A study by Schaer et al.,1 which appears in this issue of Circulation Research, provides evidence suggesting that CD163 acts as a hemoglobin (Hb) transporter and, via activation of macrophages, heme oxygenase-1 (HO-1) provides antiinflammatory activity, presumably by an increase in ferritin. Induction of HO-1 was observed to occur when the cultured macrophages, endothelial cells or tubular cells were exposed to heme or hemoglobin (for a review see Abraham and Kappas2). Heme and denatured hemoglobin toxicity play an important role in a broad spectrum of pathological circumstances such as myocardial ischemia, hypertension, cardiomyopathy, reperfusion, organ transplantation, pulmonary disorders, and inflammation among others.3 In the cell free system, hemoglobin is bound to haptoglobin before clearance by the macrophage hemoglobin scavenger receptor CD163. Schaer et al.3 demonstrated that CD163-hemoglobin transport is regarded as a critical step in the hemoglobin clearance pathway in the macrophage, especially under conditions of extreme hemoglobin release resulting from hemolysis. Binding hemoglobin-haptoglobin to CD163 cells also elicits IL-10 secretion, which contributes to the induction of HO-1.4 Thus, CD163 has a functional role as an antioxidant by enhancing HO-1, the major cytoprotective response. This links heme transport directly to a known receptor with well characterized endocytic properties and signaling functions.5 Heme-hemopexin is also taken up by receptor with well characterized endocytic properties and an antioxidant by enhancing HO-1, the major cytoprotective

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Circulation Research is available at http://circres.ahajournals.org
DOI: 10.1161/01.RES.0000249616.10003.d6

911
either because of an increased rate of synthesis or a decreased rate of removal by CD163 and other binding proteins, the excess of heme will inhibit ALA synthase or activity. Schaer et al have elegantly shown that macrophage CD163, by binding to circulating hemoglobin, will result in activation of HO-1 and thus prevent the accumulation of hemoglobin/heme and prooxidants, as well as attenuate reactive oxygen species (ROS) and cell damage. Therefore, CD163 plays an important role in regulating heme degradation by HO-1. It should be noted that a CD163-mediated increase in HO-1 does not decrease the constitutive heme proteins, such as COX-1, eNOS or mitochondrial proteins, but it will decrease those heme proteins with a rapid turnover, i.e., inducible enzymes such as iNOS, COX-2, and tryptophane pyrrolase. Therefore, the CD163-mediated transport of hemoglobin to macrophages will increase HO-1 at the site needed, such as the vascular system, whereas decreasing iNOS and COX-2 and increasing ferritin, CO, and bilirubin.

Carbon monoxide, which can act as both a messenger and a signaling molecule, is not an antioxidant per se, but can cause the induction of antioxidant genes, decrease the levels of superoxide (O$_{2}^{-}$), increase reduced glutathione (GSH) levels (needed to enhance the redox state) and cyclic guanosine monophosphate (cGMP) (a vasodilator). CO has an antiapoptotic effect (for review see Ryter et al). The third product of heme degradation, iron, is rapidly bound to ferritin as manifest by a rapid increase in the levels of ferritin as Schaer et al have described. Thus, the induction of HO-1, the primary response to oxidant stress, results in a multifaceted defense against oxidative damage in the cell. Toxic levels of
the hemoglobin/heme are removed by HD-1 and released iron sequestered by ferritin, also capable of diminishing formation of lipid peroxidation through hemoglobin-mediated generation of free radicals. In addition, CO is generated and biliverdin/bilirubin is produced, the former acting as an antioxidant through its role as a messenger and signaling molecule, the latter through their potent antioxidant properties.

As noted in Figure 3, the ability of bilirubin to prevent the oxidant-mediated vasoconstrictive actions of tumor necrosis factor and angiotensin II has been reported. Bilirubin, in low concentrations, is a scavenger of ROS in vitro, reduces oxidant-induced cellular injury and attenuates oxidant stress in vivo. It would be remiss not to point out that the above beneficial protective effects of CO, biliverdin/bilirubin and iron occur at physiological concentrations. They, like heme, are toxic when present in the cell at high levels, eg, kernicterus in newborn infants and iron storage diseases.

The known effects of HO-1 activity will decrease heme, a powerful oxidant, and increase CO and bilirubin, thus preventing endothelial cell dysfunction and death by conserving NO, which is normally lost because of its binding to hemoglobin. Thus, CD163 transport of hemoglobin to macrophages with the subsequent induction of HO-1 by Hb may function as a protective mechanism to preserve NO-mediated vascular function. Increasing the macrophage expression of HO-1 in vivo, as described by Schae et al, may provide a protective mechanism in the preservation of NO in HO-dependent mechanisms. HO-1–derived CO and bilirubin are crucial not only for the increase in cGMP and but also for restoration of vascular functions in diseases such as diabetes and hypertension where NOS is impaired. HO-1 product activity is associated with upregulation of other important antioxidant systems that protect the vasculature, such as extracellular SOD (EC-SOD), plasma catalase activity, and decreased superoxide production. Increased EC-SOD and decreased O$_2^-$ formation which are essential factors in preserving the levels of NO necessary for other functions, including endothelial cell progenitor function (Figure 3).

For the first time, Schae et al demonstrate a link between noninflammatory effect of hemoglobin clearance via increase in HO-1 expression and HO activity. This is an important initial step in the elucidation of the antiinflammatory activity associated with CD163 positive macrophages. They have ruled out the possibility that the hemoglobin CD163 pathway acts via an oxidative stress-signaling pathway. There remain numerous other potential avenues of exploration, including CO- and bilirubin-mediated protective pathways, signaling pathways, etc. CD163 represents a major pathway for the uptake of extracellular hemoglobin and free heme in the circulation. This pathway requires further examination to elucidate the mechanism of removal of hemoglobin and heme from circulation. The article by Schae et al is an important first step in elucidating the relationship between CD163 and HO-1 induction and the mechanisms that are involved in noninflammatory hemoglobin clearance, opens up new strategic approaches for the effective management of Hb for a number of clinical disorders.

Acknowledgments

We thank Jennifer Brown for her excellent editorial and secretarial assistance.

Sources of Funding

This work was supported by NIH grants DK068134, HL55601, and HL34300 (N.G.A.).

Disclosures

None.
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Key Words: CD163 ■ heme oxygenase ■ antiinflammatory ■ carbon monoxide ■ bilirubin antioxidants
CD163-Mediated Hemoglobin-Heme Uptake Activates Macrophage HO-1, Providing an Antiinflammatory Function
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Circ Res. 2006;99:911-914
doi: 10.1161/01.RES.0000249616.10603.d6

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/99/9/911

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