Commentary

Macrophage migration inhibitory factor: controller of systemic inflammation

Douglas F Larson and Katherine Horak

Sarver Heart Center and Departments of Surgery and Medical Pharmacology, College of Medicine, The University of Arizona, Tucson, Arizona, USA

Corresponding author: Douglas F Larson, dflarson@u.arizona.edu

Published: 6 April 2006
This article is online at http://ccforum.com/content/10/2/138

Critical Care 2006, **10:**138 (doi:10.1186/cc4899)

See related research by de Mendonça-Filho *et al.* in this issue [http://ccforum.com/content/10/2/R46]

Abstract

Macrophage migration inhibitory factor (MIF) is a cytokine that is secreted by the anterior pituitary and immune cells in response to surgical stress, injury, and sepsis. This cytokine appears to be a critical regulator of the inflammatory pathways, leading to systemic inflammatory response syndrome and subsequent multiple organ dysfunction syndrome. This report provides an integrated scheme describing the manner by which MIF controls the neurohormonal response and the adaptive immune system, namely the T-helper (Th)1 and Th2 lymphocytes, which results in the release of pro-inflammatory cytokines and the anti-inflammatory cytokine interleukin-10. The development of systemic inflammatory response syndrome and subsequent development of multiple organ dysfunction syndrome appear to be related to MIF levels and the balance of Th1 and Th2 function.

Introduction

For the survival for all living creatures, an appropriate and balanced immune response to invading micro-organisms is essential. However, in the case of cardiovascular surgery, resembling sepsis and injury, an exaggerated inflammatory response, described as systemic inflammatory response syndrome (SIRS), may result in multiple organ dysfunction syndrome (MODS). The report by de Mendonça-Filho and coworkers [1] included in this issue of *Critical Care* demonstrates that a SIRS cytokine, namely macrophage migration inhibitory factor (MIF), correlates directly with MODS following open heart surgery and Sequential Organ Failure Assessment score.

Macrophage migration inhibitory factor

MIF is a distinctive cytokine because it is secreted by the immune cells and the anterior pituitary gland. T cells appear to be the main immune source of MIF, but MIF is also expressed by most other immune cell types, including those that facilitate acute inflammatory responses. Moreover, adrenocorticotropic hormone (ACTH), which increases secondary to surgical stress, in turn induces glucocorticoid hormones. Glucocorticoid hormones induce immune cell secretion of MIF. Third, proinflammatory cytokines and/or binding of the bacterial endotoxin lipopolysaccharide (LPS) also induce MIF by immune cells. The secreted MIF binds to its receptor CD74, which is expressed mainly by major histocompatibility complex class II positive cells, namely antigen presenting cells such as macrophages, lymphocytes, dendritic cells, and endothelial cells. MIF thereby stimulates the expression and secretion of the proinflammatory cytokines tumor necrosis factor-α, IFN-γ, IL-1β, IL-6, and IL-8, in addition to macrophage inflammatory protein-2, cyclo-oxygenase-2, nitric oxide, and products of the arachidonic acid pathway [2].

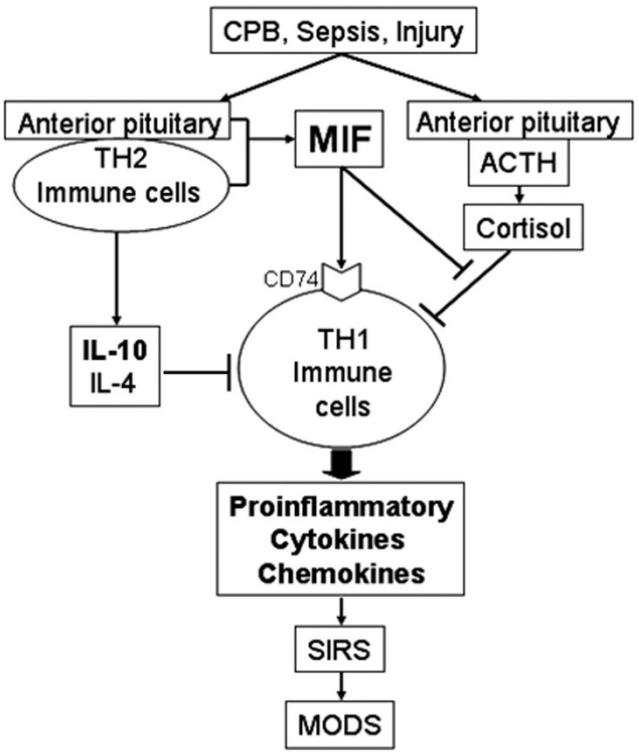
The importance of MIF as a key mediator of systemic inflammatory responses is supported by the observation that deletion of the MIF gene or neutralization of the protein induces protection from LPS-induced shock [3]. Therefore, the overall activity of MIF results in enhancement of the proinflammatory cytokine pathway related to SIRS, which has been directly associated with cardiovascular surgery, sepsis, and injury-mediated MODS [1].

Adaptive immune system: T-helper-1/2 cells

There are two general pathways in the adaptive immune system that are related to the expressed and secreted cytokine profiles. The cytokine profile that has been used to describe subtypes of Th ($CD4^+$) lymphocytes is Th1 and Th2; Th1 cells produce IL-2, IL-12, IFN-γ and tumor necrosis factor-α/β, and Th2 cells produce IL-4, IL-5, IL-10 and IL-13 [4]. The Th1 pathway is associated with induction of cellular

ACTH = adrenocorticotropic hormone; IFN = interferon; IL = interleukin; LPS = lipopolysaccharide; MIF = macrophage migration inhibitory factor; MODS = multiple organ dysfunction syndrome; SIRS = systemic inflammatory response syndrome; Th = T-helper (cell).

Figure 1



Scheme of macrophage migration inhibitory factor (MIF) induction of systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome (MODS) through the T-helper (TH)1/TH2 cell pathway. ACTH, adrenocorticotropic hormone; CPB, cardiopulmonary bypass; IL, interleukin.

immunity, namely activation of $CD8^+$ lymphocyte and macrophage functions. The Th2 cytokines generally support the humoral mediated responses related to B-lymphocyte function and immunoglobulin isotype.

Integration of macrophage migration inhibitory factor and the adaptive immune system

The pathways described in Figure 1 may elucidate a mechanism of MIF-mediated SIRS as a consequence of cardiovascular surgery using cardiopulmonary bypass. The initial stressors induce pituitary secretion of MIF and ACTH. ACTH-stimulated glucocorticoids and/or immunologic mediators may induce release of MIF by Th2 cells [5]. Most importantly, MIF counter-regulates the inhibitory effects of glucocorticoids on proinflammatory cytokines, thereby enhancing the cytokine-mediated SIRS. An alternate pathway is also probable because LPS has been shown to increase during cardiopulmonary bypass, which may directly induce MIF secretion by immune cells [6]. MIF thereby stimulates Th1 immune activity and induces proinflammatory cytokines and amplification of macrophage function. Within the context of inflammatory responses, the Th1 pathway controls macrophage activity, which is the main source of proinflammatory cytokines. These proinflammatory cytokines are highly pleiotropic and stimulate neutrophil and macrophage function and, in addition, induce production of acute phase proteins, fever, and cachexia. The Th2 pathway counterbalances the Th1 pathway mainly via IL-10 and to a lesser extent IL-4. IL-10 is a potent endogenous immunosuppressant cytokine that inhibits Th1 proinflammatory cytokines [7]. The principle Th1 cytokine, namely IFN-γ, is a potent stimulator of monocyte chemoattractant protein-1, which further stimulates macrophage function. The Th2 cytokine IL-13 can counterbalance this pathway through inhibition of monocyte chemoattractant protein-1. CD40 and CD40 ligand are integral membrane proteins that function to mediate interactions between cells and antigen-presenting cells. The release of sCD40 is therefore a marker of immune activation.

Conclusion

In summary, the development of SIRS and subsequent evolution of MODS appears to be related to the balance of Th1 and Th2 function. Over-expression of MIF favors Th1 and thereby results in an exaggerated SIRS condition. A dominant Th2 function leading to high expression of IL-10 should logically temper the Th1 pathway and reduce the magnitude of SIRS and resulting MODS. However, a report suggesting that genotypic variants in IL-10 predispose individuals to SIRS [8] is counter to the above logic, but it emphasizes the involvement of an additional parameter, namely the patient cytokine genotype. Therefore, the genotype of the patient also appears to be a key predictive marker of response to surgical, injury, and sepsis-mediated SIRS [9-12], which also would affect the balance of the Th1/Th2 response.

Competing interests

The authors declare that they have no competing interests.

Acknowledgement

This study was supported by NIH R01 HL079206-01, James and Linda Lee Heart Failure Research Award, and Steinbronn Heart Failure Research Award to DFL.

References

1. de Mendoça-Filho HTF, Pereira KC, Fontes M, Vieira DASA, de Mendonça MLAF, Campos LAA, Castro-Faria-Neto HC: **Circulating inflammatory mediators and organ dysfunction after cardiovascular surgery with cardiopulmonary bypass: a prospective observational study.** *Crit Care* 2006, **10:**R46.
2. Calandra T, Roger T: **Macrophage migration inhibitory factor: a regulator of innate immunity.** *Nat Rev Immunol* 2003, **3:**791-800.
3. Bernhagen J, Calandra T, Mitchell RA, Martin SB, Tracey KJ, Voelter W, Manogue KR, Cerami A, Bucala R: **MIF is a pituitary-derived cytokine that potentiates lethal endotoxaemia.** *Nature* 1993, **365:**756-759.
4. Rogge L: **A genomic view of helper T cell subsets.** *Ann N Y Acad Sci* 2002, **975:**57-67.
5. Bacher M, Metz CN, Calandra T, Mayer K, Chesney J, Lohoff M, Gemsa D, Donnelly T, Bucala R: **An essential regulatory role for macrophage migration inhibitory factor in T-cell activation.** *Proc Natl Acad Sci USA* 1996, **93:**7849-7854.
6. Bouma M, Maessen J, Weerwind P, Dentener M, Fransen E, de Jong D, Buurman W: **Release of lipopolysaccharide toxicity-modulating proteins in patients undergoing cardiopulmonary bypass using noncoated and heparin-coated extracorporeal circuits. A clinical pilot study.** *Chest* 1997, **111:**577-583.

7. Oberholzer A, Oberholzer C, Moldawer LL: **Interleukin-10: a complex role in the pathogenesis of sepsis syndromes and its potential as an anti-inflammatory drug.** *Crit Care Med* 2002, **30:**S58-S63.
8. Galley HF, Lowe PR, Carmichael RL, Webster NR: **Genotype and interleukin-10 responses after cardiopulmonary bypass.** *Br J Anaesth* 2003, **91:**424-426.
9. Holmes CL, Russell JA, Walley KR: **Genetic polymorphisms in sepsis and septic shock: role in prognosis and potential for therapy.** *Chest* 2003, **124:**1103-1115.
10. Schroeder S, Borger N, Wrigge H, Welz A, Putensen C, Hoeft A, Stuber F: **A tumor necrosis factor gene polymorphism influences the inflammatory response after cardiac operation.** *Ann Thorac Surg* 2003, **75:**534-537.
11. Tomasdottir H, Hjartarson H, Ricksten A, Wasslavik C, Bengtsson A, Ricksten SE: **Tumor necrosis factor gene polymorphism is associated with enhanced systemic inflammatory response and increased cardiopulmonary morbidity after cardiac surgery.** *Anesth Analg* 2003, **97:**944-949.
12. Watanabe E, Hirasawa H, Oda S, Shiga H, Matsuda K, Nakamura M, Abe R, Nakada T: **Cytokine-related genotypic differences in peak interleukin-6 blood levels of patients with SIRS and septic complications.** *J Trauma* 2005, **59:**1181-1189.