The role of the heme-heme oxygenase system in multiple sclerosis pathology

Van Horssen J, Wagener FA*, Van der Pol SM, Schreibelt G, de Vries HE
Dept of Molecular Cell Biology and Immunology, VU Medical Center, Amsterdam, *Dept of Tumor Immunology, University Medical Center Nijmegen, Nijmegen

Multiple sclerosis (MS) is a chronic inflammatory disorder of the central nervous system and is characterized by infiltration of monocyte-derived macrophages. These activated monocytes secrete inflammatory mediators like reactive oxygen species (ROS) that contribute to axonal damage and demyelination. The inducible heme oxygenase (HO)-1 gene responds to changes in cellular redox potential provoked by ROS. We previously demonstrated an increase of HO-1 and -2 at mRNA level by quantitative PCR and microarray analysis in experimental autoimmune encephalomyelitis (EAE) rat brains, a validated model for MS. HO breaks down heme into biliverdin, free iron and carbon monoxide (CO). The formed biliverdin is rapidly converted by biliverdin reductase (BVR) into bilirubin, which exerts potent antioxidant activity and iron is directly sequestered and inactivated by co-induced ferritin. Heme catalyses the formation of ROS and excess of heme may also act as a pro-inflammatory mediator. Both heme-mediated ROS formation and inflammatory processes may contribute to tissue damage in EAE/MS brains. The aim of our study is to identify the cellular source of HO-1 and -2, BVR and ferritin in EAE rat brains as well as in human MS lesions. Our findings demonstrate that HO-1 and -2 as well as BVR and ferritin are markedly upregulated in infiltrating macrophages, while HO-2 and ferritin are also expressed by astrocytes in active lesions. Since foamy macrophages are immunopositive for HO, BVR and ferritin, we hypothesize that heme, HO activity and heme breakdown product may be involved in transendothelial migration of monocytes. Therefore, we will study the effects of heme, HO activity, CO and bilirubin on monocyte migration in future in order to gain insight into the role of the heme-heme oxygenase system in monocyte migration across endothelial cells. Additional research is needed to further elucidate the role of the heme-HO system in the pathogenesis of MS.

Jack van Horssen, Department of Molecular Cell Biology and Immunology, VU Medical Center, Van der Boechorststraat 7, 1081 BT Amsterdam, t 0031-204448078, e-mail j.vanhorssen@vumc.nl

NEUROSCIENCE 2