| | |
|---|---|
| Title | Involvement of macrophage migration inhibitory factor (MIF) in graft-versus-host disease (GvHD) |
| Author(s) | Lo, WS; Huang, XR; Lie, AKW; Liang, RHS; Lan, HY |
| Citation | The 6th Medical Research Conference, Hong Kong, China, 13-14 January 2001, v. 23 n. 2 Supp, p. 59 |
| Issued Date | 2001 |
| URL | http://hdl.handle.net/10722/54108 |
| Rights | Creative Commons: Attribution 3.0 Hong Kong License |

## S-MP-2

### Involvement of Macrophage Migration Inhibitory Factor (MIF) in Graft-Versus-Host Disease (GvHD)

WS Lo, XR Huang, A Lie, RHS Liang, HY Lan.
Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong.

**Background:** Graft-versus-host disease (GvHD) remains the major problem in bone marrow transplantation (BMT) that limits its routine use clinically. The recent finding of macrophage migration inhibitory factor (MIF), a delayed type hypersensitivity-associated cytokine, in mediating both experimental and human renal allograft rejection suggests that MIF may a key mediator in GvHD.

**Methods:** To identify the involvement of MIF in GvHD, skin, colon and lung biopsies from GvHD patients are collected. Local MIF mRNA and protein expression, macrophage and T cell accumulation were examined by in situ hybridization and double immunohistochemistry, while systemic MIF production was measured by ELISA and RT-PCR.

**Results:** In normal skin and colon, there is weak, but constitutively, MIF mRNA and protein expression. However, marked upregulation of MIF mRNA and protein by intrinsic skin and colon cells was found with the development of local GvHD response, contributing to prominent T cell and macrophage accumulation. Moreover, MIF is also markedly up-regulated by the infiltrating T cells and macrophages, indicating that they are activated cells responsible for severe tissue damage. Importantly, up to 3 folds of serum MIF was found in the patients with GvHD ($p<0.01$) and this preceded the episode of GvHD clinically, indicating that MIF may be a cause, rather than a consequence, of GvHD. In contrast, in those without evidence of GvHD, there is no increase in MIF expression and production both locally and systemically.

**Conclusions:** We have, for the first time, demonstrated that MIF is markedly upregulated in patients with GvHD. Upregulation of MIF prior to the episode of GvHD strongly suggests that MIF may play a pathogenic role in GvHD.

## S-MP-3

### Macrophage Migration Inhibitory Factor (MIF) Up-Regulates Cyclo-Oxygenase 2 Gene Expression in Murine Macrophage Cell Line RAW264.7

DJ Tang, HY Lan.
Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong.

**Background:** Macrophage migration inhibitory factor (MIF) has been recently re-discovered as a key inflammatory mediator with many biological functions previously unrecognized. It has been shown that cyclooxygenase-2 (COX-2) is the inducible form of prostaglandin H synthase, which has been demonstrated to play an important role in the inflammatory process. Therefore, we hypothesized that MIF might regulate the expression of Cox-2 during inflammatory response.

**Methods:** A macrophage cell line Raw 264.7 cells were cultured in 6-well plates, starved for 24 hours in RPMI supplemented with 0.5% FBS before treatment. MIF was then added with or without prior treatment of MAPK inhibitors. Cells were harvested at various time points for the isolation of RNA or protein and expression of Cox-2 was analyzed by RT-PCR and Western blotting.

**Results:** Cox-2 is expressed in a low steady state level in Raw 264.7 cells. Upon stimulation with MIF, the expression of Cox-2 was markedly increased in a dose and time dependent manner. Upregulation of Cox-2 gene by MIF was observed both at mRNA and protein level. To investigate the possible pathway that involved in MIF-induced Cox-2 expression, further experiments with MAPK inhibitors was introduced into the cells before adding MIF. Unexpectedly, inhibition of MAPK activation with its inhibitor down-regulated MIF-induced Cox-2 upregulation in a dose dependent manner.

**Conclusions:** We have, for the first time, identified that MIF can upregulate Cox-2 gene expression through a MAPK dependent pathway. This finding further supports that MIF is an important proinflammatory cytokine and plays a pathogenic role in many inflammatory diseases.