

evitar complicações que possam comprometer o quadro de saúde e qualidade de vida.

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TISSUE IRON AND INFLAMMATORY STRESS MAY IMPAIR ERYTHROID MATURATION AND CONTRIBUTE TO ANEMIA IN SICKLE CELL DISEASE

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Introduction: Sickle cell disease (SCD) is a hereditary hemoglobinopathy typified by chronic hemolytic anemia, recurrent vaso-occlusive crises, and progressive multi-organ damage. In patients, iron overload and hemosiderosis typically results from frequent blood transfusions. However, tissue iron accumulation is observed in SCD model mice, suggesting that intrinsic mechanisms may contribute to iron dysregulation in SCD, in addition to transfusion therapy. Inflammatory signaling may drive iron sequestration in macrophages, restricting availability for erythropoiesis and contributing to erythroid maturation arrest. **Objectives:** Assess in vivo erythroid lineage development and iron tissue distribution in SCD mice. **Material and methods:** Bone marrow and spleen cells were collected from homozygous Townes SCD mice (HbSS) and hemizygous control mice (HbAS) for analysis of erythroid cell populations by flow cytometry. For this, cells were gated based on forward and side scatter (FSC/SSC) properties and stained with antibodies against glycophorin A (TER119) and transferrin receptor (CD71) to define early progenitors, differentiating erythroblast and late erythroid subsets. Pro erythroblasts (ProE) and differentiating erythroblasts (EryA, EryB, and EryC) were identified based on their distinct FSC/SSC profiles and expression pattern of TER119/CD71. Reticulocyte counts in peripheral blood samples were determined by flow cytometry using anti-CD71 and thiazole orange dye. Blood counts were assessed using an automated hematology analyzer. Hemosiderin was quantitated in liver sections stained with Prussian blue dye. Serum IL-6 was measured by ELISA. **Results:** HbSS mice displayed elevated leucocyte and platelet counts, and increased IL-6 levels, consistent with systemic inflammation. In addition, reticulocytes were significantly increased in HbSS mice, indicating anemia and erythropoietic stress. Flow cytometry analysis of the bone marrow revealed expansion of early erythroid progenitor populations (TER119-CD71+), including ProE, and precursors (Ter119+CD71+), suggesting a strong compensatory erythropoietic drive. Although SCD mice exhibited an increased frequency of early erythroblasts (EryA), they showed a significant reduction in late-stage erythroblasts (EryC), compared to HbAS control mice. Data indicate that erythroid precursors in the bone marrow of SCD may fail to fully mature or function properly, consistent with

features of ineffective erythropoiesis (IE). Given that chronic anemia and bone marrow dysfunction often lead to compensatory extramedullary erythropoiesis, a hallmark of IE, we further analyzed the erythroid cell population in the spleen. In SCD mice, we observed an increase in the early and differentiating erythroid subsets, EryA and EryB, accompanied by a reduction in mature EryC. This skewed maturation profile in the spleen further reflects ongoing compensatory extramedullary erythropoiesis and supports the presence of IE in SCD. Histological analysis of liver sections showed increased hemosiderin depositions of SCD mice, suggesting abnormal iron storage in parenchymal tissues. This tissue iron retention often results from sustained erythrophagocytosis and altered iron recycling due to inflammation and hemolysis. **Discussion and conclusion:** Our findings suggest that ineffective erythropoiesis in SCD mice, associated with systemic inflammation and increased hepatic iron deposition, may contribute to the worsening of chronic anemia and the pathophysiological progression of SCD. #Grant: 2024/10726-3, FAPESP.

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TRANSDUÇÃO DE CÉLULAS CD34+ SAUDÁVEIS UTILIZANDO OS VETORES LENTI-VP64 E LENTI-VP64+BCL11A PARA INDUÇÃO DE HEMOGLOBINA FETAL COMO ESTRATÉGIA DE TRATAMENTO DA DOENÇA FALCIFORME UTILIZANDO TERAPIA GÊNICA

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Introdução: A terapia gênica para tratamento da Doença Falciforme (DF) tornou-se uma realidade após aprovação de dois produtos comerciais, pelas agências reguladoras dos EUA (FDA) e União Européia (EMA). Entretanto, essas aprovações revelaram um novo obstáculo para o acesso dos pacientes - o elevado custo. Estimado em \$ 3.1 milhões para o Lovotibeglogene autotemcel (Lyfgenia, bluebird bio, Inc, EUA), o produto é inacessível para a maioria dos pacientes, sobretudo em países de média e baixa renda, nos quais a DF é mais prevalente. No Brasil, onde os produtos ainda não estão aprovados, a