

EDITORIAL

Asthma and MIF: innately Th1 and Th2

In this issue, Yamaguchi and colleagues present data showing expression of the cytokine migration inhibitory factor (MIF) in the serum and induced sputum of patients with asthma [1]. How excited should we become at this further description of another mediator with potential involvement in the complex inflammatory situation of asthma?

MIF has a long history, having first been described originally in the context of delayed hypersensitivity many years ago [2,3]. Subsequent work has suggested major roles for this cytokine in the regulation of innate and adaptive immunity.

Recent high profile studies have shown an important role for this cytokine in septic shock, from both gram-negative endotoxins (LPS) and gram-positive exotoxins (such as superantigens derived from *Staphylococcus aureus* that cause the toxic shock syndrome). MIF is secreted by primary macrophages and macrophage cell lines after stimulation with very low concentrations of exotoxin [4], and is also released in significant quantities from the pituitary in septic shock [5]. Anti-MIF antibodies are highly potent in the prevention of death in both endotoxic and exotoxic shock *in vivo* [4,6]. In the context of endotoxic shock, anti-MIF antibodies are remarkable in their ability to prevent mortality even when given 8 h after induction of sepsis by caecal puncture [6]. Similarly, the MIF-knockout mouse is resistant to endotoxic shock, associated with a reduction in TNF α generation after LPS administration [7] (although the protective effects of anti-MIF antibodies in septic shock are also seen in TNF α knockout mice [6]).

In keeping with MIF as a significant pro-inflammatory mediator, Donnelly *et al.* showed increased levels of this cytokine in the bronchoalveolar lavage fluid from patients with the Acute Respiratory Distress Syndrome (ARDS) [8]. In alveolar cells derived from these patients, secretion of TNF α was observed to be enhanced by MIF. This and other studies described the induction of MIF synthesis by glucocorticoids, and the role of MIF in mediating resistance to the anti-inflammatory effects of steroids [8–10].

MIF is highly expressed in a murine delayed-type hypersensitivity (DTH) model [11], and anti-MIF antibodies inhibit development of the DTH response. A further study also showed a role for MIF in the regulation of naive T-cell proliferation after stimulation with anti-CD3 antibodies [9]. Thus MIF might be expected to have a role in the induction and/or maintenance of Th1 responses. However, Bacher *et al.* also showed that MIF was a product of Th2-type, but

not Th1-type, T-cell clones [9]. MIF also plays a role in macrophage killing of the intracellular parasite *Leishmania major*, via induction of TNF α synthesis [12]. In the MIF-knockout mouse, it was observed that challenge of lymph node cells from *L. major* infected animals lead to increased levels of the Th2-type cytokine, IL-4 [7]. Thus MIF is likely to play a significant, but complex, role in the regulation of T-cell function and Th1/2 balance in the inflammatory process.

Following on from the initial study of the role of MIF in ARDS, Rossi *et al.* were the first group to look for a possible connection between MIF and asthma. They observed that human eosinophils stored MIF, and released it upon stimulation with PMA, C5a, or IL-5 [13]. They further showed that MIF levels were higher in the bronchoalveolar lavage of asthmatics compared with those of normal controls [13]. MIF must therefore be added to the long list of cytokines produced under varying conditions by eosinophils: for a full review of these see [14]. It is also interesting that stimulation of fibroblasts by MIF activates enzyme cascades leading to leukotriene generation [15], a pro-inflammatory bronchoconstrictive mediator currently of much interest. However, it is by no means certain in either the study of Rossi *et al.* or the study published here [1], that the raised levels of MIF detected in the patient samples have arisen exclusively from eosinophils, and both publications acknowledge the contributions likely to be made by macrophages and activated T cells [1,13].

The link between a pro-inflammatory cytokine with steroid-antagonist properties and asthma holds much of interest. It is possible that MIF levels may determine response to corticosteroid treatment, and perhaps in part explain the difficult entity of steroid-resistant asthma [1,13]. Connections between the innate immune system and the adaptive immune system are also likely to be highly relevant to human disease. Much current research is driven by the concept of asthma as a Th2-centred disease, characterized by the recruitment of T cells producing cytokines such as IL-4, IL-5, and IL-13. These pleiotropic cytokines are undoubtedly produced in human allergic inflammation as shown by many elegant studies [16–18]. There is also growing evidence that cytokines such as IL-13 are capable of mediating many of the classical pathological changes seen in acute and chronic asthma [19–21]. Inhibition of Th2-type T-cell recruitment to the lung in mice is clearly associated with the reduction of bronchial hyper-reactivity, confirming a central role for these cytokines in asthma pathology [22,23].

Yet asthma is more than a disease solely dependent upon Th2-type T cells. There is a clear role for the innate immune system and cytokines such as IFN γ , in part derived from natural killer (NK) T cells, in both the establishment and direction of the allergic phenotype [24,25]. After sensitization, Th1-type T cells probably also play an important role in disease. Using T-cell clones in adoptive transfer protocols *in vivo*, the transfer of Th2-type T-cell clones will confer features of the allergic inflammatory response to a naive animal. If Th1-type T-cells are transferred at the same time, far from the allergic inflammatory response being suppressed, it is actually enhanced [26]. This is in keeping with human responses to asthmatic triggers such as viral infections, where the cytokines aggravating clinical bronchial hyperreactivity may be of the Th1 class or associated with the innate response, such as IFN γ and TNF α (for review of this topic see [25]). Furthermore, in the response to allergen in human asthma, it is also possible that LPS associated with antigen plays a significant part in the ensuing inflammation [27–29]. Human asthma is therefore likely to be a product of inflammatory responses regulated by both the innate and adaptive immune system, comprising of both Th1- and Th2-type components.

MIF therefore holds an interesting position with regard to the inflammatory response of asthma. Its expression may play roles in the induction of immunity during the 'handover' from innate to acquired responses. The data of Rossi *et al.* and the current paper in this journal show that MIF expression is also upregulated in 'established' asthma, and suggest a role for MIF in the maintenance of this inflammation [1,13]. In this context, MIF may regulate the production of other pro-inflammatory molecules such as TNF α and leukotrienes, as well as playing a role in steroid resistance. It is encouraging that in models of sepsis, antibodies to MIF did not render the animals more susceptible to infection [6], suggesting that neutralization of this cytokine may be achievable without excessive complications. However, only further studies will elucidate whether this molecule has a central role in asthma, or is just one of many cytokines deemed to play a supportive role in the establishment of allergic inflammation.

References

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