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Review

Sickle cell disease: Hemostatic and inflammatory changes, and their interrelation

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ABSTRACT

Sickle cell disease, the most common genetic blood disorder in the world, has high clinical variability, negatively impacts quality of life and contributes to early mortality. Sickled erythrocytes cause blood flow obstruction, hemolysis, and several hemostatic changes that promote coagulation. These events, in turn, induce chronic inflammation, characterized by elevated plasma levels of pro-inflammatory markers, which aggravates the already unfavorable state of the circulatory system. Empirical evidence indicates that the hemostatic and inflammatory systems continuously interact with each other and thereby further propagate the hypercoagulability and inflammatory conditions. In this review article, we discuss the pathophysiological aspects of sickle cell disease and the hemostatic and inflammatory changes that underlie its pathogenesis.

1. Introduction

The sickle cell disease (SCD) consists a group of hereditary hemolytic anemias whose clinical phenotype may result from several genotypes [1]. In the United States, there are about 70,000 to 100,000 SCD patients, and most of them declare to be black or African descent [2]. In Brazil, an average of 3500 SCD children are born per year [3], being recognized as the most common genetic disease in the world, impacting on people's morbidity and mortality [4,5].

SCD is characterized by mutation in the sixth codon of beta globin gene that promotes the replacement of adenine nitrogenous base by thymine, and so the replacement of glutamic acid amino acid by valine, thus producing hemoglobin (Hb) S [6–8]. This mutation may be homozygous (SS), constituting the increased severity and frequency form of disease, known as sickle cell anemia [9], or combined with different hemoglobin abnormalities, such as Hb C, D, E and beta thalassemia [10]. All symptomatic forms of this gene, whether homozygous or in combination, are referred as SCD [11].

When deoxygenated, the Hb S depolymerizes, causing the erythrocyte to change its normal discoid shape and its flexibility, dehydrate, and acquire the sickle shape, giving rise to the disease name [12]. This event is reversible after reoxygenation, but its repetition frequent damages the membrane of some erythrocytes, which remain deformed independently of the intracellular state of Hb S, being the main determinant for disease severity [6,13]. Irreversibly sickle cells have reduced half-life, causing hemolytic anemia [14]. However, the clinical picture of SCD does not only depends on the symptoms caused by anemia, but mainly of occurrence of organic lesions caused by inflammation, vascular obstruction and sickle cell crises [14,15].

The varied clinical picture is a challenge for understanding and management of SCD, which may range from the mild course of disease to the most severe [16]. The most frequent clinical manifestations that affect the individuals' quality of life are painful vaso-occlusive crises [17–19], priapism, anemia, aplastic crises, splenic sequestration [20], leg ulcers [21,22] and acute chest syndrome [23].

The complex pathophysiology of this genetic disease involves abnormal activation of coagulation cascade and fibrinolysis, evidenced by the increased risk of thrombotic manifestations [24]. It is important to emphasize that almost all components of hemostasis are changed and a chronic proinflammatory environment with increased plasma levels of varied inflammatory markers (e.g. cytokines, chemokines and endothelin-1) is continuously favored, being able to activate coagulation [25,26]. In this review article, we aim to discuss the pathophysiological aspects of sickle cell disease, and the hemostatic and inflammatory

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changes that constitute this disease pathogenesis, as its complex interrelation.

2. Hemostatic changes in sickle cell disease

Patients with SCD have a high predisposition to thromboembolic manifestations, leading to stroke [27,28], pulmonary embolism [29,30], acute chest syndrome [23], damage to several organs and early death [31].

SCD is characterized by a state of hypercoagulability [32,33], which there is a tendency for blood clot formation and blood flow obstruction, even in clinically stable patients [28,34]. The vaso-occlusion occurrence makes difficult the sickle cells flow on microcirculation, promoting the adhesion of this cells to white blood cells and vascular endothelium [12], due to presence of multiple adhesion molecules [35], such as α4β1 integrin and P-selectin 1 glycoprotein (PSGL-1) [25]. As result, venous stasis occurs, and the high adhesiveness of white blood cells and sickle cells [36], unlike the normal ones, generates tissue hypoxia, converting more Hb S molecules to the deoxy-Hb S, a situation that aggravates circulatory status, which is already unfavorable [7,37,38].

Hemolysis, ischemia-reperfusion injury, inflammation, nitric oxide (NO) deficiency, exposure of membrane phospholipids, such as phosphatidylserine (PS), increase of circulating microparticles (MPs), von Willebrand Factor (VWF) and thrombospondin (THBS) [39] are factors that contribute to chronic activation of coagulation in SCD. Table 1 shows the main hemostatic events in the SCD.

The NO bioavailability reduction in SCD is mainly due to intravascular hemolysis, which is associated with PS exposure, release of Hb, heme and enzymes arginase [40] and lactate dehydrogenase (LDH) in the circulation [41]. Hb and heme in circulation consume NO, producing inert nitrate and methemoglobin (MetHb), which is unable to carry oxygen. Conversely the enzyme arginase converts L-arginine, the substrate for NO production by endothelial nitric oxide synthases, into ornithine, thus decreasing the availability of L-arginine for NO synthesis [42,43].

According to Frenette and Atwehe [36], PS is a membrane phospholipid normally located on the cellular internal surface, however, in SCD, as consequence of erythrocytes falcization in repeated cycles, PS exteriorization occurs. This event leads to platelets and coagulation proteins activation, increased expression of endothelial cell adhesion molecules, as well as hemolytic anemia, since the phagocytic system recognizes and removes these abnormal erythrocytes, reducing their half-life in the blood circulation [44].

MPs are small vesicles (diameter 0.02 to 0.1 μm) produced from endothelial cell, erythrocyte, monocyte and platelet membranes, released after cellular activation or apoptosis [45]. Its pro-coagulant properties come from the presence of tissue factor (TF) [46] and PS on its surface [47]. High MPs plasma levels already have been detected in patients with SCD, both in the stable phase [48–53] and in vascular occlusion crises [49,51,54], which may be associated with development of thrombotic complications [55]. According to Garnier and collaborators [56], MPs derived from sickle cells promote coagulation, increase the reactive oxygen species (ROS) production, and induce red blood cells adhesion to endothelium.

VWF is a plasma multimeric glycoprotein that mediates the platelets adhesion to activated and injured vessels. Under physiological conditions, when large VWF multimers are released from megakaryocytes and endothelial cells, they must be cleaved and removed from the circulation by ADAMTS13 enzyme [57]. SCD patients have higher VWF multimers plasma levels [39,58,59], which may result from their proteolysis resistance or deregulation of ADAMTS13. Thus, part of VWF multimers remains anchored in endothelium through sickle cells adhesion mediation and platelet aggregation, contributing to vaso-occlusion and thrombogenic surface generation [28,40,60]. In the cohort study with SCD patients performed by Sins et al. [61], during vaso-occlusive crises, low platelet count and high VWF reactivity were observed, perhaps justified by their resistance to proteolysis.

About THBS, BROWNE et al. [62] detected increased levels of this plasma protein in patients with HbSS in the acute painful crises' presence. THBS is an important mediator in sickle cells adhesion to vascular endothelium, besides collaborating in platelet aggregation, modulating fibrinolysis [25] and the angiogenesis inhibition [63].

Patients with SCD may exhibit increased platelet activation [64–68]. The exact mechanism of chronic platelet activation in SCD has not been well elucidated [69], but may be related to the increase in megakaryocytes and concentration of some platelet agonists, such as ADP, collagen, epinephrine, adrenaline and thrombin [22,70,71]. During the frequent painful crises, there is thrombocytopenia, probably resulting from platelet deposition in endothelium, which is followed by an increase in platelet and megakaryocyte counts, peaking 10 to 14 days after the crisis [62]. When compared with healthy people, there is an increase in platelet activation markers, among them are the platelet factors 3 [72] and 4 [73], thrombospondin-1 [62], P-selectin [35,74], CD63, CD40L [65,74], activated glycoprotein IIb/IIIa [67,74,75], β-thromboglobulin [62,67] and PS exposition [71,76].

In SCD, TF expression is increased [27,62] in endothelial cells, monocytes and MPs derived from these [77]. TF is a relevant initiator of coagulation cascade, triggered by its interaction with factor VIIa, which results in the activation of serine proteases, including factors IX, X, XII and thrombin [78]. Several plasma components may increase their expression in endothelial or hematopoietic cells, such as C-reactive protein (CRP), free heme resulting from intravascular hemolysis, thrombin, endotoxin, interleukin-1 (IL-1), and tumor necrosis factor

Table 1
Main hemostatic changes in SCD.

Hemostatic events	Changes	References
Sickle cells-endothelium interaction	Increased	[12,36,163].
Platelets Activation	Increased	[62,64–68,133].
Tissue factor (TF) expression	Increased	[27,62,77,79–82].
Phosphatidylserine (PS) exposure	Increased	[36,71,76].
Thrombin generation	Increased	[73,88,90,164].
Natural anticoagulants	Decreased	[26,86–88,90,165].
Nitric oxide availability	Decreased	[166,167].
Von Willebrand Factor (vWF)	Increased	[39,58,59,61].
Thrombospondin (THBS)	Increased	[39,62,63].
Microparticles (MPs)	Increased	[48–56,67].
Fibrinolysis activation	Increased	[67,73,88].
D-Dimer (D-Di)	Increased	[32,67,77,83,85,88,90,95,96,100,164].
Plasminogen activator inhibitor-1 (PAI-1)	Increased	[96–98].
Prothrombin fragment 1 + 2 (F1 + 2)	Increased	[67,73,74,83].
Thrombin-antithrombin complex (TAT)	Increased	[27,67,73,168].
Plasmin-antiplasmin complex (PAP)	Increased	[67,73].

alpha (TNF-α) [34,79]. In Ragab and Soliman [80], and Solovey et al. [81] studies, increased monocytes TF expression during vaso-occlusive crises was reported when compared to the stable status. When investigating the coagulation activation mechanism in a in vivo model, Sparkenbaugh et al. [82] concluded that excess of free heme was able to stimulates the activation of TF and its expression in leukocytes, and to induces thrombin generation.

SCD patients have higher thrombin plasma levels, observed by their prothrombin fragment 1 + 2 (F1 + 2) and thrombin-antithrombin complex increased levels (TAT) [67,73,74,83]. Thrombin has pro-coagulant action, as it converts fibrinogen to fibrin, activates platelets and factors V, VIII, XI and XIII, which stabilizes the fibrin clot [84]. In addition, increased thrombin generation [85] may promote chronic consumption of natural anticoagulant, including antithrombin (AT), C and S proteins [86–88], which decrease even more in painful episodes [26,89]. The Nouboussie et al. [90] study demonstrated an increase in thrombin generation in children with SCD, but there was no significant difference during vaso-occlusive crises and stable status.

Besides increased coagulation activation and reduction of natural anticoagulant levels, in SCD there are important abnormalities in the fibrinolytic system [67,73,88]. Fibrinolysis consists of fibrin clot lysis and is regulated mainly by plasminogen activator inhibitor type 1 (PAI-1) action. PAI-1 inhibits tissue plasminogen activator (t-PA) and urokinase plasminogen activator (u-PA), thus preventing the conversion of plasminogen to plasmin [91]. Plasmin is an enzyme that cleaves the fibrin clot in degradation products, being D-Dimer (D-Di), a fragment widely used as a biomarker for coagulation activation [92] in disseminated intravascular coagulation and in venous thromboembolism diagnosis and monitoring [58].

PAI-1 is synthesized by several cell types (e.g. vascular endothelium, platelets, hepatocytes and fibroblasts) and its excess is related to thrombosis increased risk [93]. Patel et al. [94] found PAI-1 high levels in lung endothelial cells, alveolar macrophages, bronchial epithelial cells and sickle cell plasma of mice. D-Di [32,73,83,85,95,96] and PAI-1 [96–98] are increased in SCD and seem to be correlated with painful crises frequency, retinopathy and vaso-occlusion [99]. D-Di plasma levels [26], when compared to healthy controls, seems to be higher in SCD patients clinically stable [85,100] and during painful vaso-occlusive episodes [32,95].

3. Inflammation in sickle cell disease

In SCD, the chronic inflammatory process is related to clinical manifestations of unsatisfactory therapeutic solution, such as chronic pain [101]. In some patients, traditional non-steroidal anti-inflammatory drugs do not relieve the severe pain, although in the acute context this same intervention is effective [102]. In this disease, inflammation can affect almost the entire organism, which is evidenced by the alteration of innumerable inflammatory markers, as described in Table 2, which is important to mention: the increase in leukocyte number and its activation [39], the cytokines [25,100,103], CRP [104], neutrophilic extracellular traps (NETs) [105,106], secretory phospholipase A2 enzyme (s-PLA2) [107–109] platelet derived CD40 ligand or CD40L [74], placental growth factor (PEGF) [110] and urinary leukotriene E4 [111]. It is appropriate to mention that the abnormal membrane of the sickle cells and the existence of chronic hemolysis are important elements that trigger the inflammatory state [36].

SCD patients have chronic leukocytosis, especially with an increase in neutrophils and monocytes [4,34,100]. These are highly activated [112,113] and can induce the expression of E-selectin, P-selectin, VCAM, ICAM in endothelial cells and other monocytes [114–116]. Leukocytosis is a risk factor for acute chest syndrome, stroke and early mortality [38,102]. It is important to point that leukocytes interaction with endothelium is essential to initiate the inflammatory response, inducing adhesion molecules [114] and cytokines [14] expression. ROS and cytokines stimulate the nuclear transcription factor kappa B (NF-kB) to produce additional cytokines and chemokines, which contribute to a higher increase of pro-inflammatory and procoagulant molecules [112,117]. Therefore, the leukocytes, erythrocytes and platelets of patients with SCD have adhesion molecules higher expression, which makes them more susceptible to inflammatory stimulus [103,118].

The inflammatory phenotype is characterized by increased levels of proinflammatory cytokines [69,103,119–122] and acute-phase proteins, such as CRP, and reduced levels of anti-inflammatory cytokines in the stable status and during vaso-occlusive crises [103,122–124].

One of the first cytokines characterized as high levels in SCD people plasma was the vascular endothelial growth factor (VEGF) [37], potent activator of endothelial cells, also capable of promoting sickle cell activation, hypoxia, vascular remodeling, angiogenesis and inflammation [37]. However, it has an advantage in vessel tone regulation by increasing NO production, partially overcoming its negative effects [125].

Interleukin-6 (IL-6), released at vaso-occlusion sites, stimulates the hepatic production of fibrinogen, haptoglobin and CRP [126]. Microvascular occlusions, infections and hemolysis also stimulate the synthesis of acute-phase proteins and cytokines [127]. Keikhaei et al. (2013) [38] identified increased serum levels of IL-6, IL-17 and transforming growth factor beta (TGF-β) in SCD patients in vaso-occlusive crises compared to normal controls. IL-17 is a proinflammatory cytokine with several biological actions, such as the induction of IL-1 synthesis, TNF-α and neutrophil recruitment during inflammatory responses. TGF-β is a complex cytokine involved in inflammation, tissue injury, wound healing, immunity, infection, cell proliferation, apoptosis, pulmonary fibrosis, growth and activation of endothelial cells, and induce fetal Hb synthesis [37].

In this genetic disease, the released cytokines stimulate the activation of vascular endothelium, sickle cells, reticulocytes, platelets, leukocytes and these blood components adhesion to vascular wall through different mechanisms, such as the production of chemokines, the induction of fibronectin expression, VCAM and deregulation of endothelial cell apoptosis, thus generating a vicious cycle that leads to vaso-occlusion [123,128,129].

Neutrophils are sophisticated cells capable of effectively regulate

Table 2
Main inflammatory events in SCD.

Inflammatory events	Changes	References
White blood cell count	Increased	[4,34,39,100,107].
White blood cell activation	Increased	[64,112,113,139,145].
Expression of adhesion molecules in leukocytes	Increased	[114–116,133].
Proinflammatory cytokines	Increased	[14,38,69,100,103,119,121–123,169,170].
Anti-inflammatory cytokines	Decreased	[103,122–124].
Neutrophilic extracellular traps (NETs)	Increased	[105,106,134].
Secretory phospholipase A2 enzyme (sPLA2)	Increased	[107–109,136].
Placental growth factor (PEGF)	Increased	[37,110,113,138,139].
Leukotriene E4	Increased	[35,111].
C-reactive protein (CRP)	Increased	[104,170].

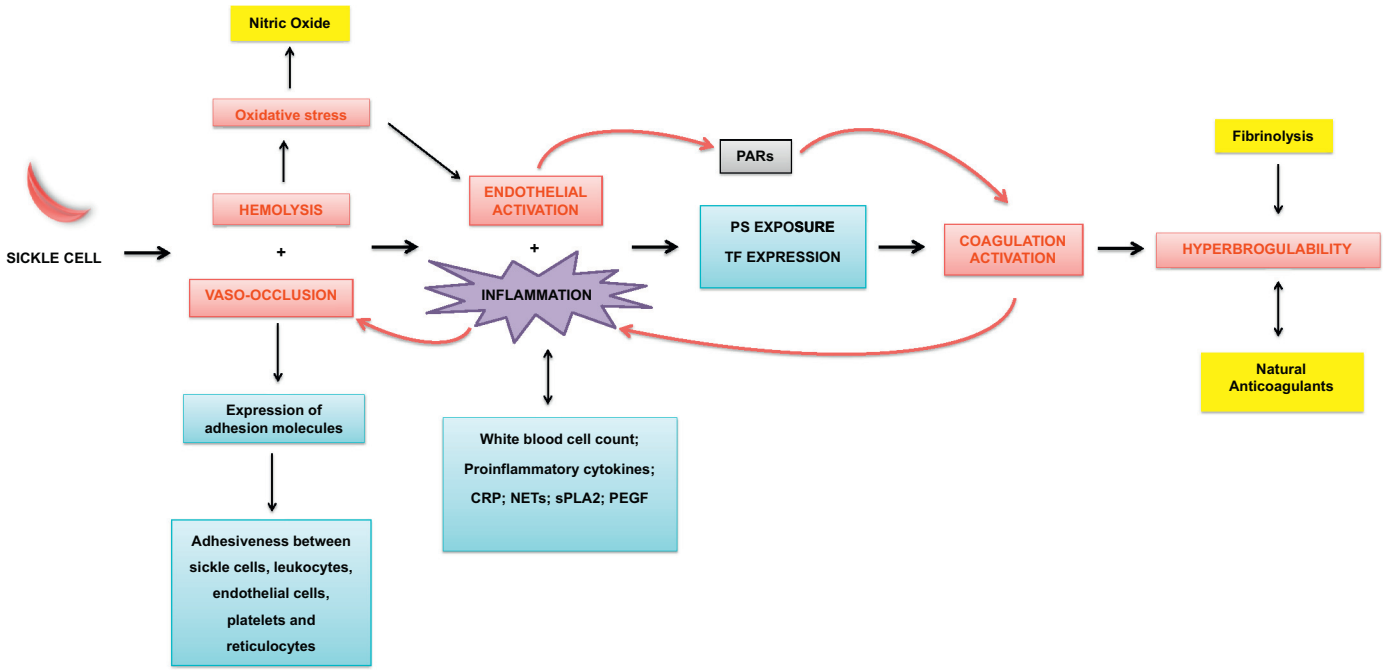

Fig. 1. Interrelation of hemostatic and inflammatory systems in SCD. Sickle cells favor hemolysis, vaso-occlusion and oxidative stress, which promote endothelial activation along with inflammation. Thus, there is coagulation activation by stimulating PS exposure, TF expression, and increasing inflammatory markers, inducing a hypercoagulable status. Coagulation activation establishes a positive return cycle (arrows in red) that contributes to inflammation, endothelial activation, vaso-occlusion and hemolysis, through the PARs. Blue rectangles indicate increase. Yellow rectangles indicate reduction. TF: tissue factor; PS: phosphatidylserine; NETs: Neutrophilic extracellular traps; PARs: protease-activated receptors; CRP: C-reactive protein; PEGF: placental growth factor; s-PLA2: secretory phospholipase A2 enzyme. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

the release of their granular enzymes, cytokines and chemokines, with a relevant role in inflammation and immunity [130]. Among the immune defense mechanisms of neutrophils, there is degranulation, phagocytosis, the cytokines production, and NETs production, which consist of deoxyribonucleic acid (DNA) networks where several proteins such as histones are adhered, and in addition of 30 components of primary and secondary granules, including cathepsin G, elastase, gelatinase, myeloperoxidase and lactoferrin [131,132]. NETs are released after chromatin decondensation, contributing to tissue damage, sepsis and organ failure [130,133]. In the Schimmel et al. [106] and Schimmer et al. [134] studies, higher concentrations of NETs were identified in SCD patients in painful crises than in the stable status. Chen et al. [105] concluded that heme plays an important role in NETs release in SCD, since it acts as a plasma factor that stimulates neutrophils NETs release both in vitro and in vivo, thus contributing to the pathogenesis of the disease.

The class of enzymes called s-PLA2 hydrolyzes phospholipids from cell membranes and lipoproteins, produces arachidonic acid, thus generating an inflammatory events cycle [34,135]. Styles et al. [136], detected high levels of this enzyme, 24 to 48 h before acute chest syndrome clinical diagnosis in patients with SCD, demonstrating its high sensitivity and specificity in prediction of this clinical complication occurrence. In the same sense, in the Styles et al. [109] study, patients in undergoing blood transfusion with s-PLA2 previous increase did not present acute chest syndrome episodes, thus suggesting the potential of s-PLA2 as a useful biomarker.

PEGF is an angiogenic growth factor belonging to the VEGF family, considered to be only produced in placenta, but is also released by hematopoietic cells [137]. Brittain et al. [138] compared PEGF levels of healthy controls and SCD patients, which were significantly elevated in the last group. In the Perelman et al. [113] study it was observed that elevated levels of PEGF in SCD patient's plasma induced monocytes activation, with a consequent increase in cytokines secretion such as IL-1 and IL-8. Sundaram et al. [110] concluded that PEGF high levels stimulated the release of endothelin-1 and, consequently, pulmonary hypertension occurrence in rats with SCD. Selvaraj et al. [139] observed that PEGF activated monocytes and increased mRNA levels of chemokines and cytokines, such as IL-, IL-8 and TNF-α. Thus, this growth factor is capable to promote the inflammatory mediators release (e.g., TNF-α), which enhances endothelial dysfunction, activate monocytes and increase adhesiveness of these to endothelium [37].

Field et al. [111] measured leukotriene E4 in urine samples from children and adults with SCD in the basal status and during painful crises, and found higher levels of E4 in the last ones, which reflects the cysteinyl leukotrienes C4 and D4 synthesis, important inflammatory mediators. These products are quickly catabolized in leukotriene E4, which can be dosed in the urine [140,141]. Leukotrienes are involved in leukocytes recruitment [142], in vascular occlusion process [143], besides promoting endothelial cells adhesiveness [144].

The platelets adhere to each other, to endothelium and to monocytes, inducing vaso-occlusion [145]. Besides, they are also new inflammatory cytokines sources [37].

4. Sickle cell disease, hemostasis and inflammation: interrelation

In SCD, as in other clinical abnormalities such as cancer [146,147], asthma [148,149], pre-eclampsia [150], pregnancy complications [151], diabetes mellitus [152,153] and dengue virus infections [154], hemostasis and inflammation are not isolated or unidirectional systems, quite the contrary, both interact continuously. In fact, the hemostatic system is able to influence the inflammatory response and vice versa [155]. New evidences indicate the interrelation between hemostasis and inflammation in several points, with emphasis on TF, cytokines, protein C system, thrombin, platelets [156,157], PEGF [113], besides fibrinolysis activators and inhibitors [158].

In SCD, hemolytic anemia causes the Hb, heme and arginase enzyme plasma release, and thus, inflammation status, endothelial dysfunction, oxidative stress and vascular proliferation. Extracellular heme, in turn,

constitutes a potent inflammatory agonist [32,70]. It is also believed that this pathology chronic inflammatory condition may favor its characteristic hypercoagulable status [7].

The vasculopathy refers to progressive arterial vasculature remodeling, which compromises blood flow [28]. The sickle cell vasculopathy pathogenesis is not yet completely elucidated, but it is known, however, that a generalized endothelial dysfunction, and contributions of genetic factors, endothelial injury, intravascular hemolysis, inflammation and chronic activation of coagulation cascade are relationed, resulting in hypoperfusion and tissue damage [31,159]. In this context, TF is very important not only for coagulation activation initiating, but also for triggering other biological pathways, such as vascular lesions and inflammation [28,160].

Fig. 1 outlines the main mechanisms of hemostatic and inflammatory processes and their interrelation in SCD. Chantrathammachart et al. [160] evaluated the TF function in coagulation activation and inflammation using in vivo models trying to understand the interrelation of these systems. The results indicate that FT contributes to coagulation activation, inflammation and vascular injury. They suggested that coagulation activation is capable of creating a positive return cycle that induce vascular occlusion, endothelial activation and inflammation via PARs and thrombosis-dependent mechanisms [40,160].

Further studies are needed to clarify the mechanisms which TF and coagulation factors, including thrombin and FXa, contribute to inflammation [40]. Sparkenbaugh et al. [161] state that SCD is one of rare pathologies which TF expression occurs not only in leukocytes but also in endothelium. They suggest that, according to TF expression site, it has different roles. When it is in endothelial cells, TF contributes to systemic inflammation by activation of PAR-2, FXa and thrombin. However, when expressed in leukocytes, it stimulates the coagulation activation, thrombin and fibrin generation. Furthermore, they affirm that FXa and thrombin can induce multiple cellular effects through the PARs activation.

5. Conclusions

SCD is a public health concern with high morbidity and early mortality [5]. Its clinical variability directly affects the individual's quality of life [18] and remains a challenge for the understanding of this hereditary disease [16]. There is a lack of high-quality evidence on the clinical management of SCD patients, corroborating to the existence of innumerable gaps and discrepancies in the guidelines, ranging from understanding of pathophysiological changes to the most appropriate therapies selection for each case [2]. Thus, it is extremely important to have a better knowledge of hemostatic and inflammatory changes, since it will allow the development of scientific knowledge of the several abnormalities that are related of hemostasis and inflammation systems in SCD. Not least, the review about the interrelation of hemostatic and inflammatory changes in this anomaly shows how closely linked these systems are, which may contribute to future biomarkers elucidation that allow the main SCD clinical complications occurrence prediction, or even the best management of these conditions. In addition, it also promotes the new therapeutic targets approach for drugs development that are more effective in preventing acute and chronic SCD complications, and has lower side effects. With knowledge advances about this disease, the greatest beneficiaries will be the patients, who will gather higher expectation and quality of life [162].

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Declarations of interest

None.

References

[1] M.H. Steinberg, Sickle cell anemia, the first molecular disease overview of molecular etiology, pathophysiology, and therapeutic approaches, Sci. World J. 8 (2008) 1295–1324, https://doi.org/10.1100/tsw.2008.157.
[2] B.P. Yawn, G.R. Buchanan, A.N. Afenyi-Annan, S.K. Ballas, K.L. Hassell, A.H. James, L. Jordan, S.M. Lanzkron, R. Lottenberg, W.J. Savage, P.J. Tanabe, R.E. Ware, M.H. Murad, J.C. Goldsmith, E. Ortiz, R. Fulwood, A. Horton, J. John-Sowah, Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members, JAMA 312 (2014) 1033–1048, https://doi.org/10.1001/jama.2014.10517.
[3] A.C.S. Pinto, I.V. Angulo, D.M. Brunetta, F.I.R. Neves, S.C. Bassi, G.C. Santis, D.T. Covas, Clinical and hematological effects of hydroxyurea therapy in sickle cell patients: a single-center experience in Brazil, São Paulo Med. J. 131 (2013) 238–243, https://doi.org/10.1590/1516-3180.2013.1314467.
[4] O.S. Platt, D.J. Brambilla, W.F. Rosse, P.F. Milner, O. Castro, M.H. Steinberg, P.P. Klug, Mortality in sickle cell disease. Life expectancy and risk factors for early death, N. Engl. J. Med. 330 (1994) 1639–1644, https://doi.org/10.1056/NEJM199406093302303.
[5] S. Rizk, E.D. Pulte, D. Axelrod, S.K. Ballas, Perinatal maternal mortality in sickle cell anemia: two case reports and review of the literature, Hemoglobin 41 (2017) 225–229, https://doi.org/10.1080/03630269.2017.1397017.
[6] P. Connes, C. Renoux, M. Romana, M. Abkarianf, P. Joly, C. Martin, M.D. Hardy-Dessources, S.K. Ballas, Blood rheological abnormalities in sickle cell anemia, Clin. Hemorheol. Microcirc. 68 (2018) 165–172, https://doi.org/10.3233/CH-189005.
[7] J.B. Stypulkowski, V. Manfredini, Changes in hemostasis in sickle cell disease patients, Rev. Bras. Hematol. Hemoter. (2009) 1–7, https://doi.org/10.1590/S1516-84842010005000001.
[8] S.B.P. Ferreira, L.C.N. Brito, M.P. Oliveira, K.F. Maciel, H.M. Junior, L.Q. Vieira, A.P.R. Sobrinho, Periapical cytokine expression in sickle cell disease, Basic Res. Biol. 41 (2015) 358–362, https://doi.org/10.1016/j.joen.2014.11.016.
[9] A.W. Macharia, G. Mochamah, S. Uyoga, C.M. Ndila, G. Nyutu, J. Makale, M. Tendwa, E. Nyatichi, J. Ojal, M. Shebe, K.O. Awuondo, N. Mturi, N. Peshu, B. Tsofa, J.A.G. Scott, K. Maitland, T.N. Williams, The clinical epidemiology of sickle cell anemia in Africa, Am. J. Hematol. 93 (2017) 363–370, https://doi.org/10.1002/ajh.24986.
[10] R.E. Ware, M. Montalembert, L. Tshilolo, M.R. Abboud, Sickle cell disease, Lancet 390 (2017) 311–323, https://doi.org/10.1016/S0140-6736(17)30193-9.
[11] M.F. Sabino, D.B.T. Gradella, Epidemiological profile of patients admitted with sickle cell anaemia in the state of Espirito Santo, Brazil (2001 – 2010), Rev. Bras. Pesq. Saúde 18 (2016) 35–41 http://periodicos.ufes.br/RBPS/article/viewFile/15082/10684.
[12] D.C. Rees, T.N. Williams, M.T. Gladwin, Sickle-cell disease, Lancet 376 (2010) 2018–2031, https://doi.org/10.1016/S0140-6736(10)61029-X.
[13] H.F. Bunn, Pathogenesis and treatment of sickle cell disease, N. Engl. J. Med. 337 (1997) 762–769, https://doi.org/10.1056/NEJM199709113371107.
[14] D. Manwani, P.S. Frenette, Vaso-occlusion in sickle cell disease: pathophysiology and novel targeted therapies, Blood 122 (2013) 3892–3898, https://doi.org/10.1182/blood-2013-05-498311.
[15] D.K. Kaul, E. Finnegan, G.A. Barabino, Sickle red cell - endothelium interactions, Microcirculation 16 (2009) 97–111, https://doi.org/10.1080/10739680802279394.
[16] D. Jain, D. Mohanty, Clinical manifestations of sickle cell disease in India: misconceptions and reality, Curr. Opin. Hematol. 25 (2018) 171–176, https://doi.org/10.1097/MOH.0000000000000422.
[17] N. Bakshi, D. Ross, L. Krishnamurti, Presence of pain on three or more days of the week is associated with worse patient reported outcomes in adults with sickle cell disease, J. Pain Res. 11 (2018) 313–318, https://doi.org/10.2147/JPR.S150065.
[18] K.S. Esham, A.M. Rodday, R.A. Weidner, R.J. Buchsbaum, H.P. Smith, S.K. Parsons, Health-related quality of life (HRQL) among hospitalized adults with sickle cell disease (SCD): incorporating patient-reported outcome (PRO) measures in clinical care, Blood 128 (2016) 5962 www.bloodjournal.org/content/128/22/5962.
[19] G. Sarri, M. Bhor, S. Abogunrin, C. Farmer, S. Nandal, R. Halloway, D.A. Revicki, Systematic literature review and assessment of patient-reported outcome instruments in sickle cell disease, Health Qual. Life Outcomes 16 (2018) 1–13, https://doi.org/10.1186/s12955-018-0930-y.
[20] N. Archer, F. Galacteros, C. Brugnara, 2015 clinical trials update in sickle cell anemia, Am. J. Hematol. 90 (2015) 934–950, https://doi.org/10.1002/ajh.24116.
[21] N.I. Umeh, B. Ajegba, A.J. Buscetta, K.E. Abdallah, C.P. Minniti, V.L. Bonham, The psychosocial impact of leg ulcers in patients with sickle cell disease: I don't want them to know my little secret, PLoS One 12 (2017) 1–13, https://doi.org/10.

1371/journal.pone.0186270.
[22] T. Wunt, T. Paglieroni, F. Tablin, J. Welborn, K. Nelson, A. Cheung, Platelet activation and aggregates in patients platelet-erythrocyte with sickle cell anemia, J. Lab. Clin. Med. 129 (1997) 507–516, https://doi.org/10.1016/S0022-2143(97)90005-6.
[23] B. Maitre, M. Djibre, S. Katsahian, A. Habibi, S.K. Stankovic, M. Khellaf, I. Bourgeon, F. Lionnet, A. Charles-Nelson, L. Brochard, F. Lemaire, F. Galacteros, C. Brun-Buisson, M. Fartoukh, D.A. Mekontso, Inhaled nitric oxide for acute chest syndrome in adult sickle cell patients: a randomized controlled study, Intensive Care Med. 41 (2015) 2121–2129, https://doi.org/10.1007/s00134-015-4060-2.
[24] D.M. Brunetta, G.C. Santis, A.C.S. Pinto, L.C.O. Oliveira, D.T. Covas, Hydroxyurea increases plasma concentrations of microparticles and reduces coagulation activation and fibrinolysis in patients with sickle cell anemia, Acta Haematol. 133 (2015) 287–294, https://doi.org/10.1159/000362148.
[25] E.Y. Chiang, P.S. Frenette, Sickle cell vaso-occlusion, Hematol. Oncol. Clin. N. Am. 19 (2005) 771–784, https://doi.org/10.1016/j.hoc.2005.08.002.
[26] M.Y. Lim, K.I. Ataga, N.S. Key, Hemostatic abnormalities in sickle cell disease, Curr. Opin. Hematol. 20 (2013) 472–477, https://doi.org/10.1097/MOH.0b013e328363442f.
[27] K.I. Ataga, N.S. Key, Hypercoagulability in sickle cell disease: new approaches to an old problem, Am. Soc. Hematol. (2007) 91–96, https://doi.org/10.1182/asheducation-2007.1.91.
[28] D. Nouboussie, N.S. Key, K.I. Ataga, Coagulation abnormalities of sickle cell disease: relationship with clinical outcomes and the effect of disease modifying therapies, Blood Rev. 30 (2017) 245–256, https://doi.org/10.1016/j.blre.2015.12.003.
[29] E.M. Novelli, C. Huynh, M.T. Gladwin, C.G. Moore, M.V. Ragni, Pulmonary embolism in sickle cell disease: a case-control study, J. Thromb. Haemost. 10 (2012) 760–766, https://doi.org/10.1111/j.1538-7836.2012.04697.x.
[30] P.D. Stein, A. Beemath, F.A. Meyers, E. Skaf, R.E. Olson, Deep venous thrombosis and pulmonary embolism in hospitalized patients with sickle cell disease, Am. J. Med. 119 (2006), https://doi.org/10.1016/j.amjmed.2006.08.015 897.e7–897.e11.
[31] G.J. Kato, R.P. Hebbel, M.H. Steinberg, M.T. Gladwin, Vasculopathy in sickle cell disease: biology pathophysiology genetics translational medicine and new research directions, Am. J. Hematol. 84 (2009) 618–625, https://doi.org/10.1002/ajh.21475.
[32] K.I. Ataga, J.E. Brittain, P. Desai, R. May, S. Jones, J. Delaney, D. Strayhorn, A. Hinderliter, N.S. Key, Association of coagulation activation with clinical complications in sickle cell disease, PLoS One 7 (2012) e29786, , https://doi.org/10.1371/journal.pone.0029786.
[33] R.P. Naik, M.B. Streiff, C. Haywood Jr., J.B. Segal, S. Lanzkron, Venous thromboembolism incidence in the cooperative study of sickle cell disease, J. Thromb. Haemost. 12 (2014) 1–14, https://doi.org/10.1111/jth.12744.
[34] G.A. Damanhouri, J. Jarullah, S. Marouf, S.I. Hindawi, G. Mushtaq, M.A. Kamal, Clinical biomarkers in sickle cell disease, Saudi J. Biol. Sci. Jeddah 22 (2015) 24–31, https://doi.org/10.1016/j.sjbs.2014.09.005.
[35] T.M. Carlos, J.M. Harlan, Leukocyte-endothelial adhesion molecules, Blood 84 (1994) 2068–2101 www.ncbi.nlm.nih.gov/pubmed/7522621.
[36] P.S. Frenette, G.F. Atweh, Sickle cell disease: old discoveries new concepts and future promise, J. Clin. Invest. 117 (2007) 850–858, https://doi.org/10.1172/JCI30920.
[37] J.E. Brittaina, L.V. Parise, Cytokines and plasma factors in sickle cell disease, Curr. Opin. Hematol. 14 (2007) 438–443, https://doi.org/10.1097/MOH.0b013e3282a4a673.
[38] B. Keikhaei, A.R. Mohseni, R. Norouzirad, M. Alinejadi, S. Ghanbari, F. Shiravi, G. Solgi, Altered levels of pro-inflammatory cytokines in sickle cell disease patients during vaso-occlusive crises and the steady state condition, Eur. Cytokine Netw Iran 24 (2013) 45–52, https://doi.org/10.1684/ecn.2013.0328.
[39] R.P. Hebbel, R. Osarogiagbon, D. Kaul, The endothelial biology of sickle cell disease: inflammation and a chronic vasculopathy, Microcirculation 11 (2004) 129–151, https://doi.org/10.1080/10739680490278402.
[40] E.M. Sparkenbaugh, R. Pawlinski, Interplay between coagulation and vascular inflammation in sickle cell disease, Br. J. Haematol. 162 (2013) 1–22, https://doi.org/10.1111/bjh.12336.
[41] G.J. Kato, V.R. Mcgowan, R.F. Machado, J.A. Little, V.J. Taylor, C.R. Morris, J.S. Nichols, X. Wang, M. Poljakovic, S.M.J.R. Morris, M.T. Gladwin, 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 107 (2006) 2279–2285, https://doi.org/10.1182/blood-2005-06-2373.
[42] J.J. Schnog, E.H. Jager, D.F.P. Van, A.J. Duits, H. Moshage, F.D. Muskiet, F.A. Muskiet, Evidence for a metabolic shift of arginine metabolism in sickle cell disease, Ann. Hematol. 83 (2004) 371–375, https://doi.org/10.1007/s00277-004-0856-9.
[43] C.R. Morris, G.J. Kato, M. Poljakovic, X. Wang, W.C. Blackwelder, V. Sachdev, S.L. Hazen, E.P. Vichinsky, S.M.J.R. Morris, M.T. Gladwin, Dysregulated arginine metabolism hemolysis associated pulmonary hypertension and mortality in sickle cell disease, JAMA 294 (2005) 81–90, https://doi.org/10.1001/jama.294.1.81.
[44] R. Huisjes, A. Bogdanova, W.W. Van Solinge, R.M. Schiffelers, L. Kaestner, W.R. Van, Squeezing for life - properties of red blood cell deformability, Front. Physiol. 9 (2018) 1–22, https://doi.org/10.3389/fphys.2018.00656.
[45] S. Nomura, Y. Ozaki, Y. Ikeda, Function and role of microparticles in various clinical settings, Thromb. Res. 123 (2008) 8–23, https://doi.org/10.1016/j.thromres.2008.06.006.
[46] F. Meziani, A. Tesse, R. Andriantsitohaina, Microparticles are vectors of paradoxical information in vascular cells including the endothelium: role in health and diseases, Pharmacol. Rep. 60 (2008) 75–84 www.ncbi.nlm.nih.gov/pubmed/18276988.
[47] J.H. Distler, L.C. Huber, S. Gay, O. Distler, D.S. Pisetsky, Microparticles as mediators of cellular cross-talk in inflammatory disease, Autoimmunity 39 (2006) 683–690, https://doi.org/10.1080/08916930601061538.
[48] G.T. Gerotziafas, D.P. Van, M. Chaari, V. Galea, A. Khaterchi, F. Lionnet, K. Stankovic-Stojanovic, O. Blanc-Brude, B. Woodhams, M. Maier-Redelsperger, R. Girot, M. Hatmi, I. Elalamy, The acceleration of the propagation phase of thrombin generation in patients with steady-state sickle cell disease is associated with circulating erythrocyte-derived microparticles, Thromb. Haemost. 107 (2012) 1044–1052, https://doi.org/10.1160/TH11-10-0689.
[49] M. Kasar, C. Boga, M. Yeral, S. Asma, I. Kozanoglu, H. Ozdogu, Clinical significance of circulating blood and endothelial cell microparticles in sickle-cell disease, J. Thromb. Thrombolysis 38 (2014) 167–175, https://doi.org/10.1007/s11239-013-1028-3.
[50] D. Nébor, M. Romana, R. Santiago, N. Vachiery, J. Picot, C. Broquere, V. Chaar, L. Doumdo, M.H. Odièvre, M. Benkerrou, J. Elion, Fetal hemoglobin and hydroxycarbamide modulate both plasma concentration and cellular origin of circulating microparticles in sickle cell anemia children, Haematologica 98 (2013) 862–867, https://doi.org/10.3324/haematol.2012.073619.
[51] A. Piccin, C. Murphy, E. Eakins, J. Kunde, D. Corvetta, A. Di Pierro, G. NEGRI, M. GUIDO, L. SAINATI, C.Mc. Mahon, O.P. Smith, W. Murphy, Circulating microparticles protein C free protein S and endothelial vascular markers in children with sickle cell anaemia, J. Extracell. Vesicles 4 (2015) 1–16, https://doi.org/10.3402/jev.v4.28414.
[52] A.S. Shet, O. Aras, K. Gupta, M.J. Hass, D.J. Rausch, N. Saba, L. Koopmeiners, N.S. Key, R.P. Hebbel, Sickle blood contains tissue factor positive microparticles derived from endothelial cells and monocytes, Blood 102 (2003) 2678–2683, https://doi.org/10.1182/blood-2003-03-0693.
[53] M. Westerman, A. Pizzey, J. Hirschman, M. Cerino, Y. Weil-Weiner, P. Ramotar, A. Eze, A. Lawrie, G. Purdy, I. Mackie, J. Porter, Microvesicles in haemoglobinopathies offer insights into mechanisms of hypercoagulability haemolysis and the effects of therapy, Br. J. Haematol. 142 (2008) 126–135, https://doi.org/10.1111/j.1365-2141.2008.07155.x.
[54] L.J. Van Tits, W.L. Van Heerde, P.P. Landburg, M.J. Boderie, F.A. Muskiet, N. Jacobs, A.J. Duits, J.B. Schnog, Plasma annexin A5 and microparticle phosphatidylserine levels are elevated in sickle cell disease and increase further during painful crisis, Biochem. Biophys. Res. Commun. 390 (2009) 161–164, https://doi.org/10.1016/j.bbrc.2009.09.102.
[55] A.A. Tantawy, A.A. Adly, E.A. Ismail, N.M. Habeeb, A. Farouk, Circulating platelet and erythrocyte microparticles in young children and adolescents with sickle cell disease: relation to cardiovascular complications, Platelets 24 (2013) 605–614, https://doi.org/10.3109/09537104.2012.749397.
[56] Y. Garnier, S. Ferdinand, M.E. Julan, G. Elana, M. Petras, L. Doumdo, B. Tressières, M.L.L. Mistrih, M.D.H. Dessources, P. Connes, M. Romana, Differences of microparticle patterns between sickle cell anemia and hemoglobin SC patients, PLoS One 12 (2017) e0177397, , https://doi.org/10.1371/journal.pone.0177397.
[57] J. Chen, D.W. Chung, Inflammation von Willebrand factor and ADAMTS13, Blood 132 (2018) 141–147, https://doi.org/10.1182/blood-2018-02-769000.
[58] S.S. Adam, N.S. Key, C.S. Greenberg, D-dimer antigen: current concepts and future prospects, Blood 113 (2009) 2878–2887, https://doi.org/10.1182/blood-2008-06-165845.
[59] J. Chen, W.E. Hobbs, J. Le, P.J. Lenting, P.G. De Groot, J.A. López, The rate of hemolysis in sickle cell disease correlates with the quantity of active von Willebrand factor in the plasma, Blood 117 (2011) 3680–3683, https://doi.org/10.1182/blood-2010-08-302539.
[60] L.C. Tonaco, D.R.A. Rios, L.M. Vieira, M.G. Carvalho, L.M.S. Dusse, Thrombotic thrombocytopenic purpura: the role of von Willebrand factor and ADAMTS13, Rev. Bras. Hematol. Hemoter. 32 (2010) 155–161, https://doi.org/10.1590/S1516-84842010005000043.
[61] J.W.R. Sins, M. Schimmel, B.M. Luken, E. Nur, S.S. Zeerleder, C.F.J. Van Tuijn, D.P.M. Brandjes, W.F. Kopatz, R.T. Urbanus, J.C.M. Meijers, B.J. Biemond, K. Fijnvandraat, Dynamics of von Willebrand factor reactivity in sickle cell disease during vaso-occlusive crisis and steady state, J. Thromb. Haemost. 15 (2017) 1392–1402, https://doi.org/10.1111/jth.13728.
[62] P.V. Browne, D.F. Mosher, M.H. Steinberg, R.P. Hebbel, Disturbance of plasma and platelet thrombospondin levels in sickle cell disease, Am. J. Hematol. 51 (1996) 96–301, https://doi.org/10.1002/(SICI)1096-8652(199604)51:4<296::AID-AJH8>3.0.CO;2-R.
[63] P.R. Lawler, J. Lawler, Molecular basis for the regulation of angiogenesis by thrombospondin-1 and -2, Cold Spring Harb. Perspect. Med. 2 (2012) 1–13.
[64] D.P. Inwald, F.J. Kirkham, M.J. Peters, R. Lane, A. Wade, J.P. Evans, N.J. Klein, Platelet and leucocyte activation in childhood sickle cell disease: association with nocturnal hypoxaemia, Br. J. Haematol. 111 (2000) 474–481, https://doi.org/10.1111/j.1365-2141.2000.02353.x.
[65] S.P. Lee, K.I. Ataga, E.P. Orringer, D.R. Phillips, L.V. Parise, Biologically active CD40 ligand is elevated in sickle cell anemia: potential role for platelet-mediated inflammation, Arterioscler. Thromb. Vasc. Biol. 26 (2006) 1626–1631, https://doi.org/10.1161/01.ATV.0000220374.00602.a2.
[66] N. Raghavachari, X. Xu, A. Harris, J. Villagra, C. Logun, J. Barb, M.A. Solomon, A.F. Suffredini, R.L. Danner, G. Kato, P.J. Munson, S.M.J.R. Morris, M.T. Gladwin, Amplified expression profiling of platelet transcriptome reveals changes in arginine metabolic pathways in patients with sickle cell disease, Circulation 115 (2007) 1551–1562, https://doi.org/10.1161/CIRCULATIONAHA.106.658641.
[67] A. Tomer, L.A. Harker, S. Kasey, Eckman Jr, Thrombogenesis in sickle cell disease,

J. Lab. Clin. Med. 137 (2001) 398–407, https://doi.org/10.1067/mlc.2001.115450.
[68] J. Villagra, S. Shiva, L.A. Hunter, R.F. Machado, M.T. Gladwin, G.J. Kato, Platelet activation in patients with sickle disease hemolysis-associated pulmonary hypertension and nitric oxide scavenging by cell-free hemoglobin, Blood 110 (2007) 2166–2172, https://doi.org/10.1182/blood-2006-12-061697.
[69] Y. Osman, C.B. Vatte, Study of platelet activation markers and plasma cytokines in sickle cell disease patients during vaso-occlusive pain crises, J. Hematop. 11 (2018) 37–44, https://doi.org/10.1007/s12308-018-0322-6.
[70] M. Aslan, B.A. Freeman, Redox - dependent impairment of vascular function in sickle cell disease, Free Radic. Biol. Med. 43 (2007) 1469–1483, https://doi.org/10.1016/j.freeradbiomed.2007.08.014.
[71] Z. Yasin, S. Witting, M.B. Palascak, C.H. Joiner, D.L. Rucknagel, R.S. Franco, Phosphatidylserine externalization in sickle red blood cells: associations with cell age density and hemoglobin F, Blood 102 (2003) 365–370, https://doi.org/10.1182/blood-2002-11-3416.
[72] A.A. Famodu, D. Oduwa, Platelet count and platelet factor 3 (PF-3) availability in sickle cell disease, Br. J. Biomed. Sci. 52 (1995) 323–324 www.ncbi.nlm.nih.gov/pubmed/8555788.
[73] A. Tomer, S. Kasey, W.E. Connor, S. Clark, L.A. Harker, J.R. Eckman, Reduction of pain episodes and prothrombotic activity in sickle cell disease by dietary n-3 fatty acids, Thromb. Haemost. 85 (2001) 966–974 www.ncbi.nlm.nih.gov/pubmed/11434703.
[74] J.A. Jakubowski, C. Zhou, S. Jurcevic, K.J. Winters, D.R. Lachno, A.L. Frelinger, N. Gupta, J. Howard, C.D. Payne, T.G. Mant, A phase 1 study of prasugrel in patients with sickle cell disease: effects on biomarkers of platelet activation and coagulation, Thromb. Res. 133 (2013) 190–195, https://doi.org/10.1111/bcp.12042.
[75] R. Proença-Ferreira, C.F. Franco-Penteado, F. Traina, S.T. Saad, F.F. Costa, N. Conran, Increased adhesive properties of platelets in sickle cell disease: roles for alphaIIb beta3-mediated ligand binding diminished cAMP signaling and increased phosphodiesterase 3A activity, Br. J. Haematol. 149 (2010) 280–288, https://doi.org/10.1111/j.1365-2141.2010.08087.x.
[76] K. De Jong, S.K. Larkin, L.A. Styles, R.M. Bookchin, F.A. Kuypers, Characterization of the phosphatidylserine-exposing subpopulation of sickle cells, Blood 98 (2001) 860–867, https://doi.org/10.1182/blood.V98.3.860.
[77] N.S. Key, A. Slungaard, L. Dandelet, S.C. Nelson, C. Moertel, L.A. Styles, F.A. Kuypers, R.R. Bach, Whole blood tissue factor procoagulant activity is elevated in patients with sickle cell disease, Blood 91 (1998) 4216–4223 http://www.bloodjournal.org/content/91/11/4216.
[78] C. Faes, E.M. Sparkenbaugh, R. Pawlinski, Hypercoagulable state in sickle cell disease, Clin. Hemorheol. Microcirc. 68 (2018) 301–318, https://doi.org/10.3233/CH-189013.
[79] B.N.Y. Setty, N.S. Key, A.K. Rao, S. Gayen-Betal, S. Krishnan, C.D. Dampier, M.J. Stuart, Tissue factor-positive monocytes in children with sickle cell disease: correlation with biomarkers of Haemolysis, Br. J. Haematol. 157 (2012) 370–380, https://doi.org/10.1111/j.1365-2141.2012.09065.x.
[80] S.M. Ragab, M.A. Soliman, Tissue factor-positive monocytes expression in children with sickle cell disease: clinical implication and relation to inflammatory and coagulation markers, Blood Coagul. Fibrinolysis 27 (2016) 862–869, https://doi.org/10.1097/MBC.0000000000000494.
[81] A. Solovey, R. Kollander, A. Shet, L.C. Milbauer, S. Choong, A. Panoskaltsis-Mortari, B.R. Blazar, R.J.J.R. Kelm, R.P. Hebbel, Endothelial cell expression of tissue factor in sickle mice is augmented by hypoxia/reoxygenation and inhibited by lovastatin, Blood 104 (2004) 840–846, https://doi.org/10.1182/blood-2003-10-3719.
[82] E.M. Sparkenbaugh, P. Chantrathammachart, S. Wang, W. Jonas, D. Kirchhofer, D. Gailani, A. Gruber, R. Kasthuri, N.S. Key, N. Mackman, R. Pawlinski, Excess of heme induces tissue factor-dependent activation of coagulation in mice, Haematologica 100 (2015) 308–314, https://doi.org/10.3324/haematol.2014.114728.
[83] K.I. Ataga, C.G. Moore, C.A. Hillery, S. Jones, H.C. Whinna, D. Strayhorn, C. Sohier, A. Hinderliter, L.V. Parise, E.P. Orringer, Coagulation activation and inflammation in sickle cell disease-associated pulmonary hypertension, Haematologica 93 (2008) 20–26, https://doi.org/10.3324/haematol.11763.
[84] D.M. Monroe, M. Hoffman, H.R. Roberts, Platelets and thrombin generation, Arterioscler. Thromb. Vasc. Biol. 22 (2002) 1381–1389 www.ncbi.nlm.nih.gov/pubmed/12231555.
[85] N. Shah, C. Thornburg, M.J. Telen, T.L. Ortel, Characterization of the hypercoagulable state in patients with sickle cell disease, Thromb. Res. 130 (2012) e241–e245, https://doi.org/10.1016/j.thromres.2012.08.307.
[86] Z. Rahimi, A. Parsian, Sickle cell disease and venous thromboembolism, Mediterr. J. Hematol. Infect. Dis. 3 (2011) 1–7, https://doi.org/10.4084/MJHID.2011.024.
[87] D.A. Tam, Protein C and protein S activity in sickle cell disease and stroke, J. Child Neurol. 12 (1997) 19–21, https://doi.org/10.1177/088307389701200103.
[88] M.P. Westerman, D. Green, A. Gilman-Sachs, K. Beaman, S. Freels, L. Boggio, S. Allen, L. Zuckerman, R. Schlegel, P. Williamson, Antiphospholipid antibodies proteins C and S and coagulation changes in sickle cell disease, J. Lab. Clin. Med. 134 (1999) 352–362, https://doi.org/10.1016/S0022-2143(99)90149-X.
[89] C.T. Esmon, The interactions between inflammation and coagulation, Br. J. Haematol. 131 (2005) 417–430, https://doi.org/10.1111/j.1365-2141.2005.05753.x.
[90] D.F. Noubouossie, P.Q. Lê, F. Corazza, F. Debaugnies, L. Rozen, A. Ferster, A. Demulder, Thrombin generation reveals high procoagulant potential in the plasma of sickle cell disease children, Am. J. Hematol. 87 (2012) 145–149, https://doi.org/10.1002/ajh.22206.
[91] M. Hoffman, D.M. Monroe, Coagulation 2006: a modern view of hemostasis, Hematol. Oncol. Clin. N. Am. 21 (2007) 1–11, https://doi.org/10.1016/j.hoc.2006.11.004.
[92] Z. Pakbaz, T. Wun, Role of the hemostatic system on SCD pathophysiology and potential therapeutics, Hematol. Oncol. Clin. North Am. 28 (2014) 355–374, https://doi.org/10.1016/j.hoc.2013.11.011.
[93] C. Longstaff, Measuring fibrinolysis: from research to routine diagnostic assays, J. Thromb. Haemost. 16 (2018) 652–662, https://doi.org/10.1111/jth.13957.
[94] N. Patel, N. Sundaram, M. Yang, C. Madigan, V.J. Kalra, P. Malik, Placenta growth factor (PlGF) a novel inducer of plasminogen activator inhibitor-1 (PAI-1) in sickle cell disease (SCD), J. Biol. Chem. 285 (2010) 16713–16722, https://doi.org/10.1074/jbc.M110.101691.
[95] S. Ahmed, A.K. Siddiqui, U. Iqbal, C.P. Sison, R.K. Shahid, M. Sheth, D.V. Patel, L.A. Russo, Effect of low-dose warfarin on D-dimer levels during sickle cell vaso-occlusive crisis: a brief report, Eur. J. Haematol. 72 (2004) 213–216, https://doi.org/10.1111/j.0902-4441.2003.00209.x.
[96] B. Nsiri, N. Gritli, F. Bayoudh, T. Messaoud, S. Fattoum, S. Machghoul, Abnormalities of coagulation and fibrinolysis in homozygous sickle cell disease, Hematol. Cell Ther. 38 (1996) 279–284 https://www.ncbi.nlm.nih.gov/pubmed/8974793.
[97] D. Hagger, S. Wolff, J. Owen, D. Samson, Changes in coagulation and fibrinolysis in patients with sickle-cell disease compared with healthy black controls, Blood Coagul. Fibrinolysis 6 (1995) 93–99 www.ncbi.nlm.nih.gov/pubmed/7605884.
[98] B. Nsiri, N. Gritli, C. Mazigh, E. Ghazouani, S. Fattoum, S. Machghoul, Fibrinolytic response to venous occlusion in patients with homozygous sickle cell disease, Hematol. Cell Ther. 39 (1997) 229–232 www.ncbi.nlm.nih.gov/pubmed/9395896.
[99] R.P. Naik, J.G. Wilson, L. Ekunwe, S. Mwasongwe, Q. Duan, Y. Li, A. Correa, A.P. Reiner, Elevated D-dimer levels in African Americans with sickle cell trait, Blood 127 (2016) 2261–2263, https://doi.org/10.1182/blood-2016-01-694422.
[100] M.H. Qari, U. Dier, S.A. Mousa, Biomarkers of inflammation growth factor and coagulation activation in patients with sickle cell disease, Clin. Appl. Thromb. Hemost. 18 (2012) 195–200, https://doi.org/10.1177/1076029611420992.
[101] L. Vincent, D. Vang, J. Nguyen, M. Gupta, K. Luk, M.E. Ericson, D.A. Simone, K. Gupta, Mast cell activation contributes to sickle cell pathobiology and pain in mice, Blood 122 (2013) 1853–1862, https://doi.org/10.1182/blood-2013-04-498105.
[102] A.O. Ansah, C.A. Ihunnah, A.L. Walker, S.F.O. Acquah, Inflammatory targets of therapy in sickle cell disease, Transl. Res. 167 (2015) 281–297, https://doi.org/10.1016/j.trsl.2015.07.001.
[103] I.C. Bandeira, L.B. Rocha, M.C. Barbosa, D.B. Elias, J.A. Querioz, M.V. Freitas, R.P. Gonçalves, Chronic inflammatory state in sickle cell anemia patients is associated with HBB*S haplotype, Cytokine 65 (2014) 217–221, https://doi.org/10.1016/j.cyto.2013.10.009.
[104] S. Krishnan, Y. Setty, S.G. Betal, V. Vijender, K. Rao, C. Dampier, M. Stuart, Increased levels of the inflammatory biomarker C-reactive protein at baseline are associated with childhood sickle cell vasocclusive crises, Br. J. Haematol. 148 (2010) 797–804, https://doi.org/10.1111/j.1365-2141.2009.08013.x.
[105] G. Chen, D. Zhang, T.A. Fuchs, D. Manwani, D.D. Wagner, P.S. Frenette, Heme-induced neutrophil extracellular traps contribute to the pathogenesis of sickle cell disease, Blood 123 (2014) 3818–3827, https://doi.org/10.1182/blood-2013-10-529982.
[106] M. Schimmel, E. Nur, B.J. Biemond, G.J.V. Mierlo, S. Solati, D.P. Brandjes, H.M. Otten, J.J. Schnog, S. Zeerleder, Nucleosomes and neutrophil activation in sickle cell disease painful crisis, Haematologica 98 (2013) 1797–1803, https://doi.org/10.3324/haematol.2013.088021.
[107] S.K. Ballas, B. Files, L. Luchtman-Jones, L. Benjamin, P. Swerdlow, L. Hilliard, T. COATES, M. ABBOUD, S. Wojtowicz-Praga, F.A. Kuypers, J. Michael Grindel, Secretory phospholipase A2 levels in patients with sickle cell disease and acute chest syndrome, Hemoglobin 30 (2006) 165–170, https://doi.org/10.1080/03630260600642260.
[108] J.T. Naprawa, B.K. Bonsu, D.G. Goodman, M.A. Ranalli, Serum biomarkers for identifying acute chest syndrome among patients who have sickle cell disease and present to the emergency department, Pediatrics 116 (2005) e420–e425, https://doi.org/10.1542/peds.2004-2107.
[109] L.A. Styles, M. Abboud, S. Larkin, M. Lo, F.A. Kuypers, Transfusion prevents acute chest syndrome predicted by elevated secretory phospholipase A2, Br. J. Haematol. 136 (2007) 343–344, https://doi.org/10.1111/j.1365-2141.2006.06409.x.
[110] N. Sundaram, A. Tailor, L. Mendelsohn, J. Wansapura, X. Wang, T. Higashimoto, M.W. Pauciulo, W. Gottliebson, V.K. Kalra, W.C. Nichols, G.J. Kato, P. Malik, High levels of placenta growth factor in sickle cell disease promote pulmonary hypertension, Blood 116 (2010) 109–112, https://doi.org/10.1182/blood-2009-09-244830.
[111] J.J. Field, R.C. Strunk, J.E. Knight-Perry, M.A. Blinder, R.R. Townsend, M.R. Debaun, Urinary cysteinyl leukotriene E4 significantly increases during pain in children and adults with sickle cell disease, Am. J. Hematol. 84 (2009) 231–233, https://doi.org/10.1002/ajh.21370.
[112] J.D. Belcher, P.H. Marker, J.P. Weber, R.P. Hebbel, G.M. Vercellotti, Activated monocytes in sickle cell disease: potential role in the activation of vascular endothelium and vaso-occlusion, Blood 96 (2000) 2451–2459 www.ncbi.nlm.nih.gov/pubmed/11001897.
[113] N. Perelman, S.K. Selvaraj, S. Batra, L.R. Luck, A. Erdreich-Epstein, T.D. Coates, V.K. Kalra, P. Malik, Placenta growth factor activates monocytes and correlates with sickle cell disease severity, Blood 102 (2003) 1506–1514, https://doi.org/10.1182/blood-2002-11-3422.

[114] L.A. Lasky, Selectins: interpreters of cell-specific carbohydrate information during inflammation, Science 258 (1992) 964–969, https://doi.org/10.1126/science.1439808.
[115] F.A. Spring, S.F. Parsons, S. Ortlepp, M.L. Olsson, R. Sessions, R.L. Brady, D.J. Anstee, Intercellular adhesion molecule-4 binds alpha(4)beta(1) and alpha (V)-family integrins through novel integrin-binding mechanisms, Blood 98 (2001) 458–466, https://doi.org/10.1182/blood.V98.2.458.
[116] B.E. Gee, O.S. Platt, Sickle reticulocytes adhere to VCAM-1, Blood 85 (1995) 268–274 https://www.ncbi.nlm.nih.gov/pubmed/7528569.
[117] C. Sultana, Y. Shen, V. Rattan, C. Johnson, V.K. Kalra, Interaction of sickle erythrocytes with endothelial cells in the presence of endothelial cell conditioned medium induces oxidant stress leading to transendothelial migration of monocytes, Blood 92 (1998) 3924–3935 https://www.ncbi.nlm.nih.gov/pubmed/9808586.
[118] D. Zhang, C. Xu, D. Manwani, P.S. Frenette, Neutrophils platelets and inflammatory pathways at the nexus of sickle cell disease pathophysiology, Blood 127 (2016) 801–809, https://doi.org/10.1182/blood-2015-09-618538.
[119] E. Charrin, S.F. Ofori-Acquah, E. Nader, S. Skinner, P. Connes, V. Pialoux, P. Joly, C. Martin, Inflammatory and oxidative stress phenotypes in transgenic sickle cell mice, Blood Cells Mol. Dis. 62 (2016) 13–21, https://doi.org/10.1016/j.bcmd.2016.10.020.
[120] P.S. Frenette, Sickle cell vaso-occlusion: multistep and multicellular paradigm, Curr. Opin. Hematol. 92 (2002) 101–106 www.ncbi.nlm.nih.gov/pubmed/11844991.
[121] S.C.O. Gilli, F.V. Pericole, B.D. Benites, E.A. Sippert, L.M. Castilho, M.A. Carvalho, M.A. Carvalho, S.T.O. Saad, Cytokine polymorphisms in sickle cell disease and the relationship with cytokine expression, Exp. Hematol. 44 (2016) 583–589, https://doi.org/10.1016/j.exphem.2016.03.008.
[122] S. Sarray, L.R. Saleh, L.F. Saldanha, H.H. Al-Habboubi, N. Mahdi, W.Y. Almawi, Serum IL-6 IL-10 and TNFα levels in pediatric sickle cell disease patients during vasoocclusive crisis and steady state condition, Cytokine 72 (2015) 43–47, https://doi.org/10.1016/j.cyto.2014.11.030.
[123] S.A. Adegokea, O.S. Smithc, A.D. Adekiled, M.S. Figueiredo, Relationship between serum 25-hydroxyvitamin D and inflammatory cytokines in pediatric sickle cell disease, Cytokine 96 (2017) 87–93, https://doi.org/10.1016/j.cyto.2017.03.010.
[124] I. Malavé, Y. Perdomo, E. Escalona, E. Rodriguez, M. Anchustegui, H. Malavé, T. Arends, Level of tumor necrosis factor alpha/cachectin (TNF alpha) in sera from patients with sickle cell disease, Acta Haematol. 90 (1993) 172–176, https://doi.org/10.1159/000204452.
[125] S. Ahmad, P.W. Hewett, P. Wang, B. Al-Ani, M. Cudmore, T. Fujisawa, J.J. Haigh, F. Le Noble, L. Wang, D. Mukhopadhyay, A. Ahmed, Direct evidence for endothelial vascular endothelial growth factor receptor-1 function in nitric oxide-mediated angiogenesis, Circ. Res. 99 (2006) 715–722, https://doi.org/10.1161/01.RES.0000243989.46006.b9.
[126] H. Baumann, J. Gauldie, The acute phase response, Immunol. Today 15 (1994) 74–80, https://doi.org/10.1016/0167-5699(94)90137-6.
[127] A. Pathare, S.A. Kindi, A.A. Alnaqdy, S. Daar, H. Knox-Macaulay, D. Dennison, Cytokine profile of sickle cell disease in Oman, Am. J. Hematol. Sultanate Oman 77 (2004) 323–328, https://doi.org/10.1002/ajh.20196.
[128] C. Lanaro, C.F. Franco-Penteado, D.M. Albuqueque, S.T. Saad, N. Conran, F.F. Costa, Altered levels of cytokines and inflammatory mediators in plasma and leukocytes of sickle cell anemia patients and effects of hydroxyurea therapy, J. Leukoc. Biol. 85 (2009) 235–242, https://doi.org/10.1189/jlb.0708445.
[129] A.C. Makis, E.C. Hatzimichael, K.L. Bourantas, The role of cytokines in sickle cell disease, Ann. Hematol. 79 (2000) 407–413 www.ncbi.nlm.nih.gov/pubmed/10985359.
[130] V.D. Rizo, M.A.M. Guzmán, L.I. Gutierrez, A.G. Orozco, A.A. Navarro, M.F. Morris, Neutrophil extracellular Traps and its implications in inflammation: an overview, Front. Immunol. 8 (2017) 1–20, https://doi.org/10.3389/fimmu.2017.00081.
[131] V. Brinkmann, A. Zychlinsky, Beneficial suicide: why neutrophils die to make NETs, Nat. Rev. Microbiol. 5 (2007) 577–582, https://doi.org/10.1038/nrmicro1710.
[132] T.A. Fuchs, U. Abed, C. Goosmann, R. Hurwitz, I. Schulze, V. Wahn, Y. Weinrauch, V. Brinkmann, A. Zychlinsky, Novel cell death program leads to neutrophil extracellular traps, J. Cell Biol. 176 (2007) 231–241, https://doi.org/10.1083/jcb.200606027.
[133] C.C. Hopp, Inflammatory mediators of endothelial injury in sickle cell disease, Hematol. Oncol. Clin. N. Am. 28 (2014) 265–286, https://doi.org/10.1016/j.hoc.2013.11.006.
[134] C. Schimmer, K. Hamouda, M. Özkur, S.P. Sommer, J. Hain, I. Aleksic, R. Leyh, Influence of storage time and amount of red blood cell transfusion on post-operative renal function: an observational cohort study, Heart Lung Vessel 5 (2013) 148–157 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3848673/.
[135] M. Murakami, K. Yamamoto, Y. Miki, R. Murase, H. Sato, Y. Taketomi, The roles of the secreted phospholipase A2 gene family in immunology, Adv. Immunol. 132 (2016) 91–134, https://doi.org/10.1016/bs.ai.2016.05.001.
[136] L.A. Styles, A.J. Aarsman, E.P. Vichinsky, F.A. Kuypers, Secretory phospholipase A(2) predicts impending acute chest syndrome in sickle cell disease, Blood 96 (2000) 3276–3278 https://www.ncbi.nlm.nih.gov/pubmed/11050014.
[137] V.K. Kalra, S. Zhang, P. Malik, S.M. Tahara, Placenta growth factor mediated gene regulation in sickle cell disease, Blood 32 (2018) 61–70, https://doi.org/10.1016/j.blre.2017.08.008.
[138] J.E. Brittain, B. Hulkower, S.K. Jones, D. Strayhorn, L. De Castro, M.J. Telen, E.P. Orringer, A. Hinderliter, K.I. Ataga, Placenta growth factor in sickle cell disease: association with hemolysis and inflammation, Blood 115 (2010) 2014–2020, https://doi.org/10.1182/blood-2009-04-217950.
[139] S.K. Selvaraj, R.K. Giri, N. Perelman, C. Johnson, P. Malik, V.K. Kalra, Mechanism of monocyte activation and expression of proinflammatory cytochemokines by placenta growth factor, Blood 102 (2003) 1515–1524, https://doi.org/10.1182/blood-2002-11-3423.
[140] M.P. Golden, W.R. Henderson Jr., Leukotrienes, N. Engl. J. Med. 357 (2007) 1841–1854, https://doi.org/10.1056/NEJMra071371.
[141] M. Kumlin, Measurement of leukotrienes in humans, Am. J. Respir. Crit. Care Med. 161 (2000) S102–S106, https://doi.org/10.1164/ajrccm.161.supplement_1.ltta-20.
[142] L.A. Laitinen, A. Laitinen, T. Haahtela, V. Vilkka, B.W. Spur, T.H. Lee, Leukotriene E4 and granulocyticinfiltration into asthmatic airways, Lancet 34 (1993) 989–990, https://doi.org/10.1016/0140-6736(93)91073-U.
[143] J.M. Drazen, Leukotrienes as mediators of airway obstruction, Am. J. Respir. Crit. Care Med. 158 (1998) S193–S200, https://doi.org/10.1164/ajrccm.158.supplement_2.13tac180.
[144] Y.H. Datta, M. Romano, B.C. Jacobson, D.E. Golan, C.N. Serhan, B.M. Ewenstein, Peptido-leukotrienes are potentagonists of von Willebrand factor secretion and P-selectin surface expressionin human umbilical vein endothelial cells, Circulation 92 (1995) 3304–3311 https://www.ncbi.nlm.nih.gov/pubmed/7586318.
[145] T. Wun, M. Cordoba, A. Rangaswami, A.W. Cheung, T. Paglieroni, Activated monocytes and plateletmonocyte aggregates in patients with sickle cell disease, Clin. Lab. Haematol. 24 (2002) 81–88, https://doi.org/10.1046/j.1365-2257.2002.00433.x.
[146] S. Danckwardt, M.W. Hentze, A.E. Kulozik, Pathologies at the nexus of blood coagulation and inflammation: thrombin in hemostasis cancer and beyond, J. Mol. Med. 91 (2013) 1257–1271, https://doi.org/10.1007/s00109-013-1074-5.
[147] X. Wang, E. Wang, J.J. Kavanagh, R.S. Freedman, Ovarian cancer the coagulation pathway and inflammation, J. Transl. Med. 3 (2005) 1–20, https://doi.org/10.1186/1479-5876-3-25.
[148] J.D. Boer, C.J. Majoor, C.V. Veer, E.H.D. Bel, T.V.D. Poll, Asthma and coagulation, Blood 119 (2012) 3236–3244, https://doi.org/10.1182/blood-2011-11-391532.
[149] B.N. Lambrecht, H. Hammad, Asthma and coagulation, N. Engl. J. Med. 369 (2013) 1964–1966, https://doi.org/10.1056/NEJMcibr1311045.
[150] L.M. Dusse, D.R.A. Rios, M.B. Pinheiro, A.J. Cooper, B.A. Lwaleed, Pre-eclampsia: relationship between coagulation fibrinolysis and inflammation, Clin. Chim. Acta 412 (2011) 17–21, https://doi.org/10.1016/j.cca.2010.09.030.
[151] G. Girardi, Role of tissue factor in pregnancy complications: crosstalk between coagulation and inflammation, Thromb. Res. 127 (2011) S43–S46, https://doi.org/10.1016/S0049-3848(11)70012-3.
[152] K. Hess, P.J. Grant, Inflammation and thrombosis in diabetes, Thromb. Haemost. 105 (2011) S43–S54, https://doi.org/10.1160/THS10-11-0739.
[153] N. Zheng, X. Shi, X. Chen, W. Lv, Associations between inflammatory markers hemostatic markers and microvascular complications in 182 Chinese patients with type 2 diabetes mellitus, Lab. Med. 46 (2015) 180–189, https://doi.org/10.1309/LMF8R2KSTOW3FLKD.
[154] A. Huerta-Zepeda, C. Cabello-Gutiérrez, J. Cime-Castillo, V. Monroy-Martínez, M.E. Manjarrez-Zavala, M. Gutiérrez-Rodríguez, R. Izaguirre, B.H. Ruiz-Ordaz, Crosstalk between coagulation and inflammation during Dengue virus infection, Thromb. Haemost. 99 (2008) 936–943, https://doi.org/10.1160/TH07-08-0438.
[155] M. Levi, S.M. Opal, Coagulation abnormalities in critically ill patients, Crit. Care 10 (2006) 1–9, https://doi.org/10.1186/cc4975.
[156] M. Levi, The coagulant response in sepsis and inflammation, Hamostaseologie 30 (2010) 10–16 https://www.ncbi.nlm.nih.gov/pubmed/20162247.
[157] M. Levi, T.V.D. Poll, Two-way interactions between inflammation and coagulation, Trends Cardiovasc. Med. 15 (2005) 254–259, https://doi.org/10.1016/j.tcm.2005.07.004.
[158] F. Blasi, P. Carmeliet, uPAR: a versatile signalling orchestrator, Nat. Rev. Mol. Cell Biol. 3 (2002) 932–943, https://doi.org/10.1038/nrm977.
[159] P. Connes, S. Verlhac, F. Bernaudin, Advances in understanding the pathogenesis of cerebrovascular vasculopathy in sickle cell anaemia, Br. J. Haematol. 161 (2013) 484–498, https://doi.org/10.1111/bjh.12300.
[160] P. Chantrathammachart, N. Mackman, E. Sparkenbaugh, J.G. Wang, L.V. Parise, D. Kirchhofer, N.S. Key, R. Pawlinski, Tissue factor promotes activation of coagulation and inflammation in a mouse model of sickle cell disease, Blood 120 (2012) 636–646, https://doi.org/10.1182/blood-2012-04-424143.
[161] E.M. Sparkenbaugh, P. Chantrathammachart, J. Mickelson, J.V. Ryn, R.P. Hebbel, D.M. Monroe, N. Mackman, N.S. Key, R. Pawlinski, Differential contribution of FXa and thrombin to vascular inflammation in a mouse model of sickle cell disease, Blood 123 (2014) 1747–1756, https://doi.org/10.1182/blood-2013-08-523936.
[162] D.K. Mcclish, L.T. Penberthy, V.E. Bovbjerg, J.D. Roberts, I.P. Aisiku, J.L. Levenson, S.D. Roseff, W.R. Smith, Health related quality of life in sickle cell patients: the PiSCES project, Health Qual. Life Outcomes 3 (2005) 1–17, https://doi.org/10.1186/1477-7525-3-50.
[163] B.N.Y. Setty, M.J. Stuart, C. Dampier, D. Brodecki, J.L. Allen, Hypoxaemia in sickle cell disease: biomarker modulation and relevance to pathophysiology, Lancet. 362 (2003) 1450–1455, https://doi.org/10.1016/S0140-6736(03)14689-2.
[164] B.N.Y. Setty, A.K. Rao, M.J. Stuart, Thrombophilia in sickle cell disease: the red cell connection, Blood 98 (2001) 3228–3233, https://doi.org/10.1182/blood.V98.12.3228.
[165] M.F. Whelihan, M.Y. Lim, M.J. Mooberry, M.G. Piegore, A. Ilich, A. Wogu, J. Cai, D.M. Monroe, K.I. Ataga, K.G. Mann, N.S. Key, Thrombin generation and cell-dependent hypercoagulability in sickle cell disease, J. Thromb. Haemost. 14 (2016) 1941–1952, https://doi.org/10.1111/jth.13416.
[166] M.T. Gladwin, J.H. Crawford, R.P. Patel, The biochemistry of nitric oxide nitrite and hemoglobin: role in blood flow regulation, Free Radic. Biol. Med. 36 (2004)

707–717, https://doi.org/10.1016/j.freeradbiomed.2003.11.032.
[167] A.K. Mack, G.J. Kato, Sickle cell disease and nitric oxide: a paradigm shift? Int. J. Biochem. Cell Biol. 38 (2006) 1237–1243, https://doi.org/10.1016/j.biocel.2006.01.010.
[168] E.J. Van Beers, H.M.H. Spronk, H. Ten Cate, A.J. Duits, D.P.M. Brandjes, J.W.J. Van Esser, B.J. Biemond, J.B. Schnog, No association of the hypercoagulable state with sickle cell disease related pulmonary hypertension, Haematologica 93 (2008) e42–e44, https://doi.org/10.3324/haematol.12632.
[169] A.E. Alagbe, J.A. Olaniyi, O.W. Aworanti, Adult sickle cell anaemia patients in bone pain crisis have elevated proinflammatory cytokines, Mediterr J. Hematol. Infect Dis. 10 (2018) 1–9, https://doi.org/10.4084/MJHID.2018.017.
[170] J.M. Hibbert, L.L. Hsu, S.J. Bhathena, I. Irune, B. Sarfo, M.S. Creary, B.E. Gee, A.L. Mohamed, I.D. Buchanan, A. Al-Mahmoud, J.K. Stiles, Proinflammatory cytokines and the hypermetabolism of children with sickle cell disease, Exp. Biol. Med. (Maywood) 230 (2005) 68–74 www.ncbi.nlm.nih.gov/pmc/articles/PMC4033607/.