Pathophysiology of Sickle Cell Disease

Subjects: Biology

Contributor: Yann Lamarre, Elie Nader, Philippe Connes, Marc Romana, Yohann Garnier

Sickle cell disease (SCD) is the most common hemoglobinopathy worldwide. It is characterized by an impairment of shear stress-mediated vasodilation, a pro-coagulant, and a pro-adhesive state orchestrated among others by the depletion of the vasodilator nitric oxide, by the increased phosphatidylserine exposure and tissue factor expression, and by the increased interactions of erythrocytes with endothelial cells that mediate the overexpression of adhesion molecules such as VCAM-1, respectively. Extracellular vesicles (EVs) have been shown to be novel actors involved in SCD pathophysiological processes. Medium-sized EVs, also called microparticles, which exhibit increased plasma levels in this pathology, were shown to induce the activation of endothelial cells, thereby increasing neutrophil adhesion, a key process potentially leading to the main complication associated with SCD, vaso-occlusive crises (VOCs). Small-sized EVs, also named exosomes, which have also been reported to be overrepresented in SCD, were shown to potentiate interactions between erythrocytes and platelets, and to trigger endothelial monolayer disruption, two processes also known to favor the occurrence of VOCs.

Keywords: sickle cell disease ; SCD ; extracellular vesicles ; EVs ; microparticles

1. Physiological Hemostasis and Inflammation

The pathophysiology of SCD relies on the disturbance of several physiological processes, among which coagulation, vasoregulation, and inflammation are crucial. “Hemostasis” comprises all the processes permitting to prevent excessive blood loss following injury, including vasoregulation, which refers to the mechanisms allowing to modulate blood vessels diameter. The term “inflammation” corresponds to the reactions to fight against a pathogen. However, in SCD these reactions can occur in the absence of microorganisms and are associated with hemolysis-mediated release of DAMPs (damage-associated molecular patterns) [1] and MPs, among others.

1.1. Normal Hemostasis

When a blood vessel is severed or punctured, a three-step process occurs to prevent further loss of blood: vascular spasm (a vasoconstriction step to reduce blood losses), platelet plug formation and finally coagulation. In vascular spasm, the smooth muscle regulating the vessel diameter contracts to reduce blood losses. Moreover, owing to the injury, the vessel wall conjunctive tissue is exposed, and platelets adhere to its collagen fibers. Platelets begin to clump together and to release molecules from their granules to maintain vasoconstriction and expand the platelet plug, by activating nearby platelets. The last step to ensure hemostasis, is called coagulation, and consists in forming a blood clot. Coagulation factors contained in the plasma, or produced by aggregated platelets and damaged endothelial cells, are activated sequentially. This coagulation cascade leads to the conversion of prothrombin into its active form called thrombin, and ends to the thrombin-mediated conversion fibrinogen into fibrin, which forms a mesh in which red blood cells and platelets are trapped.

Coagulation cascade comprises 12 known factors, which bear a subscript “a” to indicate their activated state. This cascade can start by an extrinsic or an intrinsic pathway, which merge into a third one called common final pathway. The extrinsic pathway, also known as the tissue factor pathway, lasts only few seconds, and is initiated due to a trauma undergone by extravascular cells, which provokes the exposure of tissue factor, the coagulation factor III. The intrinsic pathway, also called contact activation pathway, typically begins by the activation of factor XII, when it encounters anionic molecules of the damaged vessel wall, and is completed within a few minutes. The extrinsic and intrinsic pathways lead to the formation of complex that is able to activate factor X, and is so called “tenase complex”. After factor X activation by an extrinsic or an intrinsic tenase complex, the complex called “prothrombinase complex”, composed of factors Xa and Va, converts prothrombin (factor II) into thrombin (Factor IIa). Once produced, thrombin amplifies the cascade by activating factors XI, VIII, V and VII to trigger the production of even more thrombin, and so even more fibrin. Importantly, both the intrinsic tenase and the prothrombinase complexes assemble on negatively charged phospholipids, it is to say on phosphatidylserine.

Nitric oxide (or NO) is the main vasodilator [2]. It inhibits the action of the most potent vasoconstrictor, endothelin-1 [3], by acting at the transcriptional and translational levels, but also by impeding its release [4]. NO was also shown to inhibit the expression of adhesion molecules by erythrocytes and leukocytes [5], and to prevent platelet aggregation [6]. The production of this vasodilator gas by NO synthase (NOS), from arginase, is stimulated by shear stress, platelet aggregation, and thrombin; whereas hypoxia and some pro-inflammatory cytokines increase endothelin-1 concentration. However, wall shear stress (WSS), the dragging frictional force generated by blood flow and blood viscosity, is the main physiological NOS stimulus [7]. Moreover, both increase [8] and decrease [9][10] in arterial caliber in response to increases or decreases in WSS, respectively, and have been shown to involve endothelial release of NO. These results highlight the key role of NO, to allow vessels to adapt their diameter variations in WSS.

1.2. Normal Inflammation

In case of infection, neutrophils are the first recruited leukocytes. Circulating neutrophils have a diameter of 7-10µm and represent 50-70% of circulating leukocytes. When they encounter a pathogen, they can phagocytose it, release granules containing antibacterial proteins into the extracellular milieu to kill it, or in case of a high activation level, release neutrophil extracellular traps (NETs) to trap the microorganism [11] and facilitate its phagocytosis. The notion that NETs could not only trap, but kill pathogens thanks to their decorating antimicrobial proteins [12], is still a matter of debate.

Typically, neutrophil recruitment to an infected site requires its tethering, rolling, firm adhesion, crawling, and transmigration to reach the infected site. Tissue-resident leukocytes release inflammatory mediators to change the endothelium adhesive properties, or endothelial cells can be activated following the detection of pathogens by means of pattern-recognition receptors (PRRs). Therefore, endothelial cells express P-selectin at their membrane, within minutes. Indeed, P-selectin is pre-stored in Weibel-Palade bodies. P-selectin interaction with neutrophil P-selectin glycoprotein ligand-1 (PSGL-1), allow the tethering (that is, the capture) of the free-circulating leukocyte. Neutrophil rolling occurs at shear stress of 1-10 dynes/cm and involves, to resist to shear stress, the formation of long tethers at the rear, supported by P-selectin-PSGL-1 interactions. Endothelial cell activation also triggers *de novo* synthesis and as such upregulation of E-selectin, within about 90 min [13][14]. E-selectin, which preferentially binds neutrophil L-selectin, projects less further above the endothelial surface of endothelial surface than P-selectin, and have partially overlapping functions with this last protein, allows to slow neutrophil rolling [15]. After disconnection of the tether at the rear, it arrives at the front of the rolling neutrophil, where it will act as a sling that can subsequently wrap around the leukocyte to slow it down. Additionally, firm adhesion stems from interaction of integrins with intercellular adhesion molecule-1 (ICAM-1) and ICAM-2 endothelial molecules. Lymphocyte function-associated antigen-1 (LFA-1, also called CD11a-CD18) and macrophage-1 antigen (MAC-1, also known as CD11b-CD18) are constitutively expressed by neutrophils but, to allow adhesion they require activation by a combination of mechanisms involving: positively charged chemokines [16], MRP8/14 secretion [17], talin, and kindlin-3 binding to the β chain of LFA-1, which, respectively, also cause conformational changes to further decrease rolling velocity and to allow neutrophil arrest [18]. The leukocyte then begins a MAC-1 dependent crawling step towards the exit site [19]. It is worthwhile noting that neutrophils recruitment in other tissues, where high shear stress is encountered, such as the brain for instance: platelets which can express more P-selectin than endothelial cells, first adhere to the endothelium, and then allow neutrophils recruitment [20]. However, after firm adhesion and crawling, it generally takes 2–5 min for the neutrophils to cross the endothelium through the preferential paracellular process, or 20-30 minutes using the transcellular pathway, and then 5–15 min to cross the basement membrane [13]. Subsequently, neutrophils are directed by a gradient of two types of chemo-attractants. The first type is released by intermediary sites, whereas the second one emerges closer to the pathogen and has a higher chemotactic impact [21]. This entry focuses on intravascular adhesive mechanisms, and only briefly deals with extravasation given that this process is less relevant to SCD pathophysiology; but for more specific details readers are encouraged to refer to excellent research by Ley et al., 2007, and Vestweber, 2015 [13][17].

2. Dysregulated Mechanisms in SCD

SCD is a complex, evolutive, and clinically heterogeneous disease. In deoxygenated vascular areas, HbS forms polymers, which makes sickled red blood cells (RBCs) less deformable and more fragile. The resulting hemolysis stimulates the bone marrow and accounts for the elevated count of stress reticulocytes of SCD patients. Whereas the transit time of RBCs in deoxygenated territories should be insufficient to cause their sickling [22]; platelets, neutrophils, and endothelium pro-adhesive phenotypes observed in SCD, may decrease microvascular blood flow, thereby increasing RBC transit time and allowing their sickling before leaving the microcirculation [23]. These sickled RBCs, but also activated neutrophils, platelets, endothelial cells are the main actors in SCD. Therefore, although SCD results from a single point mutation, its pathophysiology relies on the disturbance of several pathways, owing to abnormalities such as elevated hemolysis level and stress undergone by the vascular endothelium.

2.1. Pro-Coagulant State

A procoagulant state is one of SCD pathophysiology hallmark [24][25]. SCD hypercoagulable state has been associated with increased risks of pulmonary hypertension [26], in situ thrombosis of small vessels and venous thrombosis [27]. SCD patients exhibit low protein C and S levels, suggesting their chronic consumption due to a constantly activated coagulation cascade [28]. Tissue factor (TF) was reported to be elevated on SCD patients' monocytes [29], neutrophils [30], and circulating endothelial cells [30]. Heme has been shown to promote TF expression by mononuclear and endothelial cells [31][32]. This is consistent with the constant detection in SCD patients' plasma, of high levels of coagulation markers such as D-dimers, plasmin-antiplasmin (PAP) complexes, thrombin-antithrombin (TAT) complexes, and prothrombin fragment 1.2 (F1.2) [28].

The hyperactivity of the coagulation system in SCD is also caused by reticulocytes or RBCs exhibiting externalized phosphatidylserine (PS). Owing to intravascular and extravascular hemolysis, SCD patients exhibit erythropoiesis expansion and, therefore, increased reticulocytosis. Although PS exposure by immature reticulocytes seems to be normal during hematopoiesis, hyposplenia, or functional asplenia observed in SCD due to abnormal RBCs trapping, increases the count of PS-exposing circulating mature reticulocytes [33]. Moreover, increased intracellular calcium concentration due to sickling and dehydration, but also oxidative stress, account for elevated counts of PS-exposing sickle RBC and reticulocytes [34][35][36]. These cells may promote the activation of the coagulation cascade, since PS is known to provide a docking site for tenase and prothrombinase complexes, which activates the intrinsic pathway. This correlates with reports of correlations between F 1.2, D-dimers and PAP complexes, and PS-bearing sickle RBCs [37][38].

2.2. Decreased Nitric Oxide Bioavailability

SCD patients are known for having a 50% increase in cardiac output [39], and a lack of RBC deformability [40]. These two altered parameters contribute to the increased WSS observed by Belhassen et al. in SCD patients [7]. Intriguingly, this augmented level was accompanied by an unchanged vessel diameter, when compared to healthy controls; thereby suggesting an impaired capacity to adjust vessel caliber to WSS in SCD. This failure to adjust arteries diameter could result from defects in the transduction of the shear stress signal, from impairments in the synthesis or the release of NO, or from an accelerated degradation of NO. The results of this group excluded the two first hypothesis, in the favor of the last one. Consistently, NO bioavailability is known to be drastically reduced in SCD owing to the elevated hemolytic rate [41]. Indeed, hemolysis allows the release of arginase, which impedes NO production by using L-arginine to produce ornithine. Hemolysis also induces the release of hemoglobin in the plasma, which reacts with NO to form methemoglobin and nitrate. Consistently, decreased L-arginine concentration, coinciding with high arginase plasma levels, were reported in SCD patients [42], but also elevated concentrations of free hemoglobin and methemoglobin [42][43], which all account for a decreased NO bioavailability [44] and, therefore, a reduced WSS-mediated vasodilation. The decreased bioavailability of NO and the resulting endothelial dysfunction have been associated with an increased risk of pulmonary hypertension [45], legs ulcers [46], stroke [47] and priapism [48]. Besides, NO being an inhibitor of endothelin-1 (ET-1), the decrease of its bioavailability accounts for the high level of ET-1 observed in SCD. ET-1 binding to its receptor, has been shown to increase calcium concentration inside erythrocytes and to facilitate Gardos channel opening, thereby potentiating erythrocyte dehydration and so increasing HbS concentration and its propensity to polymerize [49]. Moreover, since NO is an inhibitor of the expression of adhesive proteins by the vascular endothelium [5], NO-scavenging by free heme and arginase-mediated decrease in NO production both have a role in the pro-adhesive phenotype of endothelial cells in SCD.

2.3. Pro-Inflammatory State

Blood flow obstruction during VOCs, causes severe pain, and repeated VOCs can lead to organ failure. A substantial proportion of the knowledge regarding the adhesive processes leading to VOCs was acquired thanks to murine models of the disease [50][51] or to microfluidics [52]. The etiology of the main SCD-associated complication, VOC, involves the capture of neutrophils by the activated endothelium. Upon rolling, these neutrophils exhibit active integrin that allow their full arrest. This adhesion in post-capillary venules causes trapping of platelets, other neutrophils, and above all RBCs, which lead to the occurrence of a vascular occlusion [53]. The key role of neutrophils is highlighted by the absolute contraindication of myeloid growth factors such as granulocyte macrophage colony-stimulating factor (GM-CSF) or granulocyte colony-stimulating factor (G-CSF) in SCD patients [54][55][56][57]. Aged neutrophils [58], which are overrepresented in SCA patients [59], present a 70% increase in the adhesive molecule MAC-1 [60]. This last integrin appears to have a crucial role in SCD since it allows neutrophils to adhere to endothelial ICAM-1, but also to capture circulating RBCs [23].

The RBC lifespan, which is normally of 120 days, is reduced in SCD to about 12 days. Hemolysis favors the release from the bone marrow, of reticulocytes; reaching a tenfold increase in their count, compared to normal conditions. These

reticulocytes express high levels of adhesion molecules, among which intercellular molecule-4 (ICAM-4), a molecule shown to bind to MAC-1 and so allow RBC-neutrophil interactions [61]. Sickle patient RBCs commonly exhibit externalized PS, what promotes their adhesion [34]. Sickle red cells also exhibit alterations leading to the abnormal activation of erythroid adhesion molecules such as Lu/BCAM, ICAM-4 and CD44 [62][63]. As a consequence, erythrocytes interactions with the endothelium or with circulating of adherent platelets and neutrophils are facilitated [51][64][65]. In addition, the pro-adhesive phenotype of RBCs of SCD patients and the reduced vasodilatory capacity account for an increased number of interactions between RBCs and endothelial cells, which was shown to upregulate the expression of VCAM-1 and ICAM-1 genes [66].

Besides, enhanced oxidative stress, partly due to HbS auto-oxidation, which induces superoxide anion, hydrogen peroxide, and hydroxyl radical production [67][68], is associated with vascular alterations in SCD patients [69]. Free heme promotes the secretion of pro-inflammatory cytokines by activating monocytes/macrophages [70], platelets [71], endothelial cells [31], and neutrophils [72]. Moreover, NETs released by the latter cell type, were detected at high concentration in the plasma of SCD patients at steady state, with a further increase during crisis [72][73].

3. EVs as Novel Biomarkers in SCD

Circulating EV concentration has been shown to be increased in several cardiovascular diseases [74][75]. Since plasma EVs concentration and composition reflects specific signatures of cellular activation and injury, EVs characteristics may represent in the future, a useful diagnostic and prognostic tool in several diseases.

In SCD, the concentration of the two most commonly identified MPs subtypes, RBC-, and platelet-MPs is increased, compared to healthy controls [76][77]. HU treatment impact on MPs concentration is controversial, since several reports showed decreases [76][77][78], unchanged [79][80], or increased [81][82] levels. These conflicting results could be accounted for by the large interindividual variation in MPs concentration in SCD. However, a longitudinal study reported no change in MPs concentration in patients receiving HU for 24 months [83]. To further characterize the biomarker status of MPs, an observational study with an estimated enrollment of 360 participants has also been initiated (NCT012422878). A positive history of osteonecrosis of the femoral head [84], leg ulcers [85], acute chest syndrome, and pulmonary hypertension [77] has been associated with elevated concentration of MPs from various cell types. During VOC, the concentration of PLT- and RBC-MPs was also reported to be increased in cross-sectional settings [81][86][87], and in longitudinal studies including 17 SCD patients [88] or 32 SCA patients [89]. The group reported that SCA patients with frequent VOCs had increased levels of PLT-MPs, compared to SCA patients with rare crises [90]. In SCA patients, researchers showed using two longitudinal cohorts, that circulating PLT- and RBC-MPs PS exposure level was increased during VOC, but decreased after two years under HU treatment, when compared to steady-state conditions [83][89][91]. Therefore, PS exposure by these MPs subtypes seems to be a promising marker of clinical severity and of HU treatment efficacy. Further studies based on large cohorts are warranted to determine if MPs PS exposure is a prognosis marker. Moreover, it seems important to determine if the cost effectiveness of such a test is favorable, above all for the medical monitoring of patients having frequent VOCs or patients who cannot be treated with HU. Moreover, the 2-year long HU treatment provoked an increase in the size of RBC-MPs, probably resulting from the improved RBC hydration provided by this drug [83].

Unlike for MPs, only a few reports regarding exosomes in SCD have been published, and none dealing with apoptotic bodies. Researchers collaborated with a group who showed that circulating exosome concentration was increased in SCD patients, compared to the controls [92][93]. They also reported associations between the severity of the disease and the counts of exosomes produced by monocytes, lymphocytes, and endothelial cells [93]. Of note, the same group reported a signature of microRNAs contained into circulating exosomes, which distinguished severe from mild clinical profile between SCA patients [93]. These results suggest that circulating exosomes could become useful diagnostic and prognostic tools used in clinical settings.

4. Effects of EVs in SCD

The externalization of PS is a key feature of MPs. Indeed, as stated before, MPs PS provides a docking site for the intrinsic tenase and the prothrombinase complex [94][95][96]. In line with the pro-coagulant role of MPs due to their PS and TF [86], Scott syndrome, characterized by a defect in platelet-derived MPs production, has been associated with increased bleeding [97]. MPs generated *ex vivo* by platelets or erythrocytes, have also been shown to trigger thrombin generation via factor XIIa [98]. However, whether circulating MPs have similar biological properties remains unknown. Moreover, although PLT-MPs are known to represent the commonest MPs subtypes in the circulation, most studies in SCD, report associations between the concentration of RBC-MPs and coagulation cascade activation. This paradox may be explained

by the higher exposure of PS by RBC-MPs, compared to PLT-MPs observed at steady state, in HU-treated or untreated patients, and even during crisis [91][99].

PS was shown to allow MPs binding to endothelial cells [100][101]. Consistently, increased PS exposure was associated to increased fusion with these cells [91][100][102]. These results are supported by the report of the expression of a PS receptor (PSR) by endothelial cells [32], thereby allowing MPs to bind to these cells, and to modify their phenotype. Moreover, PS was shown to allow MPs to retain heme, which was hereafter transferred to endothelial cells [103]. RBC-MPs were shown to be internalized by myeloid cells and to promote inflammatory cytokine secretion along with adhesion to endothelial cells [104]. Barry and colleagues reported that PLT-MPs induced endothelial ICAM-1 expression [105], and Wang et al. showed that monocyte-derived MPs increased ICAM-1, VCAM-1, and E-selectin expression, also in endothelial cells [106]. These results may partly explain why the infusion of MPs was shown to trigger vaso-occlusion mice kidney [103]. Since the content of MPs is known to be influenced by the stimuli triggering their production and by their cell type of origin, the group used circulating MPs, instead of MPs generated *ex vivo*. The results showed that MPs circulating during VOC, triggered a PS-dependent ICAM-1 overexpression, compared to MPs from the same patients but at steady state [91]. On the contrary, ICAM-1 expression was reduced when MPs were isolated from the plasma of SCA patients under HU treatment. Moreover, the adhesion of SCD neutrophils to MPs-stimulated endothelial cells was decreased when using MPs from HU-treated patients, and increased in an ICAM-1 dependent manner using MPs from patients in VOC. Researchers also showed that RBC-MPs from SCA patients at steady state, increased ICAM-1 expression and cytokines production in a TLR-4-dependent manner, compared to MP from healthy controls [107].

Exosomes generated *ex vivo* by mesenchymal stem cells, multipotent progenitors found in various tissues and having tissue-repair functions, were recently shown to have procoagulant activities thanks to their PS and TF [108]. If such exosomes are found in sufficient levels in the blood of SCD patients, they could play a crucial procoagulant role in this disease. Vats et al. showed that pretreatment of platelets with LPS induced inflammasome activation and the production of EVs richly packaged with IL-1β [109]. These EVs had a size corresponding to the one of exosomes, between 50 and 100µm for most of them. Injection of such EVs from SCD platelets, was sufficient to induce lung vaso-occlusion in SCD mice. Moreover, this deleterious effect of platelet-derived exosomes was reduced using an IL-1 receptor antagonist. Their results suggest that drugs preventing platelet exosomes production may be of benefit in SCD. Contrary to the previous group, which used exosomes generated *ex vivo*, another one used circulating exosomes. The mode of the size distribution curve for their EVs was 95nm, and these EVs were rich in exosomal proteins (CD63 and flottilin-1). This group showed that SCD exosomes cause endothelial monolayer disruption [92][93][110]. Importantly, the extent of the endothelial disruption was even greater using exosomes circulating during acute chest syndrome [110] or during VOC [111], compared to exosomes purified from the plasma of patients at steady state.

References

1. Gladwin, M.T.; Ofori-Acquah, S.F. Red Cells, Iron, & Erythropoiesis: Erythroid DAMPs Drive Inflammation in SCD. Blood 2014, 123, 3689.
2. Dautov, R.F.; Stafford, I.; Liu, S.; Cullen, H.; Madhani, M.; Chirkov, Y.Y.; Horowitz, J.D. Hypoxic Potentiation of Nitrite Effects in Human Vessels and Platelets. Nitric Oxide 2014, 40, 36–44.
3. Unic, A.; Derek, L.; Hodak, N.; Marijancevic, D.; Ceprnja, M.; Serdar, T.; Krhac, M.; Romic, Z. Endothelins—Clinical Perspectives. Biochem. Med. 2011, 3, 231–242.
4. Boulanger, C.; Luscher, T.F. Release of Endothelin from the Porcine Aorta. Inhibition of Endothelium-Derived Nitric Oxide. J. Clin. Investig. 1990, 85, 587–590.
5. Gryglewski, R.J.; Botting, R.M.; Vane, J.R. Mediators Produced by the Endothelial Cell. Hypertension 1988, 12, 530–548.
6. Myers, P.R.; Tanner, M.A. Vascular Endothelial Cell Regulation of Extracellular Matrix Collagen: Role of Nitric Oxide. Arterioscler. Thromb. Vasc. Biol. 1998, 18, 717–722.
7. Belhassen, L.; Pelle, G.; Sediame, S.; Bachir, D.; Carville, C.; Bucherer, C.; Lacombe, C.; Galacteros, F.; Adnot, S. Endothelial Dysfunction in Patients with Sickle Cell Disease Is Related to Selective Impairment of Shear Stress–Mediated Vasodi-lation. Blood 2001, 97, 1584–1589.
8. Tronc, F.; Wassef, M.; Esposito, B.; Henrion, D.; Glagov, S.; Tedgui, A. Role of NO in Flow-Induced Remodeling of the Rabbit Common Carotid Artery. Arterioscler. Thromb. Vasc. Biol. 1996, 16, 1256–1262.

9. Langille, B.L.; O'Donnell, F. Reductions in Arterial Diameter Produced by Chronic Decreases in Blood Flow Are Endothelium-Dependent. Science 1986, 231, 405–407.
10. Langille, B.L.; Bendeck, M.P.; Keeley, F.W. Adaptations of Carotid Arteries of Young and Mature Rabbits to Reduced Carotid Blood Flow. Am. J. Physiol. Heart Circ. Physiol. 1989, 256, H931–H939.
11. Saitoh, T.; Komano, J.; Saitoh, Y.; Misawa, T.; Takahama, M.; Kozaki, T.; Uehata, T.; Iwasaki, H.; Omori, H.; Yamaoka, S.; et al. Neutrophil Extracellular Traps Mediate a Host Defense Response to Human Immunodeficiency Virus-1. Cell Host Microbe 2012, 12, 109–116.
12. Brinkmann, V.; Reichard, U.; Goosmann, C.; Fauler, B.; Uhlemann, Y.; Weiss, D.S.; Weinrauch, Y.; Zychlinsky, A. Neutrophil Extracellular Traps Kill Bacteria. Science 2004, 303, 1532–1535.
13. Ley, K.; Laudanna, C.; Cybulsky, M.I.; Nourshargh, S. Getting to the Site of Inflammation: The Leukocyte Adhesion Cascade Updated. Nat. Rev. Immunol. 2007, 7, 678–689.
14. Petri, B.; Phillipson, M.; Kubes, P. The Physiology of Leukocyte Recruitment: An In Vivo Perspective. J. Immunol. 2008, 180, 6439–6446.
15. Su, Y.; Lei, X.; Wu, L.; Liu, L.; Liu, L. The Role of Endothelial Cell Adhesion Molecules P-Selectin, E-Selectin and Intercellular Adhesion Molecule-1 in Leucocyte Recruitment Induced by Exogenous Methylglyoxal. Immunology 2012, 137, 65–79.
16. Kolaczkowska, E.; Kubes, P. Neutrophil Recruitment and Function in Health and Inflammation. Nat. Rev. Immunol. 2013, 13, 159–175.
17. Vestweber, D. How Leukocytes Cross the Vascular Endothelium. Nat. Rev. Immunol. 2015, 15, 692–704.
18. Lefort, C.T.; Rossaint, J.; Moser, M.; Petrich, B.G.; Zarbock, A.; Monkley, S.J.; Critchley, D.R.; Ginsberg, M.H.; Fässler, R.; Ley, K. Distinct Roles for Talin-1 and Kindlin-3 in LFA-1 Extension and Affinity Regulation. Blood 2012, 119, 4275–4282.
19. Phillipson, M.; Heit, B.; Colarusso, P.; Liu, L.; Ballantyne, C.M.; Kubes, P. Intraluminal Crawling of Neutrophils to Emigration Sites: A Molecularly Distinct Process from Adhesion in the Recruitment Cascade. J. Exp. Med. 2006, 203, 2569–2575.
20. Carvalho-Tavares, J.; Hickey, M.J.; Hutchison, J.; Michaud, J.; Sutcliffe, I.T.; Kubes, P. A Role for Platelets and Endothelial Selectins in Tumor Necrosis Factor-Alpha-Induced Leukocyte Recruitment in the Brain Microvasculature. Circ. Res. 2000, 87, 1141–1148.
21. Foxman, E.F.; Campbell, J.J.; Butcher, E.C. Multistep Navigation and the Combinatorial Control of Leukocyte Chemotaxis. J. Cell Biol. 1997, 139, 1349–1360.
22. Mozzarelli, A.; Hofrichter, J.; Eaton, W.A. Delay Time of Hemoglobin S Polymerization Prevents Most Cells from Sickling in Vivo. Science 1987, 237, 500–506.
23. Zhang, D.; Xu, C.; Manwani, D.; Frenette, P.S. Neutrophils, Platelets, and Inflammatory Pathways at the Nexus of Sickle Cell Disease Pathophysiology. Blood 2016, 127, 801–809.
24. Ataga, K.I.; Key, N.S. Hypercoagulability in Sickle Cell Disease: New Approaches to an Old Problem. Hematology / the Education Program of the American Society of Hematology. American Society of Hematology. Educ. Program 2007, 2, 91–96.
25. de Franceschi, L.; Cappellini, M.D.; Olivieri, O. Thrombosis and Sickle Cell Disease. Semin. Thromb. Hemost. 2011, 37, 226–236.
26. Ataga, K.I.; Moore, C.G.; Hillery, C.A.; Jones, S.; Whinna, H.C.; Strayhorn, D.; Sohier, C.; Hinderliter, A.; Parise, L.V.; Orringer, E.P. Coagulation Activation and Inflammation in Sickle Cell Disease-Associated Pulmonary Hypertension. Haematologica 2008, 93, 20–26.
27. Naik, R.P.; Streiff, M.B.; Haywood, C.; Nelson, J.A.; Lanzkron, S. Venous Thromboembolism in Adults with Sickle Cell Disease: A serious and under-Recognized Complication. Am. J. Med. 2013, 126, 443.
28. Noubouossie, D.; Key, N.S.; Ataga, K.I. Coagulation Abnormalities of Sickle Cell Disease: Relationship with Clinical Outcomes and the Effect of Disease Modifying Therapies. Blood Rev. 2016, 30, 245–256.
29. Setty, B.N.Y.; Key, N.S.; Rao, A.K.; Gayen-Betal, S.; Krishnan, S.; Dampier, C.D.; Stuart, M.J. Tissue Factor-Positive Monocytes in Children with Sickle Cell Disease: Correlation with Biomarkers of Haemolysis. Br. J. Haematol. 2012, 157, 370–380.
30. Solovey, A.; Gui, L.; Key, N.S.; Hebbel, R.P. Tissue Factor Expression by Endothelial Cells in Sickle Cell Anemia. J. Clin. Investig. 1998, 101, 1899–1904.

31. Belcher, J.D.; Chen, C.; Nguyen, J.; Milbauer, L.; Abdulla, F.; Alayash, A.I.; Smith, A.; Nath, K.A.; Hebbel, R.P.; Vercellotti, G.M. Heme Triggers TLR4 Signaling Leading to Endothelial Cell Activation and Vaso-Occlusion in Murine Sickle Cell Disease. Blood 2014, 123, 377–390.

32. Setty, B.N.Y.; Betal, S.G. Microvascular Endothelial Cells Express a Phosphatidylserine Receptor: A Functionally Active Receptor for Phosphatidylserine-Positive Erythrocytes. Blood 2008, 111, 905–914.

33. Mankelow, T.J.; Griffiths, R.E.; Trompeter, S.; Flatt, J.F.; Cogan, N.M.; Massey, E.J.; Anstee, D.J. Autophagic Vesicles on Mature Human Reticulocytes Explain Phosphatidylserine-Positive Red Cells in Sickle Cell Disease. Blood 2015, 126, 1831–1834.

34. Kuypers, F.A.; Jong, K. The Role of Phosphatidylserine in Recognition and Removal of Erythrocytes. Cell. Mol. Biol. 2004, 50, 147–158.

35. Abed, M.; Feger, M.; Alzoubi, K.; Pakladok, T.; Frauenfeld, L.; Geiger, C.; Towhid, S.T.; Lang, F. Sensitization of Erythrocytes to Suicidal Erythrocyte Death Following Water Deprivation. Kidney Blood Press. Res. 2013, 37, 567–578.

36. Joiner, C.H.; Jiang, M.; Franco, R.S. Deoxygenation-Induced Cation Fluxes in Sickle Cells. IV. Modulation by External Calcium. Am. J. Physiol. 1995, 269 Pt 1, C403–C409.

37. Yamaja Setty, B.N.; Koneti Rao, A.; Stuart, M.J. Thrombophilia in Sickle Cell Disease: The Red Cell Connection. Blood 2001, 98, 3228–3233.

38. Setty, B.N.; Kulkarni, S.; Rao, A.K.; Stuart, M.J. Fetal Hemoglobin in Sickle Cell Disease: Relationship to Erythrocyte Phosphatidylserine Exposure and Coagulation Activation. Blood 2000, 96, 1119–1124.

39. Covitz, W.; Espeland, M.; Gallagher, D.; Hellenbrand, W.; Leff, S.; Talner, N. The Heart in Sickle Cell Anemia. The Coop-erative Study of Sickle Cell Disease (CSSCD). Chest 1995, 108, 1214–1219.

40. Bucherer, C.; Ladjouzi, J.; Lacombe, C.; Lelièvre, J.C.; Vandewalle, H.; Beuzard, Y.; Galacteros, F. Effect of Deoxygenation on Rheological Behavior of Density Separated Sickle Cell Suspensions. Clin. Hemorheol. Microcirc. 1992, 12, 415–425.

41. Chirico, E.N.; Pialoux, V. Role of Oxidative Stress in the Pathogenesis of Sickle Cell Disease. IUBMB Life 2012, 64, 72–80.

42. Morris, C.R.; Kato, G.J.; Poljakovic, M.; Wang, X.; Blackwelder, W.C.; Sachdev, V.; Hazen, S.L.; Vichinsky, E.P.; Morris, S.M.; Gladwin, M.T. Dysregulated Arginine Metabolism, Hemolysis-Associated Pulmonary Hypertension, and Mortality in Sickle Cell Disease. JAMA 2005, 294, 81–90.

43. Jeffers, A.; Gladwin, M.T.; Kim-Shapiro, D.B. Computation of Plasma Hemoglobin Nitric Oxide Scavenging in Hemolytic Anemias. Free Radic. Biol. Med. 2006, 41, 1557–1565.

44. Chen, K.; Piknova, B.; Pittman, R.N.; Schechter, A.N.; Popel, A.S. Nitric Oxide from Nitrite Reduction by Hemoglobin in the Plasma and Erythrocytes. Nitric Oxide 2008, 18, 47–60.

45. Gladwin, M.T.; Sachdev, V.; Jison, M.L.; Shizukuda, Y.; Plehn, J.F.; Minter, K.; Brown, B.; Coles, W.A.; Nichols, J.S.; Ernst, I.; et al. Pulmonary Hyper-tension as a Risk Factor for Death in Patients with Sickle Cell Disease. N. Engl. J. Med. 2004, 3509350, 886–895.

46. Kato, G.J.; McGowan, V.; Machado, R.F.; Little, J.A.; Taylor VI, J.; Morris, C.R.; Nichols, J.S.; Wang, X.; Poljakovic, M.; Morris, S.M.; et al. Lactate Dehydrogenase as a Biomarker of Hemolysis-Associated Nitric Oxide Resistance, Priapism, Leg Ulceration, Pulmonary Hypertension, and Death in Patients with Sickle Cell Disease. Blood 2006, 107, 2279–2285.

47. Bernaudin, F.; Verlhac, S.; Chevret, S.; Torres, M.; Coic, L.; Arnaud, C.; Kamdem, A.; Hau, I.; Neonato, M.G.; Delacourt, C. G6PD Deficiency, Absence of Alpha-Thalassemia, and Hemolytic Rate at Baseline Are Significant Independent Risk Factors for Abnormally High Cerebral Velocities in Patients with Sickle Cell Anemia. Blood 2008, 112, 4314–4317.

48. Baldwin, C.; Nolan, V.G.; Wyszynski, D.F.; Ma, Q.L.; Sebastiani, P.; Embury, S.H.; Bisbee, A.; Farrell, J.; Farrer, L.; Steinberg, M.H. Association of Klotho, Bone Morphogenic Protein 6, and Annexin A2 Polymorphisms with Sickle Cell Osteonecrosis. Blood 2005, 106, 372.

49. Rivera, A. Reduced Sickle Erythrocyte Dehydration in Vivo by Endothelin-1 Receptor Antagonists. Am. J. Physiol. Cell Physiol. 2007, 293, C960–C966.

50. Liu, Z.; Miner, J.J.; Yago, T.; Yao, L.; Lupu, F.; Xia, L.; McEver, R.P. Differential Regulation of Human and Murine P-Selectin Expression and Function In Vivo. J. Exp. Med. 2010, 207, 2975–2987.

51. Hidalgo, A.; Chang, J.; Jang, J.E.; Peired, A.J.; Chiang, E.Y.; Frenette, P.S. Heterotypic Interactions Enabled by Polarized Neutrophil Microdomains Mediate Thromboinflammatory Injury. Nat. Med. 2009, 15, 384–391.

52. Aich, A.; Lamarre, Y.; Sacomani, D.P.; Kashima, S.; Covas, D.T.; de la Torre, L.G. Microfluidics in Sickle Cell Disease Research: State of the Art and a Perspective Beyond the Flow Problem. Front. Mol. Biosci. 2021, 7, 558982.

53. Morikis, V.A.; Hernandez, A.A.; Magnani, J.L.; Sperandio, M.; Simon, S.I. Targeting Neutrophil Adhesive Events to Address Vaso-Occlusive Crisis in Sickle Cell Patients. Front. Immunol. 2021, 12, 1256.

54. Wei, A.; Grigg, A. Granulocyte Colony-Stimulating Factor-Induced Sickle Cell Crisis and Multiorgan Dysfunction in a Patient with Compound Heterozygous Sickle Cell/Beta+ Thalassemia. Blood 2001, 97, 3998–3999.

55. Adler, B.K.; Salzman, D.E.; Carabasi, M.H.; Vaughan, W.P.; Reddy, V.V.B.; Prchal, J.T. Fatal Sickle Cell Crisis after Granulocyte Colony-Stimulating Factor Administration. Blood 2001, 97, 3313–3314.

56. Abboud, M.; Laver, J.; Blau, C.A. Granulocytosis Causing Sickle-Cell Crisis. Lancet 1998, 351, 959.

57. Wali, Y.; Beshlawi, I.; Fawaz, N.; Alkhayat, A.; Zalabany, M.; Elshinawy, M.; Al-Kindi, S.; Al-Rawas, A.H.A.; Klein, C. Coexistence of Sickle Cell Disease and Severe Congenital Neutropenia: First Impressions Can Be Deceiving. Eur. J. Haematol. 2012, 89, 245–249.

58. Lard, L.R.; Mul, F.P.J.; de Haas, M.; Roos, D.; Duits, A.J. Neutrophil Activation in Sickle Cell Disease. J. Leukoc. Biol. 1999, 66, 411–415.

59. Canalli, A.A.; Franco-Penteado, C.F.; Saad, S.T.O.; Conran, N.; Costa, F.F. Increased Adhesive Properties of Neutrophils in Sickle Cell Disease May Be Reversed by Pharmacological Nitric Oxide Donation. Haematologica 2008, 93, 605–609.

60. Lum, A.; Wun, T.; Staunton, D.; Simon, S. Inflammatory Potential of Neutrophils Detected in Sickle Cell Disease. Am. J. Hematol. 2004, 76, 126–133.

61. Hermand, P.; Gane, P.; Huet, M.; Jallu, V.; Kaplan, C.; Sonneborn, H.H.; Cartron, J.P.; Bailly, P. Red Cell ICAM-4 Is a Novel Ligand for Platelet-Activated Alpha IIbbeta 3 Integrin. J. Biol. Chem. 2003, 278, 4892–4898.

62. Zennadi, R.; Hines, P.C.; de Castro, L.M.; Cartron, J.P.; Parise, L.V.; Telen, M.J. Epinephrine Acts through Erythroid Signaling Pathways to Activate Sickle Cell Adhesion to Endothelium via LW-Alphavbeta3 Interactions. Blood 2004, 104, 3774–3781.

63. Zennadi, R.; Whalen, E.J.; Soderblom, E.J.; Alexander, S.C.; Thompson, J.W.; Dubois, L.G.; Moseley, M.A.; Telen, M.J. Erythrocyte Plasma Membrane-Bound ERK1/2 Activation Promotes ICAM-4-Mediated Sickle Red Cell Adhesion to Endothelium. Blood 2012, 119, 1217–1227.

64. Wun, T.; Paglieroni, T.; Tablin, F.; Welborn, J.; Nelson, K.; Cheung, A. Platelet Activation and Platelet-Erythrocyte Aggregates in Patients with Sickle Cell Anemia. J. Lab. Clin. Med. 1997, 129, 507–516.

65. Brittain, J.E.; Knoll, C.M.; Ataga, K.I.; Orringer, E.P.; Parise, L.V. Fibronectin Bridges Monocytes and Reticulocytes via Integrin Alpha4beta1. Br. J. Haematol. 2008, 141, 872–881.

66. Shiu, Y.T.; Udden, M.M.; McIntire, L.V. Perfusion with Sickle Erythrocytes Up-Regulates ICAM-1 and VCAM-1 Gene Expression in Cultured Human Endothelial Cells. Blood 2000, 95, 3232–3241.

67. Hebbel, R.P.; Morgan, W.T.; Eaton, J.W.; Hedlund, B.E. Accelerated Autoxidation and Heme Loss Due to Instability of Sickle Hemoglobin. Proc. Natl. Acad. Sci. USA 1988, 85, 237–241.

68. Nagababu, E.; Fabry, M.E.; Nagel, R.L.; Rifkind, J.M. Heme Degradation and Oxidative Stress in Murine Models for Hemoglobinopathies: Thalassemia, Sickle Cell Disease and Hemoglobin C Disease. Blood Cells Mol. Dis. 2008, 41, 60–66.

69. Nader, E.; Conran, N.; Romana, M.; Connes, P. Vasculopathy in Sickle Cell Disease: From Red Blood Cell Sickling to Vascular Dysfunction. Compr. Physiol. 2021, 11, 1785–1803.

70. Vinchi, F.; da Silva, M.C.; Ingoglia, G.; Petrillo, S.; Brinkman, N.; Zuercher, A.; Cerwenka, A.; Tolosano, E.; Muckenthaler, M.U. Hemopexin Therapy Reverts Heme-Induced Proinflammatory Phenotypic Switching of Macrophages in a Mouse Model of Sickle Cell Disease. Blood 2016, 127, 473–486.

71. Bourne, J.H.; Colicchia, M.; Di, Y.; Martin, E.; Slater, A.; Roumenina, L.T.; Dimitrov, J.D.; Watson, S.P.; Rayes, J. Heme Induces Human and Mouse Platelet Activation through C-Type-Lectin-like Receptor-2. Haematologica 2021, 106, 626–629.

72. Chen, G.; Zhang, D.; Fuchs, T.A.; Manwani, D.; Wagner, D.D.; Frenette, P.S. Heme-Induced Neutrophil Extracellular Traps Contribute to the Pathogenesis of Sickle Cell Disease. Blood 2014, 123, 3818–3827.

73. Schimmel, M.; Nur, E.; Biemond, B.J.; van Mierlo, G.J.; Solati, S.; Brandjes, D.P.; Otten, H.M.; Schnog, J.J.; Zeerleder, S. Nucleosomes and Neutrophil Activation in Sickle Cell Disease Painful Crisis. Haematologica 2013, 98, 1797–1803.

74. Ridger, V.C.; Boulanger, C.M.; Angelillo-Scherrer, A.; Badimon, L.; Blanc-Brude, O.; Bochaton-Piallat, M.L.; Boilard, E.; Buzas, E.I.; Caporali, A.; Dignat-George, F.; et al. Microvesicles in Vascular Homeostasis and Diseases. Position Paper of the European Society of Cardiology (ESC) Working Group on Atherosclerosis and Vascular Biology. Thromb. Haemost. 2017, 117, 1296–1316.

75. Jansen, F.; Nickenig, G.; Werner, N. Extracellular Vesicles in Cardiovascular Disease: Potential Applications in Diagnosis, Prognosis, and Epidemiology. Circ. Res. 2017, 120, 1649–1657.

76. Nébor, D.; Romana, M.; Santiago, R.; Vachiery, N.; Picot, J.; Broquere, C.; Chaar, V.; Doumdo, L.; Odièvre, M.H.; Benkerrou, M.; et al. Fetal Hemoglobin and Hydroxycarbamide Modulate Both Plasma Concentration and Cellular Origin of Circulating Microparticles in Sickle Cell Anemia Children. Haematologica 2013, 98, 862–867.

77. Tantawy, A.A.G.; Adly, A.A.M.; Ismail, E.A.R.; Habeeb, N.M.; Farouk, A. Circulating Platelet and Erythrocyte Microparticles in Young Children and Adolescents with Sickle Cell Disease: Relation to Cardiovascular Complications. Platelets 2013, 24, 605–614.

78. Westerman, M.; Pizzey, A.; Hirschman, J.; Cerino, M.; Weil-Weiner, Y.; Ramotar, P.; Eze, A.; Lawrie, A.; Purdy, G.; Mackie, I.; et al. Microvesicles in Haemoglobinopathies Offer Insights into Mechanisms of Hypercoagulability, Haemolysis and the Effects of Therapy. Br. J. Haematol. 2008, 142, 126–135.

79. Witwer, K.W.; Soekmadji, C.; Hill, A.F.; Wauben, M.H.; Buzás, E.I.; di Vizio, D.; Falcon-Perez, J.M.; Gardiner, C.; Hochberg, F.; Kurochkin, I.V.; et al. Updating the MISEV Minimal Requirements for Extracellular Vesicle Studies: Building Bridges to Reproducibility. J. Extracell. Vesicles 2017, 6, 1396823.

80. Olatunya, O.S.; Lanaro, C.; Longhini, A.L.; Penteado, C.F.F.; Fertrin, K.Y.; Adekile, A.; Saad, S.T.O.; Costa, F.F. Red Blood Cells Microparticles Are Associated with Hemolysis Markers and May Contribute to Clinical Events among Sickle Cell Disease Patients. Ann. Hematol. 2019, 98, 2507–2521.

81. Piccin, A.; Murphy, C.; Eakins, E.; Kunde, J.; Corvetta, D.; di Pierro, A.; Negri, G.; Guido, M.; Sainati, L.; Mahon, C.M.; et al. Circulating Microparticles, Protein C, Free Protein S and Endothelial Vascular Markers in Children with Sickle Cell Anaemia. J. Extracell Vesicles 2015, 4, 28414.

82. Brunetta, D.M.; de Santis, G.C.; Silva-Pinto, A.C.; Oliveira De Oliveira, L.C.; Covas, D.T. Hydroxyurea Increases Plasma Concentrations of Microparticles and Reduces Coagulation Activation and Fibrinolysis in Patients with Sickle Cell Anemia. Acta Haematol. 2015, 133, 287–294.

83. Garnier, Y.; Ferdinand, S.; Connes, P.; Garnier, M.; Etienne-Julan, M.; Lemonne, N.; Romana, M. Decrease of Externalized Phosphatidylserine Density on Red Blood Cell-Derived Microparticles in SCA Patients Treated with Hydroxycarbamide. Br. J. Haematol. 2017, 182, 427–456.

84. Marsh, A.; Schiffelers, R.; Kuypers, F.; Larkin, S.; Gildengorin, G.; van Solinge, W.; Hoppe, C. Microparticles as Biomarkers of Osteonecrosis of the Hip in Sickle Cell Disease. Br. J. Haematol. 2015, 168, 135–138.

85. Dembélé, A.K.; Lapoumeroulie, C.; Diaw, M.; Tessougue, O.; Offredo, L.; Diallo, D.A.; Diop, S.; Elion, J.; Colin-Aronovicz, Y.; Tharaux, P.L.; et al. Cell-Derived Microparticles and Sickle Cell Disease Chronic Vasculopathy in Sub-Saharan Africa: A Multinational Study. Br. J. Haematol. 2021, 192, 634–642.

86. Shet, A.S.; Aras, O.; Gupta, K.; Hass, M.J.; Rausch, D.J.; Saba, N.; Koopmeiners, L.; Key, N.S.; Hebbel, R.P. Sickle Blood Contains Tissue Factor-Positive Microparticles Derived from Endothelial Cells and Monocytes. Blood 2003, 102, 2678–2683.

87. Kasar, M.; Boğa, C.; Yeral, M.; Asma, S.; Kozanoglu, I.; Ozdogu, H. Clinical Significance of Circulating Blood and Endothelial Cell Microparticles in Sickle-Cell Disease. J. Thromb. Thrombolysis 2014, 38, 167–175.

88. van Tits, L.J.; van Heerde, W.L.; Landburg, P.P.; Boderie, M.J.; Muskiet, F.A.J.; Jacobs, N.; Duits, A.J.; Schnog, J.B. Plasma Annexin A5 and Microparticle Phosphatidylserine Levels Are Elevated in Sickle Cell Disease and Increase Further during Painful Crisis. Biochem. Biophys. Res. Commun. 2009, 390, 161–164.

89. Hierso, R.; Lemonne, N.; Villaescusa, R.; Lalanne-Mistrih, M.L.; Charlot, K.; Etienne-Julan, M.; Tressières, B.; Lamarre, Y.; Tarer, V.; Garnier, Y.; et al. Exacerbation of Oxidative Stress during Sickle Vaso-Occlusive Crisis Is Associated with Decreased Anti-Band 3 Autoantibodies Rate and Increased Red Blood Cell-Derived Microparticle Level: A Prospective Study. Br. J. Haematol. 2017, 176, 805–813.

90. Nebor, D.; Bowers, A.; Connes, P.; Hardy-Dessources, M.D.; Knight-Madden, J.; Cumming, V.; Reid, M.; Romana, M. Plasma Concentration of Platelet-Derived Microparticles Is Related to Painful Vaso-Occlusive Phenotype Severity in Sickle Cell Anemia. PLoS ONE 2014, 9, e87243.

91. Garnier, Y.; Ferdinand, S.; Garnier, M.; Cita, K.-C.; Hierso, R.; Claes, A.; Connes, P.; Hardy-Dessources, M.-D.; Lapouméroulie, C.; Lemonne, N.; et al. Plasma Microparticles of Sickle Patients during Crisis or Taking Hydroxyurea Modify Endothelium Inflammatory Properties. Blood 2020, 136, 247–256.

92. Lapping-Carr, G.; Khalyfa, A.; Rangel, S.; Darlington, W.; Beyer, E.C.; Peddinti, R.; Cunningham, J.M.; Gozal, D. Exosomes Contribute to Endothelial Integrity and Acute Chest Syndrome Risk: Preliminary Findings. Pediatr. Pulmonol. 2017, 52, 1478–1485.

93. Khalyfa, A.; Khalyfa, A.A.; Akbarpour, M.; Connes, P.; Romana, M.; Lapping-Carr, G.; Zhang, C.; Andrade, J.; Gozal, D. Extracellular Microvesicle MicroRNAs in Children with Sickle Cell Anaemia with Divergent Clinical Phenotypes. Br. J. Haematol. 2016, 174, 786–798.
94. Ruf, W.; Rehemtulla, A.; Edgington, T.S. Phospholipid-Independent and -Dependent Interactions Required for Tissue Factor Receptor and Cofactor Function. J. Biol. Chem. 1991, 266, 2158–2166.
95. Bach, R.; Gentry, R.; Nemerson, Y. Factor VII Binding to Tissue Factor in Reconstituted Phospholipid Vesicles: Induction of Cooperativity by Phosphatidylserine. Biochemistry 1986, 25, 4007–4020.
96. Piccin, A.; Murphy, W.G.; Smith, O.P. Circulating Microparticles: Pathophysiology and Clinical Implications. Blood Rev. 2007, 21, 157–171.
97. Castaman, G.; Yu-Feng, L.; Battistin, E.; Rodeghiero, F. Characterization of a Novel Bleeding Disorder with Isolated Prolonged Bleeding Time and Deficiency of Platelet Microvesicle Generation. Br. J. Haematol. 1997, 96, 458–463.
98. van der Meijden, P.E.J.; van Schilfgaarde, M.; van Oerle, R.; Renné, T.; ten Cate, H.; Spronk, H.M.H. Platelet- and Erythrocyte-Derived Microparticles Trigger Thrombin Generation via Factor XIIa. J. Thromb. Haemost. 2012, 10, 1355–1362.
99. Garnier, Y.; Ferdinand, S.; Etienne-Julan, M.; Elana, G.; Petras, M.; Doumdo, L.; Tressières, B.; Lalanne-Mistrih, M.L.; Hardy-Dessources, M.D.; Connes, P.; et al. Differences of Microparticle Patterns between Sickle Cell Anemia and Hemoglobin SC Patients. PLoS ONE 2017, 12, e0177397.
100. Rautou, P.-E.; Leroyer, A.S.; Ramkhelawon, B.; Devue, C.; Duflaut, D.; Vion, A.-C.; Nalbone, G.; Castier, Y.; Leseche, G.; Lehoux, S.; et al. Microparticles from Human Atherosclerotic Plaques Promote Endothelial ICAM-1-Dependent Monocyte Adhesion and Transendothelial Migration. Circ. Res. 2011, 108, 335–343.
101. Al-Nedawi, K.; Meehan, B.; Kerbel, R.S.; Allison, A.C.; Rak, J. Endothelial Expression of Autocrine VEGF upon the Uptake of Tumor-Derived Microvesicles Containing Oncogenic EGFR. Proc. Natl. Acad. Sci. USA 2009, 106, 3794–3799.
102. Kinnunen, P.K.J.; Holopainen, J.M. Mechanisms of Initiation of Membrane Fusion: Role of Lipids. Biosci. Rep. 2000, 20, 465–482.
103. Camus, S.M.; de Moraes, J.A.; Bonnin, P.; Abbyad, P.; le Jeune, S.; Lionnet, F.; Loufrani, L.; Grimaud, L.; Lambry, J.C.; Charue, D. Circulating Cell Membrane Microparticles Transfer Heme to Endothelial Cells and Trigger Vasoocclusions in Sickle Cell Disease. Blood 2015, 125, 3805–3814.
104. Awojoodu, A.O.; Keegan, P.M.; Lane, A.R.; Zhang, Y.; Lynch, K.R.; Platt, M.O.; Botchwey, E.A. Acid Sphingomyelinase Is Activated in Sickle Cell Erythrocytes and Contributes to Inflammatory Microparticle Generation in SCD. Blood 2014, 124, 1941–1950.
105. Barry, O.P.; Praticò, D.; Savani, R.C.; FitzGerald, G.A. Modulation of Monocyte-Endothelial Cell Interactions by Platelet Microparticles. J. Clin. Investig. 1998, 102, 136–144.
106. Wang, J.G.; Williams, J.C.; Davis, B.K.; Jacobson, K.; Doerschuk, C.M.; Ting, J.P.Y.; Mackman, N. Monocytic Microparticles Activate Endothelial Cells in an IL-1beta-Dependent Manner. Blood 2011, 118, 2366–2374.
107. Nader, E.; Romana, M.; Guillot, N.; Fort, R.; Stauffer, E.; Lemonne, N.; Garnier, Y.; Skinner, S.C.; Etienne-Julan, M.; Robert, M.; et al. Association Between Nitric Oxide, Oxidative Stress, Eryptosis, Red Blood Cell Microparticles, and Vascular Function in Sickle Cell Anemia. Front. Immunol. 2020, 2885, 11.
108. Silachev, D.N.; Goryunov, K.V.; Shpilyuk, M.A.; Beznoschenko, O.S.; Morozova, N.Y.; Kraevaya, E.E.; Popkov, V.A.; Pevzner, I.B.; Zorova, L.D.; Evtushenko, E.A.; et al. Effect of MSCs and MSC-Derived Extracellular Vesicles on Human Blood Coagulation. Cells 2019, 8, 258.
109. Vats, R.; Brzoska, T.; Bennewitz, M.F.; Jimenez, M.A.; Pradhan-Sundd, T.; Tutuncuoglu, E.; Jonassaint, J.; Gutierrez, E.; Watkins, S.C.; Shiva, S.; et al. Platelet Extracellular Vesicles Drive Inflammasome-IL1β-Dependent Lung Injury in Sickle Cell Disease. Am. J. Respir. Crit. Care Med. 2020, 201, 33–46.
110. Lapping-Carr, G.; Gemel, J.; Mao, Y.; Beyer, E.C. Circulating Extracellular Vesicles and Endothelial Damage in Sickle Cell Disease. Front. Physiol. 2020, 11, 1063.
111. Gemel, J.; Zhang, J.; Mao, Y.; Lapping-carr, G.; Beyer, E.C. Circulating Small Extracellular Vesicles May Contribute to Vaso-Occlusive Crises in Sickle Cell Disease. J. Clin. Med. 2022, 11, 816.

Retrieved from https://encyclopedia.pub/entry/history/show/66978