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Platelets should be at the Frontline: HIV Researchers and Care Providers Needs a lot of Sticky Notes

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Most scientists and health care providers learned during training that platelets are small, simple, anucleated cells, responsible for making clots and regulating hemostasis. Many even argue against calling them cells; instead, they were viewed as sticky, small fragments circulating in the blood. Indeed, since they are the smallest and the lightest blood components, they have been categorized as cell debris, assisting the process of coagulation [1]. The problem is that these are one of the most inaccurate statements made by our predecessors. Even worse, students still are learning an inaccurate and unscientific definition of platelets.

In this modern world science is frequently reinvented, and sticky notes need to be pasted in outdated books to correct old paradigms. As described below, the platelet chapter needs a lot of sticky notes. Hopefully in the near future platelet parameters will be more carefully analyzed, because thus far, they only garner attention when numbers are too low, which could induce massive bleeding, or when they are too high, which causes overly active clotting.

Escaping the Nuclear Confines: Platelets Can Sustain Replication. A Paradigm Change

For most cells the nucleus takes center stage, as it controls the transcription of DNA to RNA. Consequently, the anucleated status of platelets has stereotyped them as cells without any replication potential [1]. Yet, the old concept that platelets cannot reproduce in the blood stream has been proven incorrect. Both fresh and stored platelets can produce functional progeny [2]. Thus, platelets are not so static and dead-end after all!

The newly recognized capacity for platelets to replicate raises the possibility that pathogens can also reproduce inside platelets. Newman's group demonstrated that messenger RNA (mRNA) reside in platelets. Additional studies provide evidence that platelets synthesize biologically relevant proteins, which are regulated via gene expression programs at the translational level [3]. This process does not require a nucleus: platelets contain ribosomes, essential spliceosome factors, small nuclear RNAs, endogenous pre-mRNAs, and translational factors necessary for protein synthesis [3-9].

Beyond the classical methods, platelets have developed extra-nuclear mechanisms to process and efficiently translate mRNAs into proteins [3-9]. Specialized post-transcriptional and translational mechanisms are now considered part of the platelet's functional repertoire. Indeed, in the 90's Boyd group demonstrated platelet-associated reverse transcriptase. Furthermore, they were able to demonstrate replication of HERVs (human endogenous retrovirus) inside of platelets [5]. Last year, Simon et al. demonstrated that platelets can replicate the positive sense single-stranded RNA genome of the dengue virus by up to -4-fold over 7 days. Using an elegant *in vitro* model, they demonstrated production of the viral NS1 protein of the dengue virus [4]. Vaccinia virus, cytomegalovirus, HIV, influenza virus, and hepatitis C virus are examples of viruses that are known to directly interact with platelets. Therefore, we need to be open minded about the possibility that viruses can be sheltered, replicated, and use platelets as Trojan horses. Such studies will help scientists to better understand if and how the virus populates and re-seeds infection. It can also explain why platelets are significant predictors of CD4, viral load responses, morbidity and mortality.

In a parallel field, the platelet proteome has been in the spot light as researchers have found over 1000 proteins secreted by platelets. These proteins were either inherited from the megakaryocytes, or produced *de novo*, using a retrotranscription RNA process and spliceosome. Further challenging the old concept of platelets, McRedmond et al. found an abundance of histone genes in their "proteome platelet-specific analysis" [8].

Although platelets' activation does not include NF-κB–driven gene expression, platelets can splice stored intron-containing heteronuclear RNA to produce mature mRNA, from which cytokines are produced [9]. The list of cytokines *de novo* produced by platelets now includes: TGF-β1, IL-4, IL-8, IL-13, IL-17, IFNα and TNFα [9-11].

Not only are platelets genuine cells, but they are more versatile than we were taught to believe.

Thus, let us rediscover platelets:

Platelets Expanding Role in the Immune Response Against Pathogens

Contemporary themes in platelet immunobiology increasingly recognize the key role of platelets in shaping the immune and inflammatory response upon encountering infectious pathogens [12-15]. Descriptions go from how platelets rapidly deploy host-defense peptides, to enhancing cell recruitment in the context of infection control. The first study of this kind described the interaction of PLTs with *Streptococcus;* yet thereafter, researchers have demonstrated that the open canalicular system of platelets contributes to the engulfment (and/or "filtration") of several bacterium, viruses, and parasites [10-11]. Notably, prior studies detected higher percentages of dengue viral RNA in PLTS than in plasma and a high positive rate (43%) of dengue viral RNA in PLTs, indicating that PLTs sustain viral replication [4]. If this holds true for HIV upon arrest of therapy, PLTs can participate in the rebound of HIV [15].

The platelet-HIV interaction was described decades ago, yet scientists seem to overlook these key findings. Studies have

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demonstrated that cell-free viruses rapidly attach to platelets from non-infected donors, and intake is facilitated by the presence of CXCR1, 2, 4 and CCR3, CCR5 and DC- SIGN receptors on the platelet's surface. Disjointed observations suggest that once inside the platelets two distinctive scenarios occur: In the first one, the HIV is located on the surface-connected canalicular system, exposed to PLT secreted proteins, and destroyed. This phenomenon, similar to the one observed in macrophages, is often referred to as Virus-Containing Compartments. In the second one, HIV is located in endocytic vesicles and rests protected from the extracellular fluids, which are lethal for the virus. However, using this "Trojan horse", the HIV could be transported to distant sites by platelets and take advantage of interactions between platelets and other cells, allowing for viral spread [14-17].

Platelets and Inflammation

How might platelets be placed in this response?

The first evidence of the involvement of platelets in the inflammatory response emerged over two decades ago when scientists realized that some adverse reactions to the transfusion of platelets were associated to platelet-derived inflammatory cytokines such as interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF). Interrogation of an arrayed cDNA library proved that platelets contain many cytokine messenger RNAs [9-11].

Second, platelets have been shown to express chemokine receptors, such as MIP-1α, PDGF, and RANTES (the Macrophage Inflammatory Protein, the Platelet derived growth factor and the Regulated on Activation, Normal T Cell Expressed and Secreted) that trigger the chemotaxis of other cells to the sites of inflammation [9-11,18].

Third, beyond the storage and production of cytokines and chemokines, platelets release soluble CD40 ligand (sCD40L), which is for some considered to be the main culprit responsible for perpetuating the inflammatory response. Notably, CD40 and platelets have been recently linked to intestinal pathological processes, which can elicit microbial transmigration and thus create a vicious cycle by inducing further inflammation [9-11,18]. CD40-CD40L interaction also suppresses interferon α production, which is a well-known player in the antiviral response. Therefore, this PLT-induced inflammatory response can lead to the expansion of the viral reservoir and can sustain viral replication. Based on these results, platelets should be "licensed" as immune cells.

Indeed, platelets should be ranked high, given: 1) the lengthier list of signaling immune molecules released by platelets, 2) their unique role as a bridge between the immune and the cardiovascular system, 3) role as liaison between the immune and neurological systems; and 4) based on these findings, we now understand that many anti-inflammatory drugs such as aspirin, COX inhibitors, and Non-steroidal anti-inflammatory medications work by inhibiting platelet activation.

Platelets Role in the Central Nervous System

Since the beginning of the HIV epidemic, it has become clear that a dysfunction of the Blood Brain Barrier was an early event that lead to neurocognitive deficits. Yet the mechanisms of such a dysfunction are still under investigation [18-23]. Our group started by documenting the close relationship between thrombocytopenia, a condition characterized by low platelets, and cognitive alterations [19]. We further demonstrated that altered platelets have a remarkable ability to damage and cross the blood brain barrier [20]. This is not unexpected, since platelets are the source of multiple pro-inflammatory substances, including TNF, IL-6 and CD40, which are known for altering the BBB [18-23]. Besides their role in pathogenesis, platelets might also play a key role in the regulation of brain function. Wachtman et al. identified in the Northeast AIDS cohort a close relationship between platelet's decline of 100,000/uL or more and increased risk of HIV Dementia [22]. This risk was independent of virologic control, antiretroviral therapy, concurrent HIV-related illness, duration of infection, and levels of education. Platelets carry serotonin, platelet activating factor, brain derived neurotrophic factor, thymus and activation-regulated chemokine, monoamine oxidase, and arachidonic acid products which may negatively impact cognition and mood [18]. All these factors confer platelets a prominent role in maintaining cognitive status [17-22]. Beyond that, a recent analyses of the Multicenter AIDS Cohort Study structural brain imaging sub-study discovered a positive significant relationship between platelet decline and reduced gray matter. Unfortunately, the mechanisms mediating such observations remain highly speculative and highlight the urgency of additional studies. Yet, these findings further confirm that the brain is not free from the action of platelets, and emphasizes the need to revise old platelet paradigms [23].

Translational Research

In summary, platelets are indispensable cells for the cardiovascular system, the immune response, and the maintenance of homeostasis in the central nervous system. Because knowledge needs to be precise, we can no longer ignore these compelling findings: scientists, health care providers, academia and even health websites should revisit their definition of platelets, and revise the description of its essential functions.

Beyond scientific accuracy, platelets need to be in the clinical spotlight because more and more scientists are documenting that platelets have proven to be excellent markers of disease risks and mortality. Platelets are also now explored as potential targets of therapy, given their involvement in the regulation of regenerative processes, both in the liver and in the brain by interacting with stem/progenitor cells. We hope that the readers will elicit scientific stimulation for future studies. Hopefully this brief summary will be useful for health care providers and will change clinical day-to-day practice.

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