Continual emerging roles of HO-1: protection against airway inflammation

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THE ROLE OF THE HEME OXYGENASE (HO) in pulmonary medicine is a rapidly emerging field. A regulatory role for HO has been identified in a variety of pulmonary diseases relating to vascular tone, cell growth, and apoptosis (reviewed in Refs. 1, 9, 15, and 21). Although it is known that the inducible form, HO-1, is part of the integrated response to oxidative stress and inflammation, only recently has it been implicated in the regulation of pulmonary inflammation (2, 17, 23).

However, the mechanisms by which HO-1 functions as a cytoprotective and anti-inflammatory protein remain poorly understood.

The inducible (HO-1) and constitutively expressed (HO-2 and HO-3) forms of HO catalyze the rate-limiting step of heme oxidation to biliverdin, carbon monoxide (CO), and iron (1) (Fig. 1). Biliverdin is rapidly converted to bilirubin, a potent endogenous antioxidant (16). All three products of the HO reaction (biliverdin/bilirubin, Fe/ferritin, and CO) participate in cellular defense. In addition to the physiological substrate heme, HO-1 is induced by a wide variety of stimuli associated with both oxidative stress and inflammation, such as hypoxia, hyperoxia, cytokines, nitric oxide (NO), heavy metals, ultraviolet radiation, heat shock, shear stress, hydrogen peroxide, and thiol-reactive substances (15). Specific pulmonary diseases associated with HO-1 (and other members of the heat shock protein family) include adult respiratory distress syndrome, interstitial pulmonary fibrosis, and chronic inflammatory disorders such as chronic obstructive pulmonary disease and asthma (13, 14, 18).

Asthma is a chronic inflammatory disease of the airways associated with increased reactive oxygen species and NO production and elevated levels of several inflammatory mediators in the airways, all of which may be inducers of HO-1 expression (4, 7). HO-1 is induced in asthmatic airways, but its functional role is unclear. Almolki et al. (2), in the current article in focus (Ref. 2, see p. L26 in this issue), report on the role of HO in airway inflammation and demonstrate several important protective roles for HO-1 and its products (biliverdin/bilirubin, Fe/ferritin, and CO). They demonstrate that oxidative stress in ovalbumin-challenged guinea pigs is reduced when HO-1 expression and subsequent bilirubin production are induced by hemin. Bilirubin acts as a potent antioxidant by efficiently scavenging peroxyl radicals, thereby inhibiting lipid peroxidation (16). In addition, the lower oxidant stress associated with HO-1 upregulation in the ovalbumin-challenged guinea pigs could be attributed to a reduction in the number of neutrophils, eosinophils, and lymphocytes in their airways. HO-1 has been reported to reduce inflammatory cell rolling, adhesion, and migration from the vascular compart-

ment, possibly by downregulating the function and expression of adhesion molecules on the vessel wall (19, 20). In the rat mesentery, HO-1 induction reduced leukocyte recruitment after ischemia-reperfusion (6). Bilirubin may be responsible for decreased leukocyte recruitment, since superfusion of bilirubin largely repressed the effects of HO inhibition with zinc protoporphyrin-IX. The data of Almolki et al. (2) support this two-pronged protective mechanism of bilirubin acting as an antioxidant directly by its peroxyl radical-scavenging properties as well as by decreasing inflammatory cell recruitment during airway inflammation.

The signaling properties of CO may also contribute to the anti-inflammatory effects of HO-1. CO serves a similar role as NO in signal transduction. In addition, since CO does not contain free electrons as NO does, it is relatively inert and does not generate reactive nitrogen species as NO can. In fact, in certain settings, NO may actually be proinflammatory (10).

Thus in oxidative or inflammatory settings such as asthma, the role of HO-1 and CO may be particularly important, making CO preferentially selected over NO as a signaling molecule to activate guanylyl cyclase and regulate local blood flow. By activating this second messenger system, CO can mediate numerous physiological processes, such as activities of protein kinases, ion channels, and phosphodiesterases (9, 12) that are inherently antioxidant.

In asthma, a potentially critical role for HO-1-derived CO is its ability to relax airway smooth muscle via the activation of guanylyl cyclase and formation of cGMP (8). Almolki et al. (2) demonstrate very nicely that induction of HO-1 by hemin reduced pulmonary inflation pressure in both control and ovalbumin-challenged guinea pigs that received histamine to initiate bronchoconstriction. These data provide compelling functional evidence illustrating yet another protective role of HO-1.

The clinical significance of HO-1 during asthma is still an open question. HO-1 and its products may be useful in both diagnostic and therapeutic roles. For example, recent studies demonstrate that the level of exhaled CO is associated with the clinical severity of asthma (22), which may be useful as a simple, noninvasive tool in assessing asthma severity (11). CO may also serve a therapeutic role. Low-dose inhaled CO reduced both aeroallergen-induced inflammation and airway hyperresponsiveness in mice (3, 5). Defining not only the regulation of HO-1 during airway inflammation and asthma but also diagnostic and therapeutic roles of CO and the other components of the HO-1 pathway will remain an important avenue of investigation for the foreseeable future.

GRANTS
This work was supported by National Institutes of Health Grants DK-02884 and HL-64919.
Fig. 1. Schematic of heme oxygenase (HO) enzymatic activity. Enzymatic products and physiological effects are listed. CO, carbon monoxide.

REFERENCES


