FUNCTION™ american physiological society

FUNCTION, 2022, 3(3): zqac021

https://doi.org/10.1093/function/zqac021
Advance Access Publication Date: 30 April 2022
Perspectives

PERSPECTIVES

Sickle Cell Disease and Oxidative Stress: Implications for a Role of Diminished Endothelial SOD2 in Pulmonary Complications

Nicola Conran* and Fernando F. Costa

Hematology and Transfusion Center, University of Campinas – UNICAMP, Campinas, São Paulo 13083-878, Brazil

*Address correspondence to N.C. (e-mail: conran@unicamp.br)

A Perspective on "Endothelial superoxide dismutase 2 is decreased in sickle cell disease and regulates fibronectin processing."

Sickle cell disease (SCD), an inherited monogenic disorder that significantly alters the hemoglobin molecule (HbS), is now also recognized as an inflammatory disease that sustains extensive oxidative stress. The genetic conditions comprising SCD result in deoxygenation-dependent hemoglobin S polymerization, which induces the red blood cells (RBCs) to adopt a characteristic sickle shape and alters many of the RBCs' properties. An imbalanced redox status is generated in sickle RBCs by an excessive production of reactive oxygen species (ROS), due to mechanisms that include HbS autooxidation, NADPH activation, and elevated mitochondrial retention,[1] together with impaired antioxidant activity, leading to membrane structural defects. In turn, hemolytic processes, leading to hemoglobin decompartmentalization, further contribute to ROS generation in SCD, as do the processes of ischemia-reperfusion that are triggered by the vaso-occlusive events that define the disease.[2]

While oxidative stress in RBCs is well-documented in SCD, excessive ROS generation and ROS-dependent signaling also make a significant contribution to functional alterations in other cell types that are crucial to SCD pathophysiology. Cell-free heme, for example, induces neutrophil activation and upregulates the activity of cell adhesion *in vitro* via a ROS-dependent pathway,[3] while excessive mitochondrial ROS generation in platelets has been associated with increased thrombus formation in SCD.[4] Furthermore, oxidative stress is suggested to contribute to endothelial cell dysfunction and activation in SCD, mainly as the result of NADPH oxidase generation of superoxide due to continuous processes of ischemia-reperfusion and hemolysis in patients.[2] Activation of the endothelium leads to the production and release of numerous potent inflammatory molecules and the membrane surface expression of adhesion molecules, which prompt the recruitment of leukocytes and RBCs to the blood vessel walls, thereby driving vaso-occlusive processes.

In this issue of FUNCTION, Dosunmu-Ogunbi et al. present evidence for another mechanism by which the endothelial cell redox balance may be disrupted in SCD and suggest that this mechanism may lead to altered cellular function.[5] Superoxide dismutase 2 (SOD2) is a mitochondrial enzyme that dismutates the superoxide ($O_2^{\cdot -}$) radical into hydrogen peroxide (H_2O_2), thereby playing a major protective role against cellular and histological damage induced by ROS. Indeed, reduced SOD2 enzyme activity has been associated with diabetes mellitus progression and leads to increased vascular and cardiac dysfunction in aging mice.[6] Authors found that SOD2 protein expression was decreased in lung tissue samples both from patients and from transgenic mice with SCD.[5] Circulating levels of SOD2 mRNA have been previously reported as significantly decreased in SCD, and these levels correlate with echocardiographic indications of pulmonary hypertension[7]; furthermore cardiovascular dysfunction may be amplified in SCD patients exhibiting the SOD2V16A genetic variant.[8] Pulmonary tissue damage and altered lung function play roles in numerous complications of SCD, including pulmonary hypertension, recurrent acute chest syndrome, and chronic lung disease.[2] As such, the findings of Dosunmu-Ogunbi et al. lend further support for a role of excessive mitochondrial ROS generation and

Submitted: 19 April 2022; **Accepted:** 20 April 2022

diminished neutralization/antioxidation of these molecules in the pulmonary tissue in SCD, where SOD2 reactivation could represent a therapeutic target worthy of further study for this disorder.

In a series of in vitro experiments, Dosunmu-Ogunbi et al. went on to look at the consequences of knockdown of SOD2 in pulmonary endothelial cells in culture (hPMVECs).[5] SOD2 siRNA led to amplified ROS production in these cells and decreased their mitochondrial membrane potential, indicative of mitochondrial damage. In addition, SOD2 silencing significantly increased the albumin leakage of plated pulmonary endothelial cells and incurred alterations indicative of endothelial barrier disruption, possibly due to decreased H_2O_2 signaling. SOD2 knockout in hPMVECs also interfered in the ability of these endothelial cells to proliferate and migrate. Finally, SOD2 silencing impaired fibronectin matrix assembly by these pulmonary endothelial cells, indicating that SOD2 may facilitate and stabilize fibronectin dimerization via mitochondrial H_2O_2-mediated signaling, thereby playing a role in maintaining cellular migration and endothelial barrier function.

Endothelial barrier disruption has been suggested to contribute to the pathogenesis of acute complications of SCD, particularly acute chest syndrome.[9] Furthermore, endothelial cell proliferation and migration is essential for angiogenic mechanisms, where rapid migration and angiogenesis is needed in response to injury; pulmonary arterial hypertension constitutes a severe complication of SCD, in which endothelial dysfunction and impaired vascular regeneration may result in abnormal vascular remodeling and the loss of small pulmonary arteries.[10] Accordingly, reduced SOD2 activity in the lung endothelium of SCD individuals, and consequent disruption in cellular functions (adhesive interactions, migration, and barrier function), could be postulated to contribute to both of these severe complications. This elegant study by Dosunmu-Ogunbi et al. provides further support for a role for oxidative stress in altered endothelial cell function in SCD, describes a novel mechanism by which this occurs, and reveals significant consequences of the reduction of SOD2 expression in the pulmonary endothelium that have implications for comprehending some of the clinical complications of this disorder.

Funding

None declared.

Acknowledgments

N.C. and F.F.C. receive research funding from the São Paulo State Research São Paulo Research Foundation (FAPESP), Brazil (grants #2019/18886–1 and 2020/06133–6), as well as from CNPq, Brazil.

References

1. Wang Q, Zennadi R. The role of RBC oxidative stress in sickle cell disease: from the molecular basis to pathologic implications. *Antioxidants*. 2021;**10**(10) 1608.
2. Hebbel RP, Belcher JD, Vercellotti GM. The multifaceted role of ischemia/reperfusion in sickle cell anemia. *J Clin Invest*. 2020;**130**(3):1062–1072.
3. Miguel LI, Leonardo FC, Torres LS, et al. Heme induces significant neutrophil adhesion in vitro via an NFkappaB and reactive oxygen species-dependent pathway. *Mol Cell Biochem*. 2021;**476**(11):3963–3974.
4. Annarapu GK, Nolfi-Donegan D, Reynolds M, Wang Y, Shiva S. Mitochondrial reactive oxygen species scavenging attenuates thrombus formation in a murine model of sickle cell disease. *J Thromb Haemost*. 2021;**19**(9):2256–2262.
5. Dosunmu-Ogunbi A, Yuan S, Shiwarski DJ, et al. Endothelial superoxide dismutase 2 is decreased in sickle cell disease and regulates fibronectin processing. *Function*. 2022;**3**(2):zqac005.
6. Zhou RH, Vendrov AE, Tchivilev I, et al. Mitochondrial oxidative stress in aortic stiffening with age: the role of smooth muscle cell function. *Arterioscler Thromb Vasc Biol*. 2012;**32**(3):745–755.
7. Armenis I, Kalotychou V, Tzanetea R, et al. Reduced peripheral blood superoxide dismutase 2 expression in sickle cell disease. *Ann Hematol*. 2019;**98**(7):1561–1572.
8. Dosunmu-Ogunbi A, Yuan S, Reynolds M, et al. SOD2 V16A amplifies vascular dysfunction in sickle cell patients by curtailing mitochondria complex IV activity. *Blood*. 2022;**139**(11):1760–1765.
9. Santaterra VAG, Fiusa MML, Hounkpe BW, et al. Endothelial barrier integrity is disrupted in vitro by heme and by serum from sickle cell disease patients. *Front Immunol*. 2020;**11**:535147. PMCID: PMC7767881.
10. Ranchoux B, Harvey LD, Ayon RJ, et al. Endothelial dysfunction in pulmonary arterial hypertension: an evolving landscape (2017 Grover Conference Series). *Pulm Circ*. 2018;**8**(1):2045893217752912.