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Review

'Ride on the ferrous wheel' – The cycle of iron in macrophages in health and disease

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ABSTRACT

Iron homeostasis and macrophage biology are closely interconnected. On the one hand, iron exerts multiple effects on macrophage polarization and functionality. On the other hand, macrophages are central for mammalian iron homeostasis. The phagocytosis of senescent erythrocytes and their degradation by macrophages enable efficient recycling of iron and the maintenance of systemic iron balance.

Macrophages express multiple molecules and proteins for the acquisition and utilization of iron and many of these pathways are affected by inflammatory signals. Of note, iron availability within macrophages has significant effects on immune effector functions and metabolic pathways within these cells.

This review summarizes the physiological and pathophysiological aspects of macrophage iron metabolism and highlights its relevant consequences on immune function and in common diseases such as infection and atherosclerosis.

Contents

Abbreviations: ABCA1, ATP-binding cassette, subfamily A, member 1; ABCG5, ATP-binding cassette, subfamily G, member 5; ACD, anemia of chronic disease; AI, anemia of inflammation; Apo, apolipoprotein; Arg1, arginase-1; Bach1, Btb and Cnc Homology, basic leucine zipper transcription factor-1; BAI, brain specific angiogenesis inhibitor; BDH2, butyrate dehydrogenase-2; CD163, cluster of differentiation-163 ASA hemoglobin scavenger receptor; CD91, cluster of differentiation-91 ASA haptoglobin receptor; CO, carbon monoxide; DC, dendritic cell; DHBA, dihydroxybenzoic acid; Dmt1, divalent metal transporter-1 ASA Slc11a2; EAE, experimental autoimmune encephalomyelitis; ER, endoplasmatic reticulum; ERK, extrazellular signal-regulated kinase; Err, estrogen-related receptor; Flvcr, feline leukemia virus subgroup C receptor; Fpn1, ferroportin-1 ASA Slc40a1; Ft, ferritin; Hb, hemoglobin; Hcp1, heme carrier protein-1; HIF, hypoxia inducible factor; Hmox1, heme oxygenase-1; Hrg1, heme regulated gene-1; Hp, haptoglobin; Hpx, hemopexin; IFN, interferon; Ifnγr, interferon-gamma receptor; IL, interleukin; IL-4rα, interleukin-4 receptor subunit alpha; IRE, iron regulatory element; IRP, iron regulatory protein; Jak, Janus kinase; Keap, Kelch-like erythroid cell-derived protein with CNC homology-associated protein; Lcnr, lipocalin receptor; Lcn2, lipocalin-2; LDL, low density lipoproteins; Lf, lactoferrin; LPS, lipopolysaccharide; Lxr, liver X receptor; MAPK, mitogen activated kinase; MerTK, Mer tyrosine kinase; MDS, myelodysplastic syndrome; MFG-E, milk fat globule-EGF-factor; MHC, major histocompatibility complex; MntH, H^+-coupled manganese transporter; MPS, mononuclear phagocyte system; Mramp, mycobacterial Nramp homologue; MyD88, myeloid differentiation primary response gene 88; NF-IL6, nuclear factor-IL6; NF-κB, nuclear factor-kappa B; Nramp1, natural resistance associated macrophage protein-1 ASA Slc11a1; Nrf2, nuclear factor erythroid 2 (NFE2)-related factor-2; NO, nitric oxide; Nos2, nitric oxide synthase-2 ASA inducible Nos; PDGF, platelet-derived growth factor; RBC, red blood cell; ROS, reactive oxygen species; Scara5, scavenger receptor class A member 5; Slc11a1, solute carrier family 11 member 1; SpiC, SpiC transcription factor; SPION, superparamagnetic iron oxide nanoparticle; Stat, signal transducer and activator of transcription; TAM, tumor associated macrophage; Tf, transferrin; Tfr1, transferrin receptor-1; Tgf, transforming growth factor; Th, T helper; Tim, T-cell immunoglobulin and mucin domain-containing molecule; Tlr, toll like receptor; TNF, tumor necrosis factor; Tnfr1, TNF receptor-1; TRAM, Trif-related adaptor molecule; TRIF, Tir domain-containing adaptor inducing interferon-β; UTR, untranslated region.

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Iron cycling under physiologic conditions

From a quantitative point of view, macrophages engaged in erythrophagocytosis and iron recycling handle the body's most important iron pool (Theurl et al., 2005; Nix et al., 2007). In steady state, as little as 1–2 mg of iron are absorbed from the diet in the proximal duodenum (Evstatiev and Gasche, 2012) to compensate for iron losses during bleeding episodes and through desquamation of senescent epithelial cells from the skin and gastrointestinal tract (Fig. 1). The daily turn-over of iron, however, is approximately 20 times higher. The production of hemoglobin (Hb) during erythropoiesis consumes as much as 20–30 mg of iron per day, and the synthesis of enzymes containing heme- or iron-sulfur-moieties requires additional quantities of the metal. This demand is largely met by macrophages which eliminate senescent red blood cells (RBCs), degrade them and recycle their iron to be transferred to the circulation, so that the metal can be used for erythropoiesis and other metabolic needs (Hentze et al., 2010).

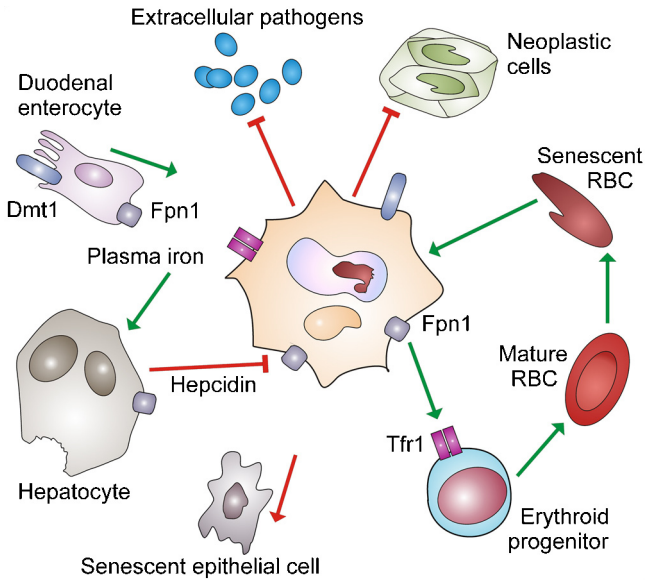

Fig. 1. Central role of macrophages in systemic iron balance. *Right-hand side*: macrophages continuously take up senescent RBCs by phagocytosis. Following degradation of engulfed erythrocytes and break-down of hemoglobin, iron is exported via Fpn1. By these mechanisms, macrophages recycle 20–25 mg of iron per day to the circulation. Erythroid progenitor cells take up iron via Tfr1 and reutilize it for heme synthesis to generate new erythrocytes as oxygen carriers. *Left-hand side*: duodenal enterocytes absorb 1–2 mg of iron per day using Dmt1 (apical surface) and Fpn1 (basolateral surface). This absorption compensates for the daily loss of 1–2 mg of iron via minor bleeding episodes and sloughing of senescent epithelial cells from the skin and gastrointestinal tract. An increase in the plasma iron pool stimulates the expression of hepcidin by hepatocytes. Hepcidin acts on Fpn1-expressing cells and limits the transfer of iron to the circulation. *Center*: in inflammatory conditions, iron uptake into macrophages is increased by erythrophagocytosis and via additional mechanisms including Tfr1 and Dmt1. Increased iron uptake in conjugation with reduced Fpn1-mediated iron efflux reduces the plasma iron pool (30 mg under steady state conditions). *Top*: inflammation drives the retention of iron within macrophages thus withholding iron from extracellular pathogens and neoplastic cells. *Bottom*: in infections with extracellular microbes, Tlr ligands and pro-inflammatory cytokines such as IL-1β, IL-6 and IL-22 induce hepcidin expression in hepatocytes. Small amounts of hepcidin are also produced by other cell types including macrophages.

Erythrocytes engulfed within macrophages are degraded, Hb is split into heme and globin chains, and heme is transferred from the phagolysosome to the cytoplasm by heme regulated gene (Hrg)-1 (White et al., 2013). The heme porphyrin ring is subsequently broken up by heme oxygenase (Hmox)-1 yielding equal amounts of bilirubin, CO and iron (Gozzelino et al., 2010). In addition, also ionic iron is shifted from the phagolysosomal compartment to the cytoplasm via natural resistance associated macrophage protein (Nramp)-1, and then leaves the cytosol through the iron exporter ferroportin (Fpn)-1. Surplus intracellular iron must be stored within cage-shaped ferritin (Ft) molecules to avoid the toxicity of unbound ionic (labile) iron which carries pro-oxidative properties (Hentze et al., 2010; Weiss, 2002; Breuer et al., 2008; Imlay et al., 1988).

The transcription factor SpiC coordinates erythrophagocytosis and iron recycling. Following exposure of macrophages to free heme, the transcriptional repressor Btb and Cnc Homology (Bach)-1 is degraded within the proteasome resulting in increased SpiC transcription. SpiC promotes the differentiation of monocytes to red pulp and bone marrow macrophages to replace resident populations that had succumbed to heme-mediated toxicity. These emerging $CD169^{+}$ macrophages also support the survival of erythroid progenitors (Haldar et al., 2014; Chow et al., 2013).

In parallel, the degradation of Bach1 activates nuclear factor erythroid 2 (NFE2)-related factor (Nrf)-2 to drive the expression of Hrg1, Hmox1 and Fpn1 thus enabling efficient iron recycling (Sun et al., 2004; Marro et al., 2010).

The transfer of iron from the mononuclear phagocyte system (MPS) to the circulation is determined by hepcidin which acts as negative feed-back regulator of duodenal iron absorption and macrophage iron export as it physically binds to Fpn1 and induces its degradation in the proteasome (Nemeth et al., 2004). Inflammatory stimuli and the presence of excess iron in the circulation induce the expression and secretion of hepcidin by hepatocytes by alternative pathways (Nemeth and Ganz, 2006) while hypoxia stimulates the secretion of platelet-derived growth factor (PDGF)-BB thus repressing hepcidin transcription (Sonnweber et al., 2014).

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