its count, shapes, and above all its life span and formation changes [6].

Aging is one of such clinical manifestation with a progressive negative association in adaptability to combat diseases. The research in the field of geriatric science has the thrust to discover biomarkers for its clinical implications to identify the onset of aging. This is necessary as aging doesn't come in a certain age but definitely in a certain phase of life. So, identification of that age in a particular phase is very urgent to counteract or minimize the sufferings from unhealthy aging by converting it into healthy aging. It is always the best discovery if this biomarker(s) is/are from a peripheral system like circulation. The platelet having mitochondria insight with different enzymes seems to be an important biomarker in diagnosis purposes in clinical practice in relation to aging and aging-induced disease(s). The present review is focused on those platelet parameters which is/are being used nowadays as biomarker(s) and/or would also be considered as biomarker(s) in geriatric clinical practice in the near future.

Platelet and Central Nervous System

In cardiovascular pathologies and cancer, the role of platelets is well established but the knowledge is not well understood about neurologic diseases [7,8]. Platelet has similarities with its basic proteins and polypeptides which cause neural depolarization. It also bears similar mechanisms of neural exocytosis [9]. Platelets carry neurogenesis-promoting molecules that regulate neurogenesis in

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the brain [10]. Following cerebral ischemia platelets microparticles promote neurogenesis [11]. Platelets change its activity during exercise mediated condition. It contributes to the running-induced increase in neural precursor cell proliferation *in vivo* [12]. Platelets carry molecules require for the running-induced increase in precursor cell proliferation in the dentate gyrus, including serotonin [13], peripheral Vascular Endothelial Growth Factor (VEGF) [14] and Insulin-like Growth Factor 1 (IGF1) [15]. Further, the platelets activation during the neuroinflammation was associated with the interaction between platelets and damaged endothelial cells and leukocytes [16,17]. It suggests that platelets could act as a messenger to communicate exercise-induced systemic changes to the brain. Recently, it has been reported that the sialated gangliosides rather than glycoproteins are responsible for the interaction of platelets with brain lipid rafts [18], though physical activity results in a range of changes in other tissues also. Exercise-induced release of muscular cathepsin B has been shown to have running-induced neurogenic effects, leading to improved spatial memory [19]. Platelets potentially act as vehicles to communicate these changes to the neurogenic niche, but the modes of action of neural precursor cell-platelet crosstalk remain unclear [20]. Since long time platelet biochemistry has been used as a peripheral biomarker for monitoring and therapeutic aspects of different diseases, but less investigated in neurodegenerative diseases [20]. Aging and aging-related diseases has the reflection of either similar or opposite observations with the central nervous system [21-23].

Platelet Monoamine Oxidase Enzyme

In the mitochondria, there are different enzymes inside and outside the membrane but among them, Monoamine Oxidase (MAO) is one of the important mitochondrial outer membrane-bound enzymes (E.C.1.4.3.4). This MAO catalyzes the monoamine reaction as $RCH_2NH_2 + H_2O + O_2 = RCHO + NH_3 + H_2O_2$. It (MAO) is present in blood platelet as well as non-neuronal and neuronal cells [23-25]. This enzyme depending on substrate specificities and inhibitor sensitivities has been classified into MAO-A and MAO-B [24]. MAO-B is found to be correlated with the aging-induced neurodegenerative disorders [25] but not with the aging [26]. The MAO-B activity which has been found to be related to dopamine concentration, and significantly lowers in patients in the late phase of AD compared to other phases of AD and/or healthy controls indicating a correlation of more severe AD symptoms and lower MAO-B activity [27]. Though, the MAO-B is predominant in blood platelets, recently the presence of other variety, MAO-A is also observed [23,28].

This MAO-A is specific to the substrate serotonin. During aging the blood platelet mitochondrial MAO-A activity reduces with a significant reduction of its Vmax and corresponding MAO-A mRNA expression [23]. This deterioration in platelet enzyme activity and mRNA expression has the opposite reflection of central MAO-A activity and mRNA expression [24] which indicates its potency to convey the central biochemical scenario during aging. The biomarker is such a parameter by means of which the scenario of internal changes may be speculated in a broad spectrum. The platelet MAO-A observes as such an index which can relay the central serotonergic system during aging [23,24]. The platelet MAO-A has a close relation with another pathological parameter, i.e. platelet count during aging in mammals.

Platelet Count

The platelet count is usually used in pathological practice to determine different pathological conditions. So, if there would any direct correlation with the platelet count and aging symptom, this may be a fantastic discovery in health sciences. It is reported that the platelet count is higher in females than males [29,30] and it is determined by genetic factors [31]. In this context (genetic) it may be mentioned that the mean platelet volume and platelet count are found to be associated with (a) a Single Nucleotide Polymorphism (SNP), rs342293, on chromosome 7q22.3 in healthy subjects [32]; (b) another haplotype located at 12q24 with different SNPs, genes, and alleles [32]; and (c) the both PIK3CG and PRKAR2B genes [31]. In addition to these genetic factors, gender, age, and seasonal factors may also play a role in determining the platelet count. The gender-dependent differences are most likely due to differences in hormone profiles as megakaryocytes and platelets express steroid hormone receptors [33]. So, the differences in hormonal profiles between male and female subjects might, therefore, be expected to result in different platelet phenotypes and count [31]. In relation to the previous portion regarding platelet MAO-A activity, it is quite obvious to mention here that the reduction in platelet MAO-A activity increases the serotonin content in the circulation. It stimulates the megakaryocytopoiesis [34] in the bone marrow and an increase in platelet formation. This, in turn, increases the platelet count during aging in circulation [23].

The increase in platelet count is also a risk factor for elderly immune thrombocytopenia, a disorder of bleeding in visceral or intracranial hemorrhage [35]. The platelet count does not change during aging-related neurodegenerative diseases like Alzheimer's Diseases (AD) and Parkinson's Disease (PD), but the mean platelet volume (the average size of platelets per unit which closely related to platelet count) is found to be higher in PD than in AD indicating a risk of platelet dysfunction [36].

These observations clearly indicate an inverse correlation between the platelet MAO-A activity and platelet count during aging [23]. So, if we can monitor these parameters in platelet after a certain age, it would be helpful for the elderly population to aware of aging-related deterioration of neurotransmitter systems, especially serotonin, and proteinopathies even in CNS. During aging the neuronal damages at the level of degeneration occurs due to several factors including proteinopathies, accumulation of proteins in the synaptic zone or within neurons in different brain regions.

Aging, an inevitable time-dependent decline in physiological organ functions and it is a major risk factor for cancer development [37]. Increased platelet count, has long been recognized to be an independent predictor of poor prognosis in a variety of cancers such as lung, mesothelioma, breast, gynecologic, colorectal, gastric, and renal cancer [38]. In addition, recent studies also show that platelet content is affected by cancer. Several angiogenesis regulatory proteins in platelets of patients with colorectal cancer and compared this to the platelet content of age-matched healthy controls [39]. Colorectal cancer in which platelet count and platelet crit (total platelet mass per unit) levels has been reported to increase with tumor-nodule-metastases stages and tumor size. The mean platelet volume and

platelet crit levels have been found to be higher with the vascular invasion stage of colorectal cancer [40].

Aging-related Neurodegeneration and Platelet Amyloid-beta (Aβ)

Amyloid Precursor Protein (APP) is present in mammalian platelets in the circulation as well as in brain tissue. The isoforms of APP (APP751, APP770) secret from APP in platelets during Alzheimer's Disease (AD) is different from the APP (APP695) found in neuronal tissue [41]. The deposition of Aβ in the brain might be due to the circulating Aβ in platelets which may cross the blood-brain barrier [41]. Platelet APP is synthesized by the megakaryocyte in the bone marrow, rather than being the result of platelet uptake of circulating APP [42]. Platelets also express all the required enzymatic activities (α, β, and γ-secretases) to produce the APP metabolites including Aβ, unlike brain Aβ1-42 and stored into intracellular granules [43,44]. Proteolytic cleavage of platelet APP may occur both within intracellular organelles of the secretory pathway, and/or on the surface of the platelets [41,45,46]. The Aβ1-40 is the main species released from activated human platelets. This circulating Aβ forms (Aβ1-40) contributes to vascular amyloid deposits while the predominant form in neuronal plaques is Aβ1-42 [44,47,48]. Aβ1-40 has the ability to activate platelets, and to trigger platelet aggregation by stimulating intracellular signaling pathways involving PLCγ2 phosphorylation, PKC activation and intracellular mobilization of Ca^{2+}[49]. Release of Aβ1-40 by activated platelets might represent a mechanism of Aβ1-40 deposition in the blood vessel walls. This leads to angiopathy occurring in aging as well as in AD [49,50].

Platelet Membrane Cholesterol Status

The platelet membrane cholesterol level in AD patients has been observed to be decreased [51]. In contrast to this observation, an increase in platelet membrane cholesterol has been observed and it has been also correlated with the increase in β-secretase activity that can generate more Aβ1-40 [52]. This increased Aβ1-40 may promote inhibition of β-Hydroxy β-Methylglutaryl-CoA (HMG-CoA) reductase, and reduces de-novo cholesterol biosynthesis [53]. This model hypothesizes a negative feedback system between membrane β-secretase activity and membrane cholesterol level in AD. Therefore, it may be suggested that a perturbation of a possible physiological homeostatic link between membrane cholesterol level and membrane β-secretase activity may occur in AD.

Phospholipase and Cyclooxygenase in Platelets

The phosphoinositide-specific Phospholipase C (PLC) is another enzyme present in platelets which generally takes part in signal transduction. The PLCδ-1 isoform of PLC is found to be accumulated abnormally in the AD brain [54]. Subsequently, its (PLC) activity significantly lowers in the platelets of AD patients. This suggests an aberrant phosphoinositides metabolism in non-neuronal tissues [55]. The PLCδ1 isozyme activity is found to be reduced in AD patient homozygous for apoE genotype carrying the ε3 allele [56]. The Phospholipase A2 (PLA2) plays an essential role in the metabolism of membrane phospholipids [57]. Its activation can also stimulate the secretion of APP [58], while in turn, the amyloid peptides are able to activate PLA2 [59]. There are also controversial reports of PLA2 activity as it is found to be increased [60] as well as decreased in platelets of individuals with AD [61], but decreased only in human AD brain [62,63].

The cyclooxygenase, an enzyme responsible for conversion of arachidonic acid to prostaglandins is present in platelets, and it is of two types, cyclooxygenase-1 and cyclooxygenase-2. The second type has been found to be increased in platelets of AD patients which indicates the activation of platelet inflammatory pathways and that may be considered as an early event in AD development [64].

Conclusion

It may be concluded from this review that platelets are an important circulating component of blood containing different enzymes like MAO, secretases, cyclooxygenase, phospholipase, etc. inside. These are altered (either increase or decrease) during aging and aging-related neuro diseases. In brief, (a) the MAO-B is the predominant in platelets and bears a good correlation with amyloid pathology; (b) the platelet MAO-A type of enzyme is the most recently discovered and have found closely related to the other pathological index, platelet count; (c) the platelet MAO-A (both activity and its mRNA expression) may be an emerging index to presume the pathological changes of central as well as circulating serotonergic system during aging; (d) in addition, platelet count may also be considered as another biomarker of aging-induced alteration of platelet MAO-A; (e) the cyclooxygenase-2 and phospholipase activities in platelets increases during aging-induced neurodegeneration; (f) platelet Aβ has the potency to relay the message of central Aβ status during Aging-related neurodegenerative disease, AD. Finally, it is not unlikely to mention that in the near future the above-mentioned footprints of platelets may be used as biomarker(s) in aging and aging-related neurodegenerative specific disease(s).

Conflict of Interest

No.

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