Experimental Cell Research xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Experimental Cell Research

journal homepage: www.elsevier.com/locate/yexcr

Heme oxygenase-1 protects bone marrow mesenchymal stem cells from iron overload through decreasing reactive oxygen species and promoting IL-10 generation

Zheng Y. Yu[a,b,c], Dan Ma[a,b,c], Zheng C. He[a,b,c], Ping Liu[a,b,c], Jun Huang[a,b,c], Qin Fang[d], Jiang Y. Zhao[a,b,c], Ji S. Wang[a,b,c,*]

[a] Department of Hematology, Affiliated Hospital of Guizhou Medical University, PR China
[b] Hematological Institute of Guizhou Province, PR China
[c] Guizhou Provincial Laboratory of Hematopoietic Stem Cell Transplantation Centre, PR China
[d] Department of Pharmacy, The Affiliated Hospital of Guizhou Medical University, PR China

ARTICLE INFO

Keywords:
Iron overload
Heme oxygenase-1
Interleukin 10
Reactive oxygen species
Bone marrow mesenchymal stem cells
ERK pathway

ABSTRACT

Iron overload (IO) caused by frequent blood transfusion in hematological diseases has become a major concern. In this study, up-regulation of heme oxygenase-1 (HO-1), a protector against oxidative stress, was observed in bone marrow mesenchymal stem cells (BMMSCs) at the early stage of IO and had favorable prognosis in an IO mouse model. Given that the protective role of HO-1 in IO damage of BMMSCs was still unknown, the mechanism was explored in vitro and in vivo. BMMSCs were transfected with HO-1/siHO-1 in vitro, and the mouse model was established to further evaluate the effect of HO-1 on IO in vivo. As a result, HO-1 decreased the apoptotic rate of BMMSCs with IO through reducing intracellular reactive oxygen species (ROS) but increasing IL-10 secretion. In addition, IL-10 was mediated by HO-1 via the ERK pathway. Intracellular iron was down-regulated by hepcidin depending on IL-10. In conclusion, HO-1 protects BMMSCs from ROS by secreting IL-10 upon iron overload.

1. Introduction

Many blood system diseases, such as β-thalassemia, myelodysplastic syndrome (MDS), lead to hemoglobin reduction inducing severe anemia. Repeated blood transfusion is needed to alleviate anemia. However, the treatment often accumulates excessive iron in the body, resulting in iron overload (IO) [1]. Iron is an important element of growth and survival, but IO reduces hematopoiesis by reactive oxygen species (ROS)-mediated signaling proteins and excessive iron deposition, thereby promoting the apoptosis of bone marrow (BM) monocytes. Heme oxygenase-1 (HO-1) is the major rate-limiting enzyme in the metabolism of heme. It catalyzes the degradation of hemoglobin to free iron, carbon monoxide and bilirubin [8–12]. HO-1 elevation can protect cells by significantly reducing ROS production. Meanwhile, HO-1 can relieve IO in tissue by reducing cellular labile iron pool (LIP) level. Bone marrow mesenchymal stem cells (BMMSCs) are pluripotent non-hematopoietic progenitor cells with regenerative, anti-inflammatory and immunomodulatory capacities, and they differentiate into mesodermal cells (osteoblasts, chondrocytes, adipocytes, heart cells, etc.), ectodermal origin of cells neurons and endodermal origin of cells (hepatic oval cells) [7,13,14]. Interleukin 10 (IL-10) is secreted by BMMMSCs and produced by regulating anti-inflammatory effects [19–22]. Increased secretion of IL-10 is a key factor in protecting cells from IO injury, which promotes the secretion of intracellular hepcidin to reduce intracellular iron content [45]. However, the relationship between HO-1 and IL-10 in the case of IO is still unknown. We found that HO-1 regulated the secretion of hepcidin by regulating IL-10 and thus affected intracellular iron content, while HO-1 regulated ROS to reduce tissue damage caused by IO. Although HO-1 can protect against iron-induced liver and spleen injuries [15–18], how HO-1 protects BMMSCs from IO-related ROS or regulates IL-10 under IO condition is still unclear. In this study, we investigated the relationship between IL-10 and HO-1 upon IO.

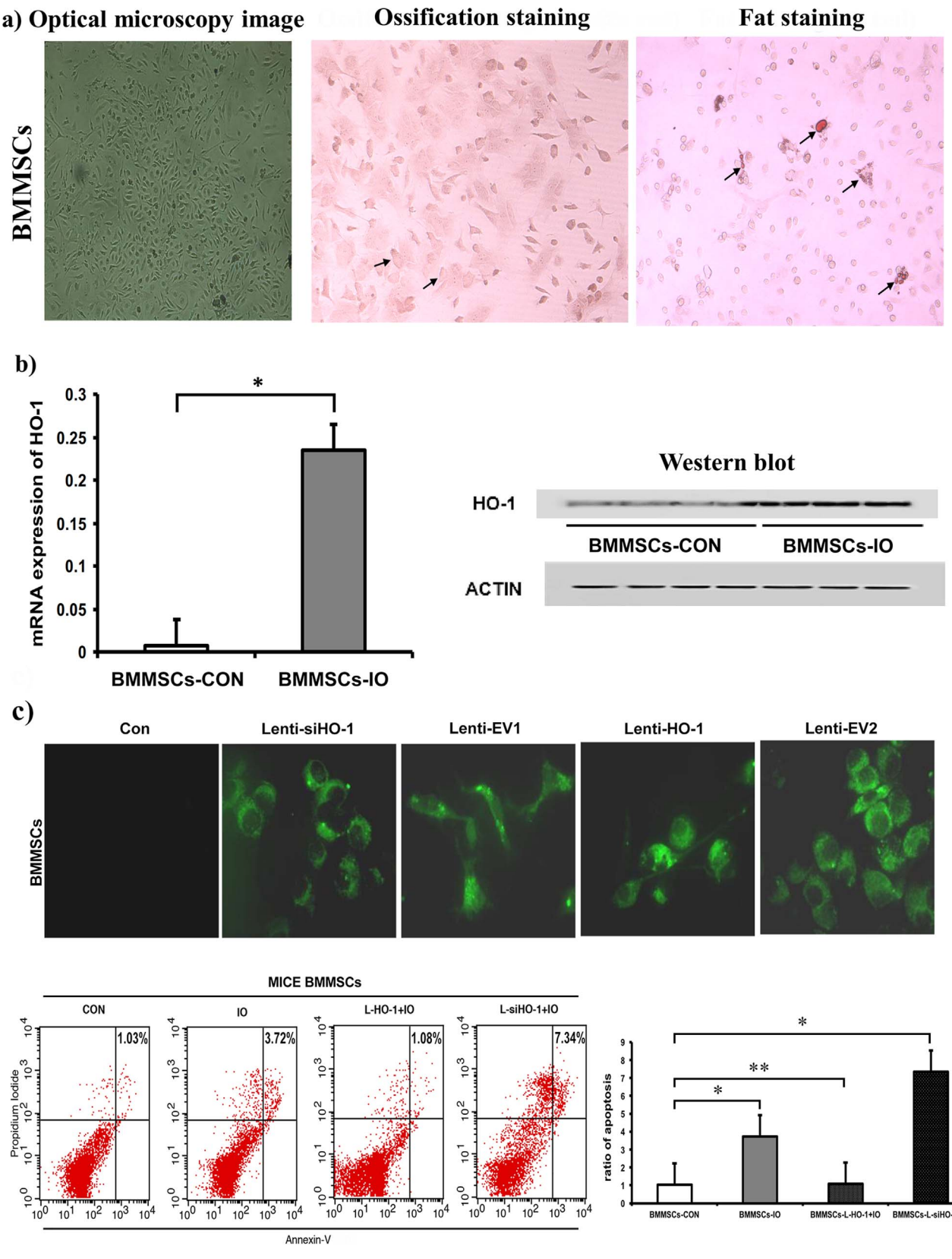
2. Materials and methods

2.1. Ethics statement

This study was approved by the Institutional Animal Care and Use Committee of PUMC and the methods were carried out in accordance

* Correspondence to: Department of Hematology, Affiliated Hospital of Guizhou Medical University, Guiyang, Guizhou 550004, PR China
E-mail address: wangjishi9646@163.com (J.S. Wang).

https://doi.org/10.1016/j.yexcr.2017.10.029
Received 9 June 2017; Received in revised form 24 October 2017; Accepted 25 October 2017



(caption on next page)