Inflammation in Sickle Cell Disease-Associated Pulmonary Complications

Subjects: Hematology

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Sickle cell disease (SCD) is the most common monogenic blood disorder, affecting approximately 100,000 Americans and millions more worldwide. Cardiopulmonary complications are a major cause of morbidity and mortality in SCD, accounting for 32–70% of deaths.

sickle cell disease lung mice

1. Introduction

Several pathophysiological processes, including anemia, hemolysis, endothelial dysfunction, and ventricular remodeling, may contribute to cardiopulmonary complications in sickle cell disease (SCD) [1][2][3]. Although the etiology of cardiopulmonary complications in SCD is somewhat different from that in the general population, there are similarities in the cellular and molecular mechanisms that underlie the pathogenesis in both scenarios and that are beginning to gain prominence. Accumulating evidence has long identified chronic low-grade inflammation as a risk factor for the progression of myocardial infarction, ventricular hypertrophy, cardiac fibrosis, diastolic dysfunction, and pulmonary hypertension in the general population [4][5][6][7][8].

2. Inflammation and Acute Chest Syndrome

Acute chest syndrome (ACS) is a pulmonary complication of SCD and the second leading cause of mortality and morbidity in both adults and children with SCD [9]. It is defined as the presence of fever and/or new respiratory symptoms such as cough, chest pain, and presence of a new pulmonary infiltrate on chest X-ray [9]. Risk factors for ACS include younger age, severe SCD genotypes (SS or $S\beta^0$ thalassemia), lower fetal hemoglobin concentrations, inflammation, higher steady-state white blood cell counts, history of asthma, and tobacco-smoke exposure [10][11]. The major causes known to trigger ACS include respiratory infection, pulmonary infarction, or fat embolism; however, no specific cause can be found in up to 30% of cases [10]. At a cellular level, an inciting trigger such as an infection permits increased adhesion of leukocytes (neutrophils) to the lung microvasculature, generation of cytokines, coupled with interactions with other cellular components such as platelets. This results in local hypoxemia and changes in rheology of the red blood cells (RBCs). This further facilitates interactions between RBCs, vascular endothelium, and leukocytes, resulting in increased oxidative stress, vaso-occlusion, and tissue hypoxia. These events in turn result in additional recruitment of leukocytes and other cellular components to the site, thereby amplifying the inflammatory cascade, resulting in a “vicious” cycle of lung injury and hypoxemia [12][13].

Evidence for heightened inflammation in the pulmonary microenvironment during ACS comes from human studies which show that children with ACS have high levels of IL-6, IL-8, CCL2, and CCL3 in their sputum [14]. These cytokines, particularly CCL2 and CCL3, have been shown to recruit leukocytes, particularly neutrophils, via upregulation of platelet activating factor (PAF) and leukotriene B-4 (LTB4). The neutrophils firmly adhere to the endothelium and become activated as assessed by shedding of CD62L and upregulation of CD11b [15]. Upregulation of CD11b in arrested leukocytes enables their interaction with GPIbα expressed on platelets [16]. Arrested neutrophils can also interact with platelets via PSGL-1 on neutrophils binding to P-selectin on platelets. This is evidenced by autopsy studies which show the presence of large neutrophil–platelet aggregates and platelet-laden aggregates in pulmonary vasculature in patients with ACS [12][17]. Indeed, preclinical studies that inhibit P-selectin and GPIbα interactions show fewer leukocyte–platelet aggregates [18], highlighting the importance of neutrophil and platelet heterotypic interactions in pathogenesis of ACS. Furthermore, a study by Ghosh et al., in a Townes sickle cell mouse model, showed that P-selectin in both platelet and endothelium compartments played a dominant role in promoting heme-induced ACS in SCD [19].

Hemolysis is a pathological feature of SCD that releases free hemoglobin and heme into the circulation due to RBC sickling and lysis, leading to the activation of inflammatory signaling pathways and vascular inflammation [20][21][22][23]. The release of free heme and cell-free hemoglobin also results in activation of neutrophils and generation of neutrophil extracellular traps (NETs) [24], iron-based generation of reactive oxidative species (ROS) with subsequent oxidization of membrane lipids [25], depletion of nitric oxide [26], and endothelial cytoskeleton remodeling resulting in barrier dysfunction [27]. Furthermore, plasma free heme and other markers of hemolysis have been associated with increased odds of developing ACS in children with SCD [28]. Additionally, a mutation in the heme-oxygenase 1 (HMOX1) short (GT)n repeat promoter that confers stronger inducibility of HMOX-1, the rate-limiting enzyme that degrades heme, was associated with a reduction in the rate of hospitalization for ACS in children with SCD [29]. These studies were validated in both Townes and Berkeley SCD mouse models using extracellular heme as a trigger for ACS. Heme exposure causes respiratory failure due to rapid hypoxemia and death, mimicking some of the events associated with ACS in SCD patients [30]. Treatment of SCD mice with D3T (3H-1,2-dithiole-3-thione), an activator of nuclear-factor erythroid 2 like 2 (NRF2), which controls HMOX1 expression, reduced lethality in a model of heme-induced ACS in SS mice [31]. Additionally, treatment with hemopexin, the plasma heme-binding protein, abrogates lung injury and mortality in a chlorine (Cl_2)-inhalation model of inducing ACS [32]. These studies suggest that therapies that target the product (heme) or molecular consequence(s) of hemolytic pathways may offer protection from ACS in SCD.

3. Inflammation and Pulmonary Hypertension

Pulmonary hypertension (PH) is an independent risk factor for early death in SCD patients [33]. Its estimated prevalence, as assessed by right heart catheterization (RHC), is about 6–10% [34], although this estimate relied on an older definition used to diagnose PH. Per the most recent guidelines, PH is now defined as mean pulmonary artery pressure of >20 mm Hg in conjunction with pulmonary artery wedge pressure of ≤15 mm Hg and a pulmonary vascular resistance (PVR) of ≥3 Wood units (WU). A diagnosis of isolated post-capillary PH is made

when PVR is <3 WU, whereas a PVR of ≥3 WU is supportive of pre-capillary PH [35]. In SCD, pre-capillary, post-capillary, and pulmonary thromboembolic PH or a combination can exist. Risk factors for PH include chronic intravascular hemolysis, pulmonary thrombosis or embolism, and heart failure [36][37].

The development of PH in SCD is complex and involves pulmonary vascular endothelial dysfunction, smooth muscle cell (SMC) proliferation and resistance to nitric oxide (NO) adventitial fibroblast accumulation, and inflammation. Interestingly, one of the unique features of PH in SCD is the presence of iron in pulmonary macrophages, a feature that is not seen in other forms of PH. An autopsy study of lung samples from SCD patients with PH and RV failure found peripheral monocytes and macrophages accumulating in the perivascular and alveolar regions of the lungs [38]. These macrophages had extensive iron accumulation concomitantly with the expression of HMOX1, ET-1, and IL-6 [38]. This suggests that, in pathological diseases with hemolysis such as SCD, circulating immune cells may be recruited into the lungs for heme degradation. However, this immune response may become maladaptive over time, as accumulated iron may contribute to oxidative stress, alter the redox balance, or induce transdifferentiation of resident lung macrophages and other alveolar cells. This underscores an important role for intravascular hemolysis in the pathogenesis of PH [39][40][41][42]. SCD is characterized by increased stress erythropoiesis as a compensatory mechanism for anemia, which increases the number of reticulocytes and younger RBCs in circulation. During hemolysis, these young RBCs release a large amount of arginase into the plasma [43]. This plasma arginase consumes plasma L-arginine, the substrate required for NO production by endothelial cells, and, in conjunction with the consumption of endothelial NO by cell-free plasma Hb, reduces NO bioavailability [44]. The depletion of NO affects intracellular calcium signaling that leads to dephosphorylation of myosin protein, preventing smooth muscle relaxation [45]. The depletion of NO also results in leukocyte recruitment via increased surface expression of leukocyte adhesion proteins such as E-selectin, VCAM, and ICAM-1 [46][47] and results in smooth muscle proliferation and vascular remodeling [48]. Heme-related generation of ROS decreases availability and or activation of soluble guanylyl cyclase or its regulators such as cytochrome b5 reductase 3 (CYB5R3), which can result in poor vasodilation of pulmonary vasculature, increasing the risk of pulmonary hypertension [49][50].

Cell-free plasma hemoglobin and heme can also independently activate platelets and neutrophils via a TLR4 signaling mechanism [24], resulting in further inflammation. In addition, cell-free hemoglobin also generates ROS, which furthers endothelial dysfunction and activates the coagulation system [51]. Chronic hemolysis also promotes transition of pulmonary endothelial cells to a mesenchymal or smooth muscle cell type and contributes to vascular remodeling [52]. Thus, heme exposure results in pathological endothelial activation, increased recruitment of leukocytes and depletion of protective mechanisms that preserve vascular integrity.

Mechanistically, endothelial dysfunction results in increased production of vasoconstrictors such as endothelin-1 (ET-1). Heme-related endothelial dysfunction can deplete peroxisome proliferator-activated receptor γ (PPARγ), which plays an active role in suppressing ET-1 production by regulating the level of microRNAs (miRs) such as miR-98 [47]. Lower levels of miR-98 are associated with increased ET-1 production and endothelial dysfunction [46]. Exposure to heme also results in increased production of placenta growth factor (PIGF) by erythroid cells via the erythroid Krüppel-like factor (EKLF) [53] and NRF2-antioxidant response signaling [54]. PIGF is an angiogenic factor

that activates endothelial cells to secrete ET-1 [55]. In an elegant study, overexpression of erythroid-specific PIGF in normal mice up to the levels seen in sickle cell mice resulted in an increase in the production of ET-1, which correlated with increased right ventricular pressure and pulmonary arteriolar thickening [56]. Elevated ET-1 and PlGF levels also correlate with severity of PH in patients with SCD [56]. PIGF was shown to activate expression of hypoxia-inducible factor 1α (HIF-1α), independently of hypoxia, which in turn can stimulate expression of ET-1, which is involved with the development and severity of PH in SCD [55].

Indeed, these cellular and molecular mechanisms have informed the current therapeutics usually used in patients with pulmonary hypertension such as endothelin receptor (ETR) antagonists (Bosentan, Ambrisetan), those which prevent the degradation of cyclic guanosine monophosphate (cGMP) (Riociguat and Sildenafil), vasodilators (Epoprostenol), and anticoagulant (warfarin), among others. Clinical trials using hemopexin, a scavenger molecule that removes heme from circulation, are underway in humans and have shown promising results in murine models [57]. Unfortunately, trials with ETR antagonists [58], Riociguat [59], and Sildenafil [60][61] were either limited by small sample size or adverse side effects, underscoring the need to better understand the pathology and the need for larger clinical trials researching PH in SCD.

4. Inflammation and Pulmonary Thrombosis Embolism

Accumulating evidence from human studies discussed below suggests that inflammation is a risk factor for thrombosis. It is therefore not surprising that a retrospective study found that the prevalence rate of venous thromboembolism (VTE) in adults with SCD was 25% and was associated with increased rates of recurrence and mortality [62][63]. Interestingly, the risk of pulmonary embolism (PE) is higher than the risk of deep vein thrombosis (DVT) [63][64][65] suggesting that thrombosis may occur more ‘in situ’ in pulmonary vasculature of individuals with SCD. Risk factors for VTE include elevated leukocyte count [66], severe phenotype as defined by >3 hospitalizations annually for vaso-occlusive crisis, presence of SCD variant genotypes, elevated tricuspid regurgitation jet velocity (TRJV) ≥2.5 m/s [62], elevated body mass index, and prior splenectomy [62][67][68]. Even in those with lower hospitalizations, the cumulative incidence rate of VTE was at 6.8% compared to 1.6% in individuals who had similar number of hospitalizations for asthma exacerbation [63], suggesting that intrinsic pathology, in addition to external risk factors, plays a role in development of PE and/or DVT.

Several cellular and molecular pathways are perturbed in SCD that leads to a prothrombotic state. Chronic hemolysis results in the release of intracellular molecules known as danger (or damage)-associated molecular patterns (DAMPs) [69]. For example, one of the most studied DAMPs or alarmins, high-mobility group box 1 (HMGB1), is significantly elevated in the plasma of SCD patients and mice at baseline compared to controls [70][71]. VOC episodes further increased HMGB1 levels in SCD patients, or acute sickling induced following hypoxia-reoxygenation in mice [70]. Furthermore, treating the TLR4 reporter cell line with plasma from SCD patients increased TLR4 receptor activity, suggesting that HMGB1 contributes to TLR4 signaling in SCD [70]. Elevated circulating HMGB1 is associated with the platelet nucleotide-binding domain, leucine-rich-containing family, and pyrin-domain-containing-3 (NLRP3) activation, which is mediated through the TLR4 and Bruton tyrosine kinase signaling pathways [71][72]. Another study in murine macrophages has shown that cell-free hemoglobin and free

heme act in synergy with HMGB1 to activate proinflammatory cytokine production in wild-type murine macrophages, and treatment with hemopexin abolishes this interaction [73]. Furthermore, treatment with hemopexin significantly suppressed the synergistic production of proinflammatory cytokines, suggesting an anti-inflammatory property of hemopexin [73]. This anti-inflammatory ability of hemopexin, in addition to its heme-scavenging function, may provide another potential therapeutic option for addressing inflammation in SCD. DAMPs have also been implicated in endothelial dysfunction [74], activation and recruitment of leukocytes [24][69] and inflammation [69], which shift the balance to a more prothrombotic state in SCD. The characteristic changes in RBC rheology contribute to the formation of venous thrombi that have a denser fibrin network and a friable thrombus [75]. In addition, red-cell-derived microparticles contribute to thrombin generation via activation of Factor XI. Indeed, red-cell-derived microparticles are associated with increased markers of coagulation activation [76]. Activated platelets promote inflammasome activation and generation of EVs, which can lead to formation of heterotypic aggregates and occlusion of the lung's microvasculature [77]. DAMPs can also activate neutrophils and monocytes, which can result in increased tissue factor (TF) expression [78], NET formation, endothelial dysfunction, and more inflammation [24], which have been linked to thrombus generation and propagation in non-SCD models [79]. Endothelial dysfunction from heme exposure results in the upregulation of adhesion molecules that attract neutrophils and platelets [24][27][74], and increased expression of TF and VWF, which can contribute to pulmonary thrombosis [80].

The exact molecular mechanisms resulting in thrombus formation in lungs in SCD are not well studied and may involve mechanisms that either increase procoagulant proteins (such as TF, VWF, thrombin) [80][81], decrease anticoagulant proteins (like low protein C and S) [82][83], and/or decrease fibrinolysis [75]. There is some evidence that abrogation of TF using anti-TF antibody reduces thrombus formation in a sickle cell mouse model, suggesting an important contribution of TF to thrombus generation in SCD. In addition, genetic or immunologic interventions that modulated expression of protein C and thrombin also diminished thrombus formation [84]. Data supporting the role of contact pathways leading to thrombosis in SCD are very sparse; however, potential plausible sources include neutrophil nuclear content, specifically nuclear DNA and histones which can initiate coagulation by activating Factor XII but also amplify thrombin-dependent factor XI activation [79][85]. Partial support for this comes from observation that inducing neutropenia results in decreased thrombosis burden in an arterial thrombosis model [84]. Thus, several cellular and molecular mechanisms may be at play in the pathogenesis of thrombosis.

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