Heme oxygenase (HO-1) is involved in the negative regulation of contact sensitivity reaction

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Abstract:
Cutaneous contact sensitivity (CS) is a subtype of delayed-type sensitivity and is mediated by either CD4⁺ or CD8⁺ CS-effector T cells. CS can be induced by skin painting with haptens like trinitrophenyl chloride (TNP-Cl). We have previously shown that CS is under the negative regulation of T regulatory cells (Treg) induced by the iv injection of a high dose of homologous antigen or via epicutaneous application of any protein antigen prior to TNP-Cl painting. In this study, we examined the role of heme oxygenase (HO-1) in the negative regulation of CS in mice.
We found that ip injection of heme, an inducer of HO-1, before TNP-Cl sensitization strongly suppresses CS when compared to uninjected controls. Using a transfer out protocol, we showed that suppressor activity can be transferred with lymph node and spleen cells isolated from mice treated with heme for 7 days before TNP-Cl or sham immunization, which suggests a lack of antigen specificity of observed suppression. Negative selection with monoclonal antibodies and complement showed that regulatory cells induced via heme injection belong to the population of TCRαβ⁺ lymphocytes. Using CBA/J (H-2k), SJL (H-2s), and DBA1 (H-2b) mice, we showed that the suppression mediated by HO-1 is major histocompatibility complex (MHC) unrestricted. in vitro treatment of heme induced Treg cells with tin protoporphyrin IX (SnPPIX), an inhibitor of HO activity, prior to adoptive transfer abolished the suppressor activity.
In summary, injection of heme results in the induction of antigen non-specific and MHC unrestricted TCRαβ⁺ Treg that suppress CS response in mice, possibly in a HO-1-dependent manner.

Key words: heme oxygenase, T regulatory cells, inflammation, contact sensitivity