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Physiology and metabolic of red blood cell

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Abstract: **Providing cells with enough oxygen led to the creation of multicellular organisms, and red blood cells (RBCs) are specialized organ that plays a key role in this process, not able to get oxygen from the air without because of diffusion, which provides energy for oxidative phosphorylation when it comes to producing energy at extremely high efficiency.**

The RBCs in your body have adapted to their function by maximizing packing hemoglobin levels that are extremely high in their cytoplasm including the release of nuclei and other organelles. Red blood cells (RBCs) have adapted over time to shed their nuclei and other organelles while loading their cytoplasm with hemoglobin. RBCs are prepared to transport oxygen by metabolic/redox enzymes during their about 120-day circulatory lifetime in humans until they collect damage and are rapidly eliminated by the reticuloendothelial system.

However, when RBCs are removed from circulation and stored hypodermically in blood banks, these complex evolutionary adaptations become ineffective due to the accumulation of storage-induced damages ("storage lesions") throughout the shelf life of stored RBCs.

COVID-19 disease is caused by the same SARS-CoV-2 beta coronavirus that causes severe acute respiratory syndrome (SARS), which manifests largely as difficulty breathing, a persistent dry cough, and fever. Since they carry oxygen throughout the body, red blood cells (RBCs) could be involved in the degree to which COVID-19 individuals suffer from hypoxemia. Recent research has shown that examines the effect of COVID-19 on RBCs using cutting-edge metabolomics, proteomics, and lipidomics techniques to molecularly diagnosed COVID-19 patients, and 23 controls. patients. Elevated concentrations were found in the red blood cells of patients with COVID-19. oxidation and fragmentation of ankyrin, spectrin beta, and the N-terminal cytosolic domain, as well as the glycolytic intermediates zone of band 3 (AE1).

This article seeks to give a holistic overview of the literature on RBC storage lesions and their putative clinical effects by including the recent exponential expansion in available data derived from technologies in addition to that published in more conventional publications.

Keywords: **red blood cells, interactions, membrane proteins, erythropoietin, erythropoietin receptor, epigenetics, erythropoiesis.**

1. INTRODUCTION

In a typical adult, about 25 trillion RBCs are floating about in the blood, each of which contains about 260 million hemoglobin molecules (Kanias T, 2010).

Due to the increasing loss of nuclei and organelles experienced by erythroblasts and reticulocytes during maturation to create room for hemoglobin, the erythrocytes' ability to manufacture new proteins is severely compromised during their 120-day existence in the human bloodstream. Indeed, hemoglobin accounts for 95% of the average adult's dry body weight (25 kg) or 670 g (or 110 fL) of the mean RBC volume (110 fL). There is one ferrous iron in each alpha and beta globin subunit in the hemoglobin tetramer, and each subunit may bind one oxygen molecule (Winslow RM., 2013).

For large warm-blooded vertebrates, the ability to survive thanks to hemoglobin and the RBC's specialized role as oxygen carriers in the body, has been sculpted through evolution. Both iron and oxygen concentrations in completely oxygenated RBCs are around 16 mM, which is unusually high given the high reactivity of ferrous iron and oxygen. Mature RBCs eliminate their mitochondria and boost their antioxidant systems to reduce oxidative stress and oxygen consumption by keeping hemoglobin iron in a reduced state even in the presence of high oxygen concentrations (D'Alessandro A, Zolla L., 2017).

The white pulp and the red pulp are two separate but equally important parts of the spleen, the biggest secondary immunological organ in the human body (Mebius RE, 2005). The red pulp acts as a primary blood filter to trap and remove harmful bacteria as well as senescent or sick red blood cells (RBCs) from circulation, while the white pulp is responsible for beginning immunological reactions to bloodborne antigens (Petroianu A, 2011). While traveling through the red pulp, RBCs enter venous sinuses via the cords and then must squeeze through interendothelial slits (IESs) between the elongated endothelial cells lining the sinus wall (Safeukui I, 2008). The red pulp's RBCs are filtered by two distinct mechanisms: (i) physicochemical filtration, in which surface-altered RBCs adhere to reticular connective tissue and macrophages before being removed by phagocytosis, and (ii) mechanical filtration, in which the IES of the sinus wall acts as a physical barrier to prevent RBCs with abnormal size, shape, and (iii) deformability from returning to general circulation (Safeukui I, 2012). Microcirculatory problems can be avoided by maintaining a consistent balance between these two sequential processes, which regulate the quality of circulating RBCs (Ndour PA, 2015).

SARS-CoV-2, a novel RNA coronavirus, is the causative agent of a severe acute respiratory syndrome (SARS) and its sequelae, which are together known as coronavirus disease 2019 (COVID-19) (Wu, F.; Zhao, 2020). The clinical signs of COVID-19 are varied and may include fever, shortness of breath, persistent dry cough, chills, muscle discomfort, headache, loss of taste or smell, renal impairment, and gastrointestinal problems (Andersen, 2020). Like other coronaviruses, SARS-CoV-2 infects host cells through interactions between its S (spike) protein and the angiotensin-converting enzyme receptor 2 (ACE2), which is highly expressed in lung epithelial cells. It has been suggested that chloroquine can hide the association between the beta coronavirus S protein and sialic acids on host-cell gangliosides, making this interaction unavailable for use in the therapy of COVID-19 (Lan, J.; Ge, 2020). Red blood cell (RBC) surface proteins interacting with angiotensin and ACE2 were discovered by proteomics (Fantini, 2020).

This raises the possibility that the virus may infiltrate RBCs, even though they are unable to support viral replication (D'Alessandro, 2017). Viruses can go after RBCs in one of two ways: Viruses and bacteria can infiltrate red blood cells (RBCs) and produce intravascular hemolysis (as seen in malaria), or they can stimulate reticuloendothelial phagocytes in the liver and spleen to eliminate RBCs more quickly from the bloodstream (McCullough, 2014). Absorption of immune complexes and complements onto RBC surfaces, the generation of cross-reacting antibodies, and genuine autoimmunity with a loss of tolerance as a result of infection are just some of the processes postulated to account for these observations. COVID-19 is notable because it triggers a severe acute-phase response and complement system dysfunction (D'Alessandro, 2020).

Due to the lack of organelles in mature RBCs, oxygen binding and off-loading are tightly regulated at the post-translational (e.g., phosphorylation,9 methylation10) or metabolic level Longo, 2014).

2. WHAT ERYTHROPOIETIN DOES TO ERYTHROID CELLS

2.1 The hormone erythropoietin upregulates the binding of the transcription factor STAT5 to multiple hundred chromosomal sites

Transcriptional regulation is triggered by external cues. Transcriptional regulation is based on factors' interpretation of the cellular genome. Patterns of erythroid expression are dynamic, and the subject of a great deal of research using genome-wide expression profiling, which has yielded a wealth of information about the molecular processes that regulate red blood cell growth (Kingsley PD, 2013).

EPO signaling regulates the expression of hundreds of genes involved in cell survival signaling and cell identity, as demonstrated by expression profiling of EPO starvation experiments in Processes generated from the primary fetal liver (An X, Schulz VP, 2014).

Even though the binding sites of the three erythroid expert regulators (GATA1, KLF1, and TAL1) have been mapped out in a variety of model systems, the relationship between EPO-dependent STAT 5 binding and the temporal patterns of erythroid gene expression is still poorly understood (Pishesha N, Thiru P, 2014).

EPO signaling activates JAK-STAT, phosphatidylinositol-3-kinase, and mitogen-activated protein kinase during erythropoiesis. It has been hypothesized that EPO acts as a rheostat or dimmer switch for STAT 5 signaling in erythroid cells via the EPO-JAK-STAT axis (Shi L, Lin YH, 2014). Erythropoiesis requires and is dependent on EPO-stimulated STAT 5 activation. But it is still a major obstacle to learning how modifications in erythroid expression are associated with STAT 5 signaling and chromatin binding. These findings are essential for understanding the molecular mechanism linking EPO stimulation and subsequent STAT5 activation to erythroid epigenetics and transcription programs (Zhang D, 2001). Though ChIP-seq data for STAT 5 are available in a small number of cancer cell lines, a complete catalog of STAT 5-binding sites in an erythroid model has been absent (Singh S, 2012).

To fill in this knowledge gap, a recent study used complementary functional genomic techniques to identify direct targets of EPO-activated STAT 5 during erythropoiesis. Rapid changes in gene expression in response to EPO stimulation were caught by nascent transcription profiling, while direct STAT 5-binding targets could be identified after only a few days in a well-designed study (Kuhrt D, 2015). Within 30 minutes of EPO stimulation, STAT 5 occupied approximately three hundred genomic sites, most of which were promoter distal enhancer regions in murine J2E cells (Love PE, 2015). EPO-JAK-STAT signaling, and the erythroid expert regulators appear to be integrated at STAT 5-binding sites that were also occupied by GATA1 and/or KLF1, suggesting a direct relationship between the two (GATA1 and/or KLF1 occupied roughly half of the STAT 5-binding sites (Grebien F, 2008). In contrast, STAT5 functioned as a primary binding partner for housekeeping genes when GATA1 and KLF1 were absent (Shin HY, 2016).

This leads us to wonder if the expert regulators (GATA1, KLF1, and TAL1) and STAT 5 are complementary in their roles in ensuring the correct timing of erythroid gene expression (Gillinder KR, 2017). What is STAT 5's biochemical role in this regulatory picture, given that GATA1 and KLF1 are known to form LDB1-mediated complexes? In conclusion, this study contributed significantly to our understanding of EPO's role in promoting erythropoiesis by identifying EPO-responsive genes, which are pertinent to treatment with EPO (Gillinder KR, 2017).

2.2 Exchange between erythropoiesis and hepcidin

In adults, macrophages are responsible for recycling iron (20-25 mg/day) generated from the breakdown of senescent erythrocytes, thus sustaining the iron needs of erythropoiesis. The amount of iron used in erythropoiesis is inversely proportional to the amount of iron provided by transferrin, which is part of the TFR1 endosomal cycle. Hepcidin production can be triggered by di ferric transferrin, which is also a ligand of TFR2.

While trying to prevent iron waste and shield cells from iron toxicity, the body applies stringent regulations. For instance, in hemolytic states like sickle cell anemia and inflammatory anemia, a temporary population of macrophages appears in the liver, phagocytoses abnormal red cells, and then differentiates into iron exporter macrophages and releases iron into the circulation, protecting the liver (and kidneys) from damage caused by iron or haem excess (Theurl et al, 2016).

There is some evidence that macrophages in the bone marrow promote erythropoiesis by helping erythroblasts mature within the erythroblast islands. Macrophages deliver iron in the form of ferritin to developing cells in culture, but whether this process is significant in vivo is unknown. Macrophages help orthochromatic erythroblasts undergo enucleation, a process regulated by iron availability (Li et al, 2017).

For example, Finch postulated the concept of an "erythroid regulator," and the discovery of ERFE provided experimental proof for this hypothesis (1994). Hepcidin expression is downregulated by ERFE, which explains why erythropoiesis requires it.

However, erythroid TFR2 regulates erythropoiesis to match the available iron. Mainly recognized for its roles as a sensor of circulating iron and an activator of hepcidin, Homologous to TFR1, the TFR2 gene is a highly prevalent cause of type 3 hemochromatosis (Camaschella et al., 2000).

circulated in the blood; expressed in erythroid cells. Here, it reacts with EPO. cell surface EPOR receptor (Forejtnikova et al. 2010). With the help of RNA interference, we were able to selectively eliminate Tfr2 in erythroid cells. the use of Tfr2/ donor bone marrow cells entering a wild-type recipient that has been irradiated to death (Nai et al, 2015).

Erythrocytosis and elevated hemoglobin levels Mice devoid of bone marrow Under regular serum conditions, TFR2 To put it another way, evidence from EPO suggests that, without TFR2, EPO We have an overactive signaling system. In line with this understanding, ERFE, like other EPO target genes, has its expression regulated increased. Therefore, one can tell there is more iron in the blood when Inhibiting EPO signaling by upregulating TFR2 helps keep erythroid numbers in check. Hepcidin helps keep iron levels stable (Nai et al, 2015).

Reduced blood-cell production Limiting iron absorption and promoting hepcidin expression are two of TFR2's many iron-suppressing effects. acquisition. In early erythroid progenitors, new evidence suggests that both TFR2 and EPOR may be bound. scrawl A receptor regulator that would aid in transporting both proteins to the cell surface (Khalil et al, 2018).

How do these in vitro results square with our in vivo observations? results still need to be investigated. One example of tissue-specific control of hepcidin is the erythropoiesis-liver interaction. It is possible that other regulators are secreted to convey specialized information. different tissues (e.g., from iron-deficient muscles). The iron could also be processed regionally, as in the cardiac iron homeostasis mediated by the hepcidin-ferroprotein axis separately from overall levels of hepcidin in the body (Lakhal-Littleton et al. 2016).

3. THE ROLE OF METABOLIC DYSFUNCTION IN THE DEVELOPMENT OF A STORAGE LESION

3.1 results for RBCs - lesions in storage

Extensive metabolomic studies showed that after about two weeks of hypothermic storage, there is a shift in the overall metabolic state, accompanied by a decrease in the amounts of high-energy chemicals like ATP and 2,3-DPG, as well as reducing equivalents like glutathione (GSH) and (NAD(P)H) (Nemkov T, 2016).

There are many enzyme reactions and ion pumps, such as Ca2+ pumps, which are negatively impacted by low ATP levels. Microparticle production is triggered by the exposure of phosphatidylserine (PS) and phosphatidylethanolamine (PE), normally contained in the inner bilayer, because of decreased ATP, which deregulates cation homeostasis and alters membrane asymmetry. Restoring membrane protein phosphorylation capability after rejuvenation of long-stored RBCs demonstrates that ATP deprivation also affects the ability of kinases to phosphorylate proteins Prudent (Rappaz M, 2014).

When ATP levels drop, the cytoskeleton undergoes a period of remodeling that results in echinocytosis (Park Y, 2010). The damage caused by oxidative stress during storage and in RBC recipients after transfusion is exacerbated by the depletion of reducing equivalents, which reduces antioxidant capacity (Reynolds JD, Ahearn GS, 2007). It is expected that poor nitric oxide bioavailability (INOBA) due to the rapid loss of S-nitrosylation (SNO) of hemoglobin in stored RBCs will interfere with vasodilation in transfused patients (40- Winslow RM, 2008).

Cells of varying ages, from those newly discharged into the circulation to those that have reached the end of their circulating life and have become senescent, are all present within a single RBC (Isbell TS, 2008). This panel uses average values for most in vitro parameters, which means that the rate of damage buildup may not be linear with storage duration or consistent amongst donors (Rodgers GP, 1983). Therefore, older circulating RBCs have less antioxidant ability (e.g., glucose 6-phosphate dehydrogenase activity declines in older circulating RBCs) and some senescent cells are present in a unit of preserved RBCs at any storage duration (Blasi B, 2012). Six to nine percent of RBCs show irreversible changes in morphology, according to assessments (Bardyn M, 2017).

As can be seen from extensive post-transfusion recovery studies, end-of-storage packed RBCs lose an average of 17.6% of their potency when transfused back to a healthy autologous donor (Mays JA, 2017). This may be because the cells' metabolic status has exhausted their capacity to manage oxidative stress during ex vivo storage for an extended time (46-Dumont LJ, 2008).

Hypothermic storage causes RBC membrane and cytoskeleton reorganization and damage as well as hemoglobin and oxidized protein binding, band breakdown, and raft protein changes (Bosman GJ, 2008). Reduced deformability that is

permanent after transfusion is induced by the accumulation of denatured methemoglobin, and damage produced by reactive oxygen species (ROS), both of which alter RBC morphology from dissociates to echinocytes by releasing microparticles (MPs). Inner membrane phospholipids are readily accessible after the oxidation of membrane lipids and proteins (PS and PE) (Prudent M, 2018).

3.2 Transfusion of RBCs containing storage defects and their physiological effects

Most red blood cells (RBCs) are removed from circulation within 24 hours after being transfused into autologous healthy individuals. Most non-viable RBCs show indications of eryptosis and are phagocytosed extra vascularly by macrophages in the recipient's reticuloendothelial system (Dumont LJ, 2008).

however, a small percentage of mechanically injured cells may hemolyze intravascularly following transfusion. Eryptosis, which may be triggered by calcium influx and K+ efflux, cell shrinkage, exposure of PS and PE from inner membrane bilayer, vehiculation of MPs with loss of surplus surface area, activation of calpains and caspases, and reduced deformability, may occur simultaneously during storage (Wojczyk BS, 2014).

Cleared red blood cell (RBC) fraction increases linearly with storage duration in healthy volunteers, from over 6% after 1 week to 11% after 6 weeks. However, non-linear exponential increases are observed after storage day thirty-five, particularly regarding circulating iron metabolites like RBC-derived non-transferrin bound iron (NTBI) (Lion N, Crettaz D, 2010).

In addition to its catalytic activity in ROS formation, free iron is tightly regulated in the body since it is the principal nutrient restricting the growth of siderophilic bacteria, which is important to keep in mind in patients with sepsis or bacteremia (Burger P, 2013). Red blood cells that have been hemolyzed in the bloodstream release iron from haeme, but this iron is immediately sequestered by transferrin (Roussel C, 2017).

When one unit of RBCs is transfused into healthy volunteers, up to 60 mL of damaged RBCs (25 percent of a unit) are eliminated extra vascularly within 24 hours, and the iron is recycled. Even though senescent RBCs are eliminated at a rate of 1 mL per hour, a single unit transfusion can overload the reticuloendothelial system and the capacity of transferrin, releasing NTBI into the circulation and potentially promoting bacterial proliferation (Kriebardis AG, 2007).

Multiple-unit transfusions and long-stored RBC units with a higher proportion of nonviable cells amplify the deleterious effects of uncontrolled NTBI in circulation (Daly A, 2014). Iron overload of tissues and organ failure can also occur in chronically transfused patients because of the excess iron from the non-viable RBCs contained in every transfused unit (Salaria ON, 2014). Oxidation of methemoglobin by reactive oxygen species (ROS) produces ferryl-hemoglobin, a proinflammatory agonist that can harm endothelium (Berezina TL, 2002).

Nitric oxide (NO) is produced by endothelial nitric oxide synthase (eNOS) close to pre-capillary arterioles and acts as a signal for vasodilation (Bennett-Guerrero E, 2007). Another key physiological impact of transfusing stored RBCs is the disruption of NO-mediated Vaso regulation, leading to dysregulation of blood flow. Insufficient oxygen is delivered to hypoxic tissues due to the actions of free haeme and MPs, which scavenge NO and result in idiopathic nocturnal breathing apnea (Rapido F, 2017). Also, because they tend to flow closer to the endothelium wall than normal RBCs, less deformable RBCs are suspected of contributing to INOBA by scavenging NO (Prestia K, 2014). In addition, RBCs have a direct impact on their NO-mediated capillary flow regulation: Blood cell hemoglobin can catalyze the reduction of nitrite in plasma to NO, and the ATP generated from red blood cells can drive endothelial nitric oxide synthase (Hod EA, 2012). When kept in standard circumstances, the concentration of glucose in the additive solution decreases, allowing endothelial cells to respond more effectively to ATP's stimulation of NO generation (Rapido F. 2017).

Cytokine, eicosanoids, and free haeme inside a unit of transfused stored RBCs can trigger a proinflammatory response, as can NTBI generated by extravascular hemolysis in the recipient (Wood JC, 2016). Researchers have found that storage lesions had similar effects on in vitro and in vivo models, including increased adherence to endothelial cells, activated complement, and altered coagulability (Donadee C, 2011). These results also cause capillary leakage by damaging the endothelium lining (Yalcin O, 2014). Even though stored RBCs are known to promote inflammation, there are also reports of them having immunological modulatory effects due to NTBI, RBC phagocytosis, and contact with T-cells (Piknova B, 2009).

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4. INTERACTIONS BETWEEN TRANSMEMBRANE TRANSPORT AND ITS MEDIATING PROTEINS

4.1 Transporters of Ions in Coupling

Anion exchanger proteins make up a sizable portion of the red blood cell membrane. These enable RBCs to keep the right balance between their extracellular water and solute content and their intracellular water and solute content, which is necessary for the maintenance of normal RBC physiological performance and homeostasis. When the amount of sodium entering the red blood cells is greater than the amount leaving the cells (through potassium efflux), the RBCs expand (Gallagher, 2017). Because of this, irregular and abnormal RBC behavior may develop if there is a significant shift or a fault in the system governing the hydration balance (Azouzi et al., 2018).

4.2 Band three

Specifically, band 3 is the primary anion exchanger protein in red blood cell membranes. RBC membrane stability is ensured by this transmembrane glycoprotein (100 kDa). Carbon dioxide transport and anion-exchange transporter roles are supported by the C-terminal integral membrane side, whereas the N-terminal cytoplasmic side participates in connecting to the membrane skeleton, glycolytic enzymes, and deoxyhemoglobin (Lux, 2016).

Macrophages mediate the clearance of abnormal and aged RBC by producing senescence-induced-antigens that are recognized by natural antibodies, and these changes can be passed from the hemoglobin level to the membrane (NAbs; Klei et al., 2017; Azouzi et al., 2018).

Band 3 communicates with other membrane proteins through its many binding sites. By doing so, a vital network is established for signal transmission between the membrane and the cytoskeleton, which controls RBC pliability, stability, and deformability. Under hypoxic conditions, Rifkind and Nagababu demonstrated, red blood cell (RBC) membrane modifications triggered by the interaction of hemoglobin (Hb) with band 3 are essential (Rifkind and Nagababu, 2013). Patients with diabetes mellitus have an increased risk of vascular complications because glycated (AGE) band 3 binds to the receptor for advance glycation end products (RAGE) present on ECs, increasing oxidant stress in the vessel wall (Schmidt et al., 1996; Grossin et al., 2009a) (Wautier et al., 2004).

4.3 PIEZO1

An essential function in regulating RBC volume homeostasis is played by PIEZO1, a non-selective cation channel found quite recently. Genetic mutations are well-known to the PIEZO1 gene and are the most common inherited cause of xerocytosis. Modifications at the genetic level affect channel dynamics, responsiveness membrane trafficking, and osmotic stress (Glogowska et al., 2017), causing a drop in calcium and other total cellular cations.

along with high potassium levels and insufficient sodium intake fluids, resulting in severe dehydration (Bae et al 2013, honore et al., 2015, parel et al., 2015). Its inherent character principally and directly on the stimulation through the application of external physical forces (such as prodding, stretching, torsion, and shear stress) (Cahalan et al., 2015; Gottlieb, 2017; Parpaitein 2017; Coste in the same year).

Numerous theories have been proposed for the Initiation of the PIEZO1 function. Some argue that membrane strain can cause lipid bilayers to rupture, supporting the "force-from-lipids" concept. changes in the area around the protein that triggers the opening of the channel. In contrast, the "force-from-filaments" hypothesis suggests a conceptualization of the channel's entwinement and interaction with proteins of the intercellular matrix or the extracellular matrix (Murthyet al., 2017).

Various parts of the brain have been shown through functional studies that proteins are more easily influenced by physical forces. then those in other areas. Plus, there are a lot of mechanical cues, like shear stress, caused by fluid motion over cells. that may have a mutual effect of activating PIEZO1 channels. A study on this topic was just published (Murthy et al., 2017). To date, however, these processes have not been fully grasped, and the potential role of PIEZO1 is a candidate for the stretch-induced cation route aging red blood cells, and shear stress in the vascular system (Bagriantsev et al., 2014). It has also been suggested that the malaria parasite uses it. an outbreak of malaria caused by Plasmodium falciparum (Zuccala et al., 2016; Ma et al., 2018). It was discovered that one-third of African the population had a new PIEZO1 variation linked to the disease, Malaria in a Petri Dish (Ma et al., 2018).

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5. INTERACTIONS MEDIATED BY PLASMA PROTEINS

5.1 Thrombospondin (TSP)

The protein thrombospondin is found in two different forms, one as an immobilized component of the extracellular matrix and another as a soluble component of the blood plasma. It can function as a linker between red blood cells and endothelial cells or platelets, promoting adhesion (Telen, 2005). As soon as CD36 is expressed on red blood cells and endothelial cells simultaneously, TSP can link the two types of receptors together (Trinh-Trang-Tan et al., 2010). Through CD36's heparin-binding domain, TSP can also interact with RBC PS (Betal and Setty, 2008). CD47 and sulfated glycolipids are two more putative TSP receptors found on RBC.

However, TPS binds to v3 integrin, which is found on the surface of ECs (Manodori et al., 2000). Heparin has been shown to impede TSP binding (Gupta et al., 1999). By binding to RBC CD47, soluble TSP triggers a pathway that in turn activates 41 for enhanced adhesion to immobilized TSP (Brittain et al., 2004). When RBCs are subjected to shear stress, this signaling pathway becomes more activated (Telen, 2005). TSP can bind CD47, CD36, 41, PS, and sulfated glycolipids on RBC, suggesting it may serve as a link between RBC and platelets in their interaction (Betal and Setty, 2008). The CD47-dependent pathway is activated by the interaction of CD36 with TSP. CD47 can interact with platelet IIb3 integrin, which in turn can interact with ICAM-4 (Lagadec et al., 2003). Vascular TSP expression is significantly upregulated in several pathologies, including cardiovascular disease, diabetes, atherosclerosis, and ischemia-reperfusion injury (IRI; Csányi et al., 2012).

5.2 Von Willebrand Factor (vWF)

Platelet-independent signaling from the endothelium receptors v3 and/or glycoprotein Ib to a receptor on RBCs is mediated by the von Willebrand factor (Setty et al., 2002; Smeets M. et al., 2017). It appears that vWF-mediated adhesion has a distinct quantitative and qualitative role in the microvascular endothelium than it does in the endothelium of big vessels (Brittain et al., 1992).

Diseases include SCD, sepsis, chronic renal disease, hemolytic uremic syndrome, hepatic failure, Wilson's disease, diabetes, Alzheimer's disease, and thrombotic thrombocytopenic have been associated to increased RBC stress. RBCs interact with monomer vWF and long multimers vWF aggregated into big insoluble fibers under these conditions, causing the RBCs to adhere to the ECs. This causes microangiopathic vascular damage, which reduces blood flow and eventually causes (multiple) organ failure (Smeets M.W. et al., 2017).

PS is an adhesion molecule that has been demonstrated to interact with vWF, hence facilitating RBC binding (Nicolay et al., 2018). The annexin V molecule is responsible for this connection because it binds not only to PS on the RBC surface but also to vWF, securing the PS-exposing membrane to the vWF or the vessel wall (Nicolay et al., 2018). Blood cells (RBC) have been shown to assemble into venous thrombi when shear stress in the vascular walls is low (Smeets M. et al., 2017).

RBC can adhere to vWF strings, which are connected to the endothelium by P-selectin or v3 integrin on the luminal surface (Smeets M.W. et al., 2017), and by the endothelial glycocalyx, when intracellular Ca2+ levels are elevated, as is the case in sickle cells but also in normal RBC (Bogdanova et al (Kalagara et al., 2018). Researchers Sultana et al. demonstrated that sickle cells cultured with ECs in the presence of multimers of vWF increased EC expression of adhesion molecules ICAM-1, E-selectin, and VCAM-1, allowing the sickle cells to more easily adhere to the ECs (Sultana et al., 1998).

5.3 Fibrinogen

Blood plasma contains the glycoprotein fibrinogen. In pathological states such excessive bleeding or liver illness, fibrinogen levels rise (Tsang et al., 1990). High fibrinogen levels are associated with cerebrovascular impairment. cause inflammation because of an increase in plasma protein levels along with heightened vascular permeability that encourages Thrombogenesis and hypercoagulability (Muradashvili and Lominadze, 2013) is cited.

There was evidence that elevated fibrinogen is associated with a rise in C-reactive protein (CRP) levels, which hemorrhagic disease has been linked to erythrocyte diagnostic tools include the sedimentation rate (ESR) and the erythrocyte parameters (Bitik et al., 2015; Flormann et al., 2015). (Bitik et al., 2015; Flormann et al., 2015).

And furthermore, studies have revealed that fibrinogen can bind to a variety of surfaces. receptors on red blood cells (such as CD47) and platelets (with IIb3- such as integrin (Carvalho et al., 2010; De Oliveira et al., 2012). As previously reported (Massberg et al., 1999). Sickle deoxygenated red blood cells; it was finally seen. tend to adhere to one another, especially when fibrinogen is present (Weiss et al, 2011).

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REFERENCES

[1] Kanias T, Acker JP. Biopreservation of red blood cells—the struggle with hemoglobin oxidation. FEBS J 2010; 277: 343-56.

[2] D'Alessandro A, Zolla L. Proteomic analysis of red blood cells and the potential for the clinic: what have we learned so far? Expert Rev Proteomics 2017; 14: 243-52.

[3] Winslow RM. Oxygen: the poison is in the dose. Transfusion 2013; 53: 424-37.

[4] Mebius RE, Kraal G (2005) Structure and function of the spleen. Nat Rev Immunol 5:606–616.

[5] Petroianu A (2011) The Spleen (Bentham Science Publishers, Hilversum, The Netherlands).

[6] Buffet PA, et al. (2006) Ex vivo perfusion of human spleens maintains clearing and processing functions. Blood 107:3745–3752.

[7] Safeukui I, et al. (2008) Retention of plasmodium falciparum ring-infected erythrocytes in the slow, open microcirculation of the human spleen. Blood 112:2520–2528.

[8] Safeukui I, et al. (2012) Quantitative assessment of the human spleen's sensing and sequestration of spherocytic erythrocytes. Blood 120:424–430.

[9] Ndour PA, et al. (2015) Role of the Spleen in Human Malaria (Springer, New York).

[10] Wu, F.; Zhao, S.; Yu, B.; Chen, Y.-M.; Wang, W.; Song, Z.-G.; Hu, Y.; Tao, Z.-W.; Tian, J.-H.; Pei, Y.-Y.; Yuan, M.-L.; Zhang, Y.-L.; Dai, F.-H.; Liu, Y.; Wang, Q.-M.; Zheng, J.-J.; Xu, L.; Holmes, E. C.; Zhang, Y.-Z. A New Coronavirus Associated with Human Respiratory Disease in China. Nature 2020, 579 (7798), 265−269.

[11] Andersen, K. G.; Rambaut, A.; Lipkin, W. I.; Holmes, E. C.; Garry, R. F. The Proximal Origin of SARS-CoV-2. Nat. Med. 2020, 26 (4), 450−452.

[12] Lan, J.; Ge, J.; Yu, J.; Shan, S.; Zhou, H.; Fan, S.; Zhang, Q.; Shi, X.; Wang, Q.; Zhang, L.; Wang, X. Structure of the SARS-CoV-2 Spike Receptor-Binding Domain Bound to the ACE2 Receptor. Nature 2020, 581, 1−6.

[13] Fantini, J.; Di Scala, C.; Chahinian, H.; Yahi, N. Structural and Molecular Modelling Studies Reveal a New Mechanism of Action of Chloroquine and Hydroxychloroquine against SARS-CoV-2 Infection. Int. J. Antimicrob. Agents 2020, 55 (5), 105960.

[14] D'Alessandro, A.; Dzieciatkowska, M.; Nemkov, T.; Hansen, K. C. Red Blood Cell Proteomics Update: Is There More to Discover? Blood Transfuse. 2017, 15 (2), 182−187.

[15] McCullough, J. RBCs as Targets of Infection. Hematology 2014, 2014 (1), 404−409.

[16] D'Alessandro, A.; Thomas, T.; Dzieciatkowska, M.; Hill, R. C.; Francis, R. O.; Hudson, K. E.; Zimring, J. C.; Hod, E. A.; Spitalnik, S. L.; Hansen, K. C. Serum Proteomics in COVID-19 Patients: Altered Coagulation and Complement Status as a Function of IL-6 Level. medRxiv 2020, DOI:10.1101/2020.05.29.20116889.

[17] Longo, V.; Marrocco, C.; Zolla, L.; Rinalducci, S. Label-Free Quantitation of Phosphuretted Changes in Erythrocyte Membranes: Towards Molecular Mechanisms Underlying Deformability Alterations in Stored Red Blood Cells. Hematological 2014, 99 (7), e122−e125.

[18] Kingsley PD, Greenfest-Allen E, Frame JM, et al. Ontogeny of erythroid gene expression. Blood 2013; 121: e5–e13.

[19] An X, Schulz VP, Li J, et al. Global transcriptome analyses of human and murine terminal erythroid differentiation. Blood 2014; 123:3466–3477.

[20] Pishesha N, Thiru P, Shi J, et al. Transcriptional divergence and conservation of human and mouse erythropoiesis. Proc Natl Acad Sci USA 2014; 111:4103–4108.

[21] Shi L, Lin YH, Sierant MC, et al. Developmental transcriptome analysis of human erythropoiesis. Hum Mol Genet 2014; 23:4528–4542.

[22] Zhang D, Johnson MM, Miller CP, et al. An optimized system for studies of EPO-dependent murine pro-erythroblast development. Exp Hematol 2001; 29:1278–1288.

[23] Singh S, Dev A, Verma R, et al. Defining an EPOR- regulated transcriptome for primary progenitors, including Tnfr-sf13c as a novel mediator of Epode pendent erythroblast formation. PLoS One 2012; 7: e38530.

[24] Kuhrt D, Wojchowski DM. Emerging EPO and EPO receptor regulators and signal transducers. Blood 2015; 125:3536–3541.

[25] Love PE, Warzecha C, Li L. Ldb1 complexes: the new master regulators of erythroid gene transcription. Trends Genet 2014; 30:1–9.

[26] Grebien F, Kerenyi MA, Kovacic B, et al. Stat5 activation enables erythropoiesis in the absence of EpoR and Jak2. Blood 2008; 111:4511–4522.

[27] Shin HY, Willi M, HyunYoo K, et al. Hierarchy within the mammary STAT5-driven Wap super-enhancer. Nat Genet 2016; 48:904–911.

[28] Gillinder KR, Tuckey H, Bell CC, et al. Direct targets of pSTAT5 signaling in erythropoiesis. PLoS One 2017; 12: e0180922.

[29] Theurl, I., Hilgendorf, I., Nairz, M., Tymoszuk, P., Haschka, D., Asshoff, M., He, S., Gerhardt, L.M., Holderried, T.A., Seifert, M., Sopper, S., Fenn, A.M., Anzai, A., Rattik, S., McAlpine, C., Nahrendorf, M., Weiss, G., Weissleder, R., Lin, H.Y. & Swirski, F.K. (2016) On-demand erythrocyte disposal and iron recycling requires transient macrophages in the liver. Nature Medicine, 22, 945–951.

[30] Li, H., Choesang, T., Bao, W., Chen, H., Feola, M., Garcia-Santos, D., Li, J., Sun, S., Follenzi, A., Pham, P., Liu, J., Zhang, J., Ponka, P., An, X., Mohandas, N., Fleming, R.E., Rivella, S., Li, G. & Ginzburg, Y.Z. (2017) Decreasing TfR1 expression reverses anemia and hepcidin suppression in beta-thalassemic mice. Blood, 129,1514–1526.

[31] Camaschella, C., Roetto, A., Cali, A., De Gobbi, M., Garozzo, G., Carella, M., Majorano, N., Totaro, A. & Gasparini, P. (2000) The gene TFR2 is mutated in a new type of hemochromatosis mapping to 7q22. Nature Genetics, 25,14–15.

[32] Forejtnikova, H., Vieillevoye, M., Zermati, Y., Lambert, M., Pellegrino, R.M., Guihard, S., Gaudry, M., Camaschella, C., Lacombe, C., Roetto, A., Mayeux, P. & Verdier, F. (2010) Transferrin receptor 2 is a component of the erythropoietin receptor complex and is required for efficient erythropoiesis. Blood, 116, 5357–5367.

[33] Nai, A., Lidonnici, M.R., Rausa, M., Mandelli, G., Pagani, A., Silvestri, L., Ferrari, G. & Camaschella, C. (2015) The second transferrin receptor regulates red blood cell production in mice. Blood, 125, 1170–1179.

[34] Khalil, S., Delehanty, L., Grado, S., Holy, M., White, Z. 3rd, Freeman, K., Kurita, R., Nakamura, Y., Bullock, G. & Goldfarb, A. (2018) Iron modulation of erythropoiesis is associated with Scribble-mediated control of the erythropoietin receptor. The Journal of Experimental Medicine, 215, 661–679.

[35] Lakhal-Littleton, S., Wolna, M., Chung, Y.J., Christian, H.C., Heather, L.C., Brescia, M., Ball, V., Diaz, R., Santos, A., Biggs, D., Clarke, K., Davies, B. & Robbins, P.A. (2016). An essential cell-autonomous role for hepcidin in cardiac iron homeostasis. Elfie 5, pii. e19804.

[36] Nemkov T, Hansen KC, Dumont LJ, D'Alessandro A. Metabolomics in transfusion medicine. Transfusion 2016; 56: 980-93.

[37] Prudent Rappaz M, B, Hamelin R, et al. Indirect activity of kinases on protein phosphorylation: loss of protein Tyr-phosphorylation during in vitro storage of human erythrocytes: impact on RBC morphology. Transfusion 2014; 54: 49A-50A.

[38] Park Y, Best CA, Auth T, et al. Metabolic remodeling of the human red blood cell membrane. Proc Natl Acad Sci U S A 2010; 107: 1289-94.

[39] Reynolds JD, Ahearn GS, Angelo M, et al. S-nitroso hemoglobin deficiency: a mechanism for loss of physiological activity in banked blood. Proc Natl Acad Sci U S A 2007; 104: 17058-62.

[40] Winslow RM, Intagli Etta M. Red cell age and loss of function: advance or SNO-job? Transfusion 2008; 48: 411-4.

[41] Isbell TS, Sun CW, Wu LC, et al. SNO-hemoglobin is not essential for red blood cell-dependent hypoxic vasodilation. Nat Med 2008; 14: 773-7.

[42] Rodgers GP, Lichtman HC, Sheff MF. Red blood cell glucose6-phosphate dehydrogenase activity in aged humans. J Am Geriatr Soc 1983; 31: 8-11.

[43] Blasi B, D'Alessandro A, Raymundo N, Zolla L. Red blood cell storage and cell morphology. Transfuse Med 2012; 22: 90-6.

[44] Bardyn M, Rappaz B, Jaferzadeh K, et al. red blood cells aging markers: a multi-parametric analysis. Blood Transfuse 2017; 15: 239-48.

[45] Mays JA, Hess JR. Modelling the effects of blood component storage lesions on the quality of hemostatic resuscitation in massive transfusion for trauma. Blood Transfuse 2017; 15: 153-7.

[46] Dumont LJ, AuBuchon JP. Evaluation of proposed FDA criteria for the evaluation of radiolabeled red cell recovery trials. Transfusion 2008; 48: 1053-60.

[47] Bosman GJ, Lasonder E, Luten M, et al. The proteome of red cell membranes and vesicles during storage in blood bank conditions. Transfusion 2008; 48: 827-35.

[48] Prudent M, Delobel J, Hubner A, et al. Proteomics of stored red blood cell membrane and storage-induced microvesicles reveals the association of Flotillin-2 with band 3 complexes. Front Physio 2018; 9: 421.

[49] Wojczyk BS, Kim N, Bandyopadhyay S, et al. Macrophages clear refrigerator storage-damaged red blood cells and subsequently secrete cytokines in vivo, but not in vitro, in a murine model. Transfusion 2014; 54: 3186-97.

[50] Lion N, Crettaz D, Rubin O, Tissot JD. Stored red blood cells: a changing universe waiting for its map(s). J Proteomics 2010; 73: 374-85.

[51] Burger P, Kostova E, Bloem E, et al. Potassium leakage primes stored erythrocytes for phosphatidylserine exposure and shedding of pro-coagulant vesicles. Br J Haematol 2013; 160: 377-86.

[52] Roussel C, Dussiot M, Marin M, et al. Spherocytic shift of red blood cells during storage provides a quantitative whole cell-based marker of the storage lesion. Transfusion 2017; 57: 1007-18.

[53] Kriebardis AG, Antonelou MH, Stamoulis KE, et al. Storage-dependent remodeling of the red blood cell membrane is associated with increased immunoglobulin G binding, lipid raft rearrangement, and caspase activation. Transfusion 2007; 47: 1212-20.

[54] Daly A, Raval JS, Waters JH, et al. Effect of blood bank storage on the rheological properties of male and female donor red blood cells. Clin Hemorheology Microcirc 2014; 56: 337-45.

[55] Salaria ON, Barodka VM, Hogue CW, et al. Impaired red blood cell deformability after transfusion of stored allogeneic blood but not autologous salvaged blood in cardiac surgery patients. Anesth Analg 2014; 118: 1179-87.

[56] Berezina TL, Zaets SB, Morgan C, et al. Influence of storage on red blood cell rheological properties. J Surg Res 2002; 102: 6-12.

[57] Bennett-Guerrero E, Veldman TH, Doctor A, et al. Evolution of adverse changes in stored RBCs. Proc Natl Acad Sci U S A 2007; 104: 17063-8.

[58] Rapido F, Brittenham GM, Bandyopadhyay S, et al. Prolonged red cell storage before transfusion increases extravascular hemolysis. J Clin Invest 2017; 127: 375-82.

[59] Prestia K, Bandyopadhyay S, Slate A, et al. Transfusion of stored blood impairs host defenses against Gram-negative pathogens in mice. Transfusion 2014; 54: 2842-51.

[60] Rapido F. The potential adverse effects of hemolysis. Blood Transfus 2017; 15: 218-21.

[61] Hod EA, Spitalnik SL. Stored red blood cell transfusions: iron, inflammation, immunity, and infection. Transfus Clin Biol 2012; 19: 84-9.

[62] Wood JC, Cohen AR, Pressel SL, et al. Organ iron accumulation in chronically transfused children with sickle cell anemia: baseline results from the TWiTCH trial. Br J Haematol 2016; 172: 122-30.

[63] Donadee C, Raat NJ, Kanias T, et al. Nitric oxide scavenging by red blood cell microparticles and cell-free hemoglobin as a mechanism for the red cell storage lesion. Circulation 2011; 124: 465-76.

[64] Yalcin O, Ortiz D, Tsai AG, et al. Microhemodynamic aberrations created by transfusion of stored blood. Transfusion 2014; 54: 1015-27.

[65] Piknova B, Keszler A, Hogg N, Schechter AN. The reaction of cell-free oxyhemoglobin with nitrite under physiologically relevant conditions: implications for nitrite-based therapies. Nitric Oxide 2009; 20: 88-94.

[66] Gallagher, P. (2017). Disorders of erythrocyte hydration. Blood 130, 2699–2708.doi: 10.1182/blood-2017-04-590810.

[67] Azouzi, S., Romana, M., Arashiki, N., Takakuma, Y., Nemer, W. E., Peyrard, T., et al. (2018). Band 3 phosphorylation induces irreversible alterations of stored red blood cells. Am. J. Hematol. 93, E110–E112.

[68] Lux, S. D. (2016). Anatomy of the red cell membrane skeleton: unanswered questions. Blood 127, 187–199. DOI: 10.1182/blood-2014-12-512772.

[69] Klei, T., Meinderts, S., van den Berg, T., and van Bruggen, R. (2017). From the cradle to the grave: the role of macrophages in erythropoiesis and erythrophagocytosis. Front. Immunol. 8:73. doi: 10.3389/fimmu.2017.00073.

[70] Rifkind, J., and Nagababu, E. (2013). Hemoglobin redox reactions and red blood cell aging. Antioxid. Redox Signal. 18, 2274–2283. DOI: 10.1089/ars.2012.4867.

[71] Schmidt, A. M., Hori, O., Cao, R., Yan, S., Brett, J., Wautier, J., et al. (1996). RAGE: a novel cellular receptor for advanced glycation end products. Diabetes 45(Suppl. 3), S77–S80.

[72] Grossin, N., Wautier, M., Picot, J., Stern, D., and Wautier, J. (2009a). Differential effect of plasma or erythrocyte AGE-ligands 286 of RAGE on the expression of transcripts for receptor isoforms. Diabetes Metab. 35, 410–417. DOI: 10.1016/j.diabet.2009.04.009.

[73] Wautier, M., Boulanger, E., Guillausseau, P., Massin, P., and Wautier, J. L. (2004). AGEs, macrophage colony-stimulating factor, and vascular adhesion molecule blood levels are increased in patients with diabetic microangiopathy. Throm. Haemost. 91, 879–885. doi: 10.1160/th03-07-0486.

[74] Glogowska, E., Schneider, E. R., Maksimova, Y., Schulz, V. P., Lezon-Geyda, K., Wu, J., et al. (2017). Novel mechanisms of PIEZO1 dysfunction in hereditary xerocytosis. Blood 130, 1845–1856. doi: 10.1182/blood-2017-05-786004.

[75] Bae, C., Gnanasambandam, R., Nicolai, C., Sachs, F., and Gottlieb, P. A. (2013). Xerocytosis is caused by mutations that alter the kinetics of the mechanosensitive channel PIEZO1. Proc. Natl. Acad. Sci. U.S.A. 110, E1162–E1168. doi: 10.1073/pnas.1219777110.

[76] Honoré, E., Martins, J. R., Penton, D., Patel, A., and Demolombe, S. (2015). The Piezo mechanosensitive ion channels: may the force be with you! Rev. Physiol. Biochem. Pharmacol. 169, 25–41. doi: 10.1007/112_2015_26.

[77] Patel, A., Demolombe, S., and Honore, E. (2015). Piezo1 Ion Channels: an alternative to force. eLife 4:e08659.

[78] Cahalan, S. M., Lukacs, V., Ranade, S. S., Chien, S., Bandell, M., and Patapoutian, A. (2015). Piezo1 links mechanical forces to red blood cell volume. eLife 4: e07370.doi: 10.7554/eLife.07370.

[79] Gottlieb, P. A. (2017). A tour de force: the discovery, properties, and function of Piezo channels. Curr. Top. Membr. 79, 1–36. doi: 10.1016/bs.ctm.2016.11.007.

[80] Parpaite, T., and Coste, B. (2017). Piezo channels. Curr. Biol. 3, R243–R258.

[81] Murthy, S., Dubin, A., and Patapoutian, A. (2017). Piezos thrive under pressure: mechanically activated ion channels in health and disease. Nat. Rev. Mol. Cell Biol. 18, 771–783. doi: 10.1038/nrm.2017.92.

[82] Bagriantsev, S. N., Gracheva, E. O., and Gallagher, P. G. (2014). Piezo proteins: regulators of mechanosensation and other cellular processes. J. Biol. Chem. 289,31673–31681. doi: 10.1074/jbc. R114.612697.

[83] Zhang, M. Y., Zhang, Y., Wu, X., Zhang, K., Lin, P., Bian, H., et al. (2018). Disrupting CD147-RAP2 interaction abrogates erythrocyte invasion by Plasmodium falciparum. Blood 131, 1111–1121. DOI: 10.1182/blood-2017-08-802918.

[84] Ma, S., Cahalan, S., LaMonte, G., Grubaugh, N., Zeng, W., Murthy, S., et al. (2018). Common PIEZO1 allele in African populations causes RBC dehydration and attenuates plasmodium infection. Cell 173, 443–455.e12. doi: 10.1016/j.cell.2018.02.047.

[85] Telen, M. J. (2005). Erythrocyte adhesion receptors: blood group antigens and related molecules. Transfus. Med. Rev. 19, 32–44. doi: 10.1016/j.tmrv.2004.09.006.

[86] Trinh-Trang-Tan, M.-M., Villela-Lamego, C., Picot, J., Wautier, M.-P., and Cartron, J.-P. (2010). Intercellular adhesion molecule-4 and CD36 are implicated in the abnormal adhesiveness of sickle cell SAD mouse erythrocytes to the endothelium. Haematologica 95, 730–737. doi: 10.3324/haematol.2009.017392.

[87] Betal, S. G., and Setty, Y. B. (2008). Phosphatidylserine-positive erythrocytes bind to immobilized and soluble thrombospondin-1 via its heparin binding domain. Transl. Res. 152, 165–177. doi: 10.1016/j.trsl.2008.07.007.

[88] Manodori, B., Barabino, G. A., Lubin, B. H., and Kuypers, F. A. (2000). Adherence of phosphatidylserine-exposing erythrocytes to endothelial matrix thrombospondin. Blood 95, 1293–1300.

[89] Gupta, K., Gupta, P., Solovey, A., and Hebbel, R. P. (1999). Mechanism of interaction of thrombospondin with human endothelium and inhibition of sickle erythrocyte adhesion to human endothelial cells by heparin. Biochim. Biophys. Acta 1453, 63–73. doi: 10.1016/s0925-4439(98)00085-4.

[90] Brittain, J. E., Han, J., Ataga, K. I., Orringer, E. P., and Parise, L. V. (2004). Mechanism of CD47-induced alpha4beta1 integrin activation and adhesion in sickle reticulocytes. J. Biol. Chem. 279, 42393–42402. doi: 10.1074/jbc.m407631200.

[91] Telen, M. J. (2005). Erythrocyte adhesion receptors: blood group antigens and related molecules. Transfus. Med. Rev. 19, 32–44. doi: 10.1016/j.tmrv.2004.09.006.

[92] Betal, S. G., and Setty, Y. B. (2008). Phosphatidylserine-positive erythrocytes bind to immobilized and soluble thrombospondin-1 via its heparin-binding domain. Transl. Res. 152, 165–177. DOI: 10.1016/j.trsl.2008.07.007.

[93] Lagadec, P., Dejoux, O., Ticchioni, M., Cottrez, F., Johansen, M., Brown, E. J., et al. (2003). Involvement of a CD47-dependent pathway in platelet adhesion on inflamed vascular endothelium under flow. Blood 101, 4836–4843. doi: 10.1182/blood-2002-11-3483.

[94] Csányi, G., Yao, M., Rodríguez, A., Al Ghouleh, I., Sharifi-Sanjani, M., Frazziano, G., et al. (2012). Thrombospondin-1 regulates blood flow via CD47 receptormediated activation of NADPH oxidase 1. Arterioscler. Thromb. Vasc. Biol. 32, 2966–2973. doi: 10.1161/ATVBAHA.112.300031.

[95] Setty, Y., Kulkarni, S., and Stuart, M. J. (2002). Role of erythrocyte phosphatidylserine in sickle red cell-endothelial adhesion. Blood 99, 1564–1571. Doi: 10.1182/blood. v99.5.1564.

[96] Smeets, M., Mourik, M., Niessen, H., and Hordijk, P. (2017). Stasis promotes erythrocyte adhesion to von Willebrand factor. Arteriosclerosis. Thrombi. Vasco. Biol. 37, 1618–1627. Doi: 10.1161/ATVBAHA.117.309885.

[97] Brittain, H. A., Eckman, J. R., and Wick, T. M. (1992). Sickle erythrocyte adherence to large vessel and microvascular endothelium under physiologic flow is qualitatively different. J. Lab. Clin. Med. 120, 538–545.

[98] Nicolay, J., Thorn, V., Daniel, C., Amann, K., Siraskar, B., Lang, F., et al. (2018). Cellular stress induces erythrocyte assembly on intravascular von Willebrand factor strings and promotes microangiopathy. Sci. Rep. 8:10945. Doi: 10.1038/s41598-018-28961-2.

[99] Bogdanova, A., Makhro, A., Wang, J., Lipp, P., and Kaestner, L. (2013). Calcium in red blood cells a perilous balance. Int. J. Mol. Sci. 14, 9848–9872. doi:10.3390/ijms14059848.

[100] Kalagara, T., Moutsis, T., Yang, Y., Pappelbaum, K., Farken, A., Cladder-Micus, L., et al. (2018). The endothelial glycocalyx anchors von Willebrand factor fibers to the vascular endothelium. Blood Adv. 2, 2347–2357. Doi: 10.1182/bloodadvances.2017013995.

[101] Sultana, C., Shen, Y., Rattan, V., Johnson, C., and Kalra, V. (1998). Interaction of sickle erythrocytes with endothelial cells in the presence of endothelial cell conditioned medium induces oxidant stress leading to trans endothelial migration of monocytes. Blood 92, 3924–3935.

[102] Tsang, S. S., Szeto, R., and Feng, C. (1990). Fibrinogen level in health and disease. Singapore Med. J. 31, 51–52.

[103] Muradashvili, N., and Lominadze, D. (2013). Role of fibrinogen in cerebrovascular dysfunction after traumatic brain injury. Brain Inj. 27, 1508–1515. Doi: 10.3109/02699052.2013.823562.

[104] Bitik, B., Mercan, R., Tufan, A., Tezcan, E., Küçük, H., ilhan, M., et al. (2015). Differential diagnosis of elevated erythrocyte sedimentation rate and C-reactive protein levels: a rheumatology perspective. Eur. J. Rheumatol. 2, 131–134. doi:10.5152/eurjrheum.2015.0113.

[105] Flormann, D., Kuder, E., Lipp, P., Wagner, C., and Kaestner, L. (2015). Is there a role of C-reactive protein in red blood cell aggregation? Int. J. Lab. Haematol. 37, 474–482. Doi: 10.1111/ijlh.12313.

[106] Carvalho, F. A., Connell, S., Miltenberger-Miltenyi, G., Pereira, S. V., Tavares, A., Ariëns, R. A., et al. (2010). Atomic force microscopy-based molecular recognition of a fibrinogen receptor on human erythrocytes. ACS Nano 4, 4609–4620. Doi: 10.1021/nn1009648.

[107] De Oliveira, S., de Almeida, V. V., Calado, A., Rosário, H. S., and Saldanha, C. (2012). Integrin-associated protein (CD47) is a putative mediator for soluble fibrinogen interaction with human red blood cells membrane. Biochim. Biophys. Acta 1818, 481–490. Doi: 10.1016/j.bbamem.2011.10.028.

[108] Massberg, S., Enders, G., and Matos, F. C. (1999). Fibrinogen deposition at the postischemic vessel wall promotes platelet adhesion during ischemia reperfusion in vivo. Blood 94, 3831–3838.

[109] Weiss, E., Rees, D. C., and Gibson, J. S. (2011). Role of calcium in phosphatidylserine externalization in red blood cells from sickle cell patients. Anemia 2011:379894. Doi: 10.1155/2011/379894.