# $O_2$- and $H_2O_2$-Dependent Verdoheme Degradation by Heme Oxygenase

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Heme oxygenase (HO) catalyzes catabolism of heme to biliverdin, CO and a free iron through three successive oxygenation steps. The third oxygenation, oxidative degradation of verdoheme to biliverdin, has been the least understood step in spite of its importance to regulate the HO activity. We have thoroughly examined degradation of a synthetic verdoheme IX$\alpha$ complexed with rat HO-1. Our major findings include: (1) HO degrades verdoheme through a dual pathway using either $O_2$ or $H_2O_2$; (2) the newly found $H_2O_2$ pathway is approximately 40-fold faster than the $O_2$-dependent degradation; (3) both reactions are initiated by the binding of $O_2$ or $H_2O_2$ to allow the first direct observation of degradation intermediates of verdoheme; and (4) Asp140 in HO-1 is critical for the verdoheme degradation regardless of the oxygen source. On the basis of these findings, we propose that the HO enzyme activates $O_2$ and $H_2O_2$ on the verdoheme iron with the aid of a nearby water molecule linked to Asp140. These mechanisms are similar to a well-established mechanism of the first oxygenation, *meso*-hydroxylation of heme, and thus, HO can utilize a common architecture to promote the first and third oxygenation steps of the heme catabolism. We will also discuss a possible involvement of the $H_2O_2$-dependent verdoheme degradation *in vivo*, and propose potential roles of the dual pathway reaction of HO against oxidative stress.