Pharmacological Reports
2008, 60, 933–940
ISSN 1734-1140

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

Monika Majewska[1], Katarzyna Zając[1], Józef Dulak[2], Marian Szczepanik[1]

[1]Department of Human Developmental Biology, Jagiellonian University College of Medicine, Kopernika 7, PL 31-034 Kraków, Poland

[2]Department of Medical Biotechnology, Faculty of Biochemistry, Biophysics and Biotechnology, Jagiellonian University, Gronostajowa 7, PL 30-387 Kraków, Poland

Correspondence: Marian Szczepanik, e-mail: mmszczep@cyf-kr.edu.pl

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 ($H\text{-}2^k$), SJL ($H\text{-}2^s$), and DBA1 ($H\text{-}2^q$) 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