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RED CELLS, IRON, AND ERYTHROPOIESIS

Comment on Menon et al, page 936

Cardiac ferroptosis: new jigsaw in SCD puzzles

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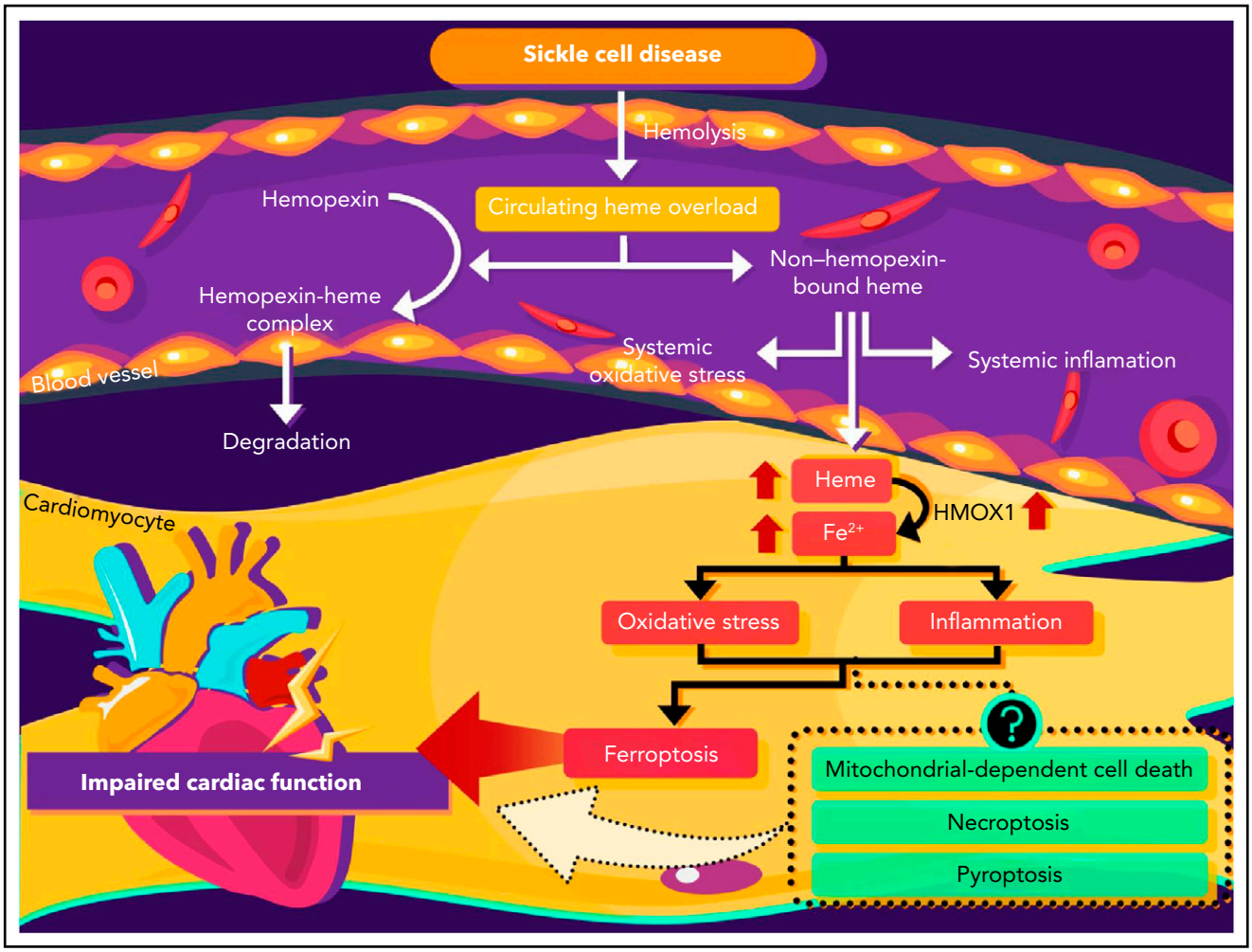
In this issue of *Blood*, Menon et al[1] demonstrate that excess circulating heme and reduced hemopexin in a murine model of sickle cell disease (SCD) led to excess non–hemopexin-bound heme (free heme). This free heme can enter cardiac cells and, thereby, upregulate the expression of the heme oxygenase 1 (HMOX1), resulting in an increased level of ferrous ion ($Fe2^{+}$) in cardiac cells. This cardiac Fe^{2+} overload was found to promote cardiomyocyte ferroptosis, a specific type of regulated cell death, potentially leading to impaired cardiac contractility. These findings revealed important mechanisms underlying cardiac complications in SCD, which enhance our previously limited knowledge of cardiac dysfunction and provide the potential for novel interventional approaches for cardioprotection in patients with SCD.

SCD is an inherited hemolytic disorder that is normally characterized by excess circulating heme due to hemolysis, together with overt systemic oxidative stress and inflammation.[2] Although vaso-occlusive events are common vascular complications in patients with SCD, cardiac complications have also been reported.[3] A recent report based on cardiac magnetic resonance imaging demonstrated that 60% of patients with SCD had cardiac abnormalities ranging from valvular disease, cardiac hypertrophy, and impaired left ventricular function.[4] Although the mechanisms underlying cardiac involvement in SCD remain unclear, systemic oxidative stress and inflammation have been shown to contribute significantly to its pathophysiological process.[2] Ferroptosis is a recently discovered form of regulated cell death. It was found to be associated with iron overload conditions, thus became known as iron-dependent ferroptosis.[5,6] Oxidative stress and inflammation play significant roles in cardiac ferroptosis in various diseases, including doxorubicin-induced cardiomyopathy and cardiac ischemia-reperfusion injury.[6] High levels of oxidative stress upregulate HMOX1 in the heart, resulting in an increase in cardiac Fe^{2+}, leading to cardiac ferroptosis and impaired cardiac function.[6] This excess intracellular Fe^{2+} is a hallmark in triggering cellular iron-dependent ferroptosis, leading to organ dysfunction.[5]

Menon et al demonstrated that cardiac ferroptosis induced by excess iron was predominantly responsible for cardiomyopathy in their murine model of SCD. In their study, upregulated cardiac HMOX1 played a pivotal role in producing Fe^{2+} from excess free heme in cardiac cells, leading to cardiac ferroptosis and impaired cardiac function.

Currently, the roles of HMOX1 in the heart are still being debated.[6,7] HMOX1 is known as cardioprotective in various pathological models, including ischemia-reperfusion injury, heart failure, and heart transplantation via its antioxidant and anti-inflammatory action, and through improved mitochondrial function.[7] Its inhibition was demonstrated to cause adverse effects since pharmacological inhibition of HMOX1 was shown to increase the severity of ischemia reperfusion injury as well as vascular injury in SCD.[8] However, in an SCD mouse model, Menon et al clearly demonstrated that upregulation of HMOX1 induced by excess free heme in cardiomyocytes led to cardiac iron overload, resulting in cardiac ferroptosis. In addition, although the role of HMOX1-associated cardiac ferroptosis has been shown previously in other pathological conditions,[6] Menon et al demonstrated for the first time in an SCD model that cardiac ferroptosis was also associated with upregulated HMOX1, which could lead to abnormal cardiac function. Specifically, excess circulating free heme (due to reduced circulating hemopexin) was shown to upregulate cardiac HMOX1, resulting in increased cardiac non–heme iron, which caused lipid peroxidation and led to cardiac ferroptosis. Pharmacological interventions to either reduce circulating free heme or inhibit HMOX1 were also shown to effectively attenuate ferroptosis, thus providing cardioprotection in these SCD mice. Inhibition of ferroptosis by ferrostatin 1 also resulted in cardioprotection. These important findings not only expand our understanding in the pathophysiological process of cardiac complications in SCD but also point to potential therapeutic approaches to either prevent or treat these adverse cardiac events.

Despite these important findings elegantly shown in this murine SCD model,[1] a number of questions remain to complete the jigsaw puzzle regarding the complex pathophysiology associated with impaired cardiac function in SCD. It is well established that cardiac iron overload can markedly impair mitochondrial function as indicated by increased production of mitochondrial reactive oxygen species, mitochondrial membrane depolarization, and mitochondrial swelling owing to the opening of mitochondrial permeability transition pores.[9] This cardiac mitochondrial dysfunction has been shown to be associated with cardiac apoptosis in various models either with or without iron overload.[9,10] In addition, several pharmacological interventions aimed at attenuating cardiac mitochondrial dysfunction have been shown to effectively reduce cardiac apoptosis and ultimately improve cardiac function.[9,10] Interestingly, Menon et al demonstrated in their study that only cardiac ferroptosis, but not apoptosis, was observed and played a major role in causing cardiomyopathy



Mechanism of HMOX1-associated cardiac ferroptosis in a murine model of SCD. Intravascular hemolysis in SCD causes an increase in circulating heme. Excess non–hemopexin-bound heme enters cardiomyocytes, and HMOX1 is upregulated, resulting in cardiomyocyte Fe^{2+} overload. These events lead to cardiomyocyte ferroptosis, which is responsible for impaired cardiac function. Although both oxidative stress and inflammation due to cardiac iron overload have been shown to cause different types of regulated cell death in cardiomyocytes, detailed knowledge concerning the type of cell death would facilitate vital care, with the potential of improved treatment of SCD.

in this murine SCD model despite cardiac iron overload. It is unclear whether the cardiac ferroptosis reported was dependent on the age and/or the duration of the disease. Further studies are essential to elucidate the roles of cardiac mitochondria in cardiac dysfunction in the SCD model. Moreover, whether different types of regulated cell death, such as mitochondrial-dependent cell death, necroptosis, or pyroptosis, could be responsible for cardiac damage and impaired cardiac function in SCD need to be further investigated (see figure). Findings from these studies may pave new ways to provide better means to fight cardiac complications in patients with SCD.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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