expression. The second hypothesis is based on the fact that because tin protoporphyrin possesses a structure similar to that of heme, it may directly induce HO-1 expression, probably by binding to specific heme binding motifs and activating the gene transcription. Moreover, the authors' observations further confirm that the activity of the protein rather than its expression or intracellular localization is required for its beneficial effects. We also agree with the authors regarding their conclusions about carbon monoxide. In fact, further studies using carbon monoxide–releasing molecules or carbon monoxide gas are required to confirm a possible interaction between carbon monoxide, nuclear factor erythroid 2–related factor 2, and nuclear factor κB under these experimental conditions. In this regard, further studies should also be performed to exclude a possible involvement of biliverdin, the other byproduct of HO activity, which has also been shown to impact on inducible nitric oxide synthase expression and activity.\(^5,7\)

In conclusion, the authors' observations are novel and intriguing and add a new, important piece in the complicated puzzle of the interaction between the HO–carbon monoxide and nitric oxide–nitric oxide synthase systems.

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