Dual role of heme oxygenase-1 in mice and men with acute graft-versus-host disease

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Abstract

Introduction

The development of acute GvHD still remains a significant limitation of an allogeneic hematopoietic stem cell transplantation (HSCT). Cell-free (cf)heme is a potent damage-associated molecular pattern (DAMP) that has been shown to play a role in diseases characterized by systemic inflammation such as sepsis, but its role in the development of acute GvHD remains unclear. Cfheme and hemoglobin are scavenged in plasma by hemopexin (HPX) and haptoglobin (HPT), respectively. The intracellular breakdown of cfheme is catabolized by heme oxygenase-1 (HO-1), a stress-inducible enzyme. In this study we aimed to further our understanding of the role of HO-1 and the scavenger proteins HPX and HPT in acute GvHD pathogenesis.

Methods

We measured plasma levels of HO-1, HPX and HPT by ELISA, protein expression of HO-1 by flow cytometry and mRNA expression of HO-1 by qPCR in a cohort of 69 allogeneic HSCT recipients with and without acute GvHD. Furthermore, we tested the effects of HO-1 induction in a humanized mouse model for acute GvHD.

Results

We found plasma levels of heme oxygenase-1 (HO-1) to be increased compared to healthy donors. HO-1 levels in plasma were particularly elevated in patients just before their acute GvHD diagnosis compared to baseline. Expression analysis further showed an increase in HO-1 expression in patients with acute GvHD at 1 month and 3 months after allogeneic HSCT compared to patients without acute GvHD. Finally, we found that induction of HO-1 in our humanized mouse model for acute GvHD led to improved survival, lower disease scores and a reduction in weight loss.

Conclusions

Overall, our data show that HO-1 expression is increased in patients with acute GvHD and that HO-1 induction might be able to provide protection against the disease, warranting further research into HO-1 as a target for clinical application.