Editorial: Heme Oxygenases: Novel Regulators of Reproductive Processes

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Keywords: Hmox1, HO-1, placenta, uterus, pregnancy, immune system, pre-eclampsia

Heme oxygenase (HO) is a ubiquitous enzyme with various properties, but its main function is catalyzing the rate-limiting step in heme degradation to produce equimolar quantities of biliverdin, iron, and carbon monoxide (CO) (Tenhunen et al., 1968). Of its three isozymes, HO-2 and HO-3 are constitutively-expressed and HO-1 is inducible and acts as stress-response protein. It is not only cytoprotective (Vile et al., 1994; Soares et al., 1998; Gozzelino et al., 2010); but also, exerts anti-inflammatory effects (Otterbein et al., 2000, 2003; Soares and Bach, 2009). Together with its modulatory effects on cell proliferation (Duckers et al., 2001; Lee and Chau, 2002), HO-1 can prevent tissue injury. Also, HO-1 is known to regulate innate and adaptive immunity, and therefore may prevent immune-mediated inflammatory diseases (Wagener et al., 2003; Soares and Bach, 2009; Soares et al., 2009). These effects can be inhibited pharmacologically and restored by CO (Brouard et al., 2000; Otterbein et al., 2000; Lee and Chau, 2002; Ryter et al., 2002; Kim et al., 2006).

Pioneering work from the late Fritz Bach revealed the importance of HO-1 in organ transplantation. Using wild-type (WT, Hmox1+/+) and Hmox1−/− mice, Soares et al. (1998) demonstrated that the rapid expression of HO-1 by xenograft endothelial cells, smooth muscle cells, and cardiac myocytes protects xenografts from rejection. The role of HO-1 in xenograft and allograft acceptance is due to its cytoprotective properties that support cell survival and function within the transplanted organ. Moreover, HO-1 can reduce the graft immunogenicity by directly modulating recipient immune response such that regulatory responses are generated. The activation of HO-1 expression in the graft and in immune cells of the recipient can prevent rejection and promote immunotolerance, and probably due to the detoxification of free heme by HO-1 (Soares and Bach, 2007).

Using a mouse model where tolerance is induced by donor-specific transfusion and anti-CD40L, Yamashita et al. (2006) observed that HO-1 is necessary for long-term graft tolerance as grafts do not survive in Hmox1−/− compared to WT control recipients. Modulation of HO-1 was necessary to promote graft tolerance. Donor-specific transfusion alone failed to prolong survival of transplanted hearts, but long-term survival and tolerance were achieved after HO-1 induction. HO-1 induction plus donor-specific transfusion was associated with increases in regulatory T-cells (Tregs) (Yamashita et al., 2006). The immunomodulatory effect on cells from graft recipients is based on the fact that HO-1 directly modulates the phenotype of dendritic cells (DCs) (Moreau et al., 2009). HO-1 is constitutively expressed in immature DCs; however, its expression decreases during DC maturation. HO-1 upregulation can maintain DCs in an immature state, which suppresses the immune response, and then leads to antigen-specific Treg generation (George et al., 2008; Schumacher et al., 2012). Because Tregs from Hmox1−/− mice are functional, it can be concluded that the suppressive function of Tregs depends upon HO-1-induced modulation of DCs rather than HO-1 expression by Tregs (Zelenay et al., 2007).
In the article by Schumacher and Zenclussen (2015), the participation of HO-1 in immunomodulation during pregnancy and organ transplantation is discussed. They report how HO-1 promotes alloantigen tolerance by blocking DC maturation reduces T-cell responses and increases Treg numbers. Further mechanisms involve the cytokine milieu, tissue protection, and apoptosis. Hence, HO-1 can mediate acceptance of a transplanted allogeneic graft through organ cytoprotection and immunotolerance. A similar scenario may be true for a growing fetus, which is semi-allogeneic to the mother, where HO-1 confers both semi-allograft cytoprotection and immunotolerance in the maternal immune system.

Because of its role in the modulation of innate and adaptive immune responses, HO-1 is linked to carcinogenesis by influencing tumor induction, growth, and metastasis (Jozkowicz et al., 2007). HO-1 is highly expressed in several tumors, and accordingly, inhibition of HO may have potential as a therapeutic approach. Because tumors are highly vascularized and prone to massive hemorrhaging, large quantities of free heme can be released, and induce HO-1 that in turn negatively influences the host and protects the tumor from oxidative injury. HO-1 is also involved in tumor angiogenesis and stimulating tumor-associated macrophages (Was et al., 2010), and thus, may regulate tumor survival and progression.

Zhao et al. (2015) discuss how HO-1 regulates similar processes in transplantation and pregnancy, particularly in invasion and neovascularization. Pregnancy is a physiological state characterized by interactions of various processes occurring at different stages. For these changes to occur, tissue and vascular remodeling as well as both pro- and anti-inflammatory processes in the uterus are required. However, once the placenta has formed and the fetus grows, the fetoplacental unit behaves more like a graft that is tolerated by its host. When pregnancy is near completion, the semi-allograft is naturally “rejected” by the mother resulting in birth.

Zenclussen et al. (2015) review how HO-1 impacts reproductive processes, highlighting its importance in placental function and fetal development. The deletion of Hmox1 in mice leads to inadequate spiral artery remodeling and suboptimal placentation followed by intrauterine growth restriction and fetal death (Zhao et al., 2009; Zenclussen et al., 2011). A partial Hmox1 deletion is compatible with pregnancy, however heterozygote females develop gestational hypertension (Linzke et al., 2014). The protective effects of HO-1 on placentation and fetal growth can be mimicked by exogenous administration of CO. CO promotes the in situ proliferation of uterine natural killer (uNK) cells, restores placentation, and fetal growth, while normalizing blood pressure (Linzke et al., 2014). Similarly, HO-1 inhibition provokes hypertension in pregnant rats (George et al., 2013).

The relevance of HO-1 in the regulation of immune responses during pregnancy is further highlighted in the article by George et al. (2015). They investigated whether HO-1 induction could attenuate TNF-α-induced hypertension in pregnancy. HO-1 induction significantly decreased blood pressure in TNF-α-infused animals, which was accompanied by a normalization of vascular parameters, supporting the notion that HO-1 is essential in counteracting the negative effects of excessive inflammation.

In summary, the HO-1/CO axis may play a pivotal role in sustaining pregnancy, and thus understanding its biology during pregnancy may reveal promising therapeutic approaches for pregnancy complications.

**AUTHOR CONTRIBUTIONS**

Both the authors contributed in writing the editorial.

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