

EDITORIAL

Approaching the immunophysiology of steroid resistance

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Abstract

Wang and colleagues have investigated a mechanistic basis for resistance to steroid therapy in systemic lupus erythematosus patients. Their examination reveals significant differences in macrophage migration inhibitory factor (MIF)-dependent expression of I κ B, which is a critical cellular regulator of the broadly proinflammatory transcription factor NF- κ B. Their studies also suggest that MIF may be a clinically useful biomarker in systemic lupus erythematosus and support the therapeutic targeting of MIF as a means to reduce clinical steroid resistance.

In the current issue of *Arthritis Research & Therapy*, Wang and colleagues provide functional immunologic data on a molecular pathway for glucocorticoid resistance in systemic lupus erythematosus (SLE) [1]. Glucocorticoids have broad and powerful effects on the immune response and, despite the advent of biologic therapies, remain the most important and frequently used immunosuppressive agents in clinical practice [2]. Indeed, if it were not for their dose-limiting toxicity, glucocorticoids in all other respects would be ideal anti-inflammatory agents: orally absorbed, rapidly acting, and highly effective at shutting down a multitude of tissue-damaging, inflammatory pathways. Despite the clinical success of disease-modifying agents, concomitant steroid use remains an integral part of effective therapy as well as an established means for controlling disease exacerbations.

Among practitioners focused on inflammatory disorders, whether rheumatologic or nonrheumatologic, there has long been the observation that some patients respond poorly to steroids or require high doses and

prolonged treatment for disease control. These patients expectedly suffer most from the treatment-related complications of glucose intolerance, hypertension, obesity, osteoporosis, and myopathy. Even among patients maintained on low doses, the therapeutic objective remains the absolute minimalization or discontinuation of glucocorticoids. This goal has gained additional prominence with the recognition that accelerated atherosclerosis is an attendant consequence of systemic inflammation and a major cause of morbidity and mortality in rheumatoid arthritis and SLE [3]. The contributing effects of steroid-induced glucose intolerance and dyslipidemia add to the pathophysiology of atherogenesis and prompt continued investigation into more effective steroid-sparing agents and safer approaches to immunosuppression.

Wang and colleagues provide evidence of a specific pathway for steroid resistance in patients with treatment-unresponsive SLE [1]. The authors investigated the expression and function of the immunoregulatory cytokine macrophage migration inhibitory factor (MIF), which shares a unique regulatory relationship with glucocorticoids, in the peripheral blood monocyte responses of steroid-resistant SLE patients. Experimental work had previously established that MIF counter-regulates the immunosuppressive action of glucocorticoids on pro-inflammatory cytokine expression [4]. In human subjects, MIF circulates in a diurnal rhythm in phase with corticosteroids, but it is rapidly upregulated by stress or inflammatory stimuli [5]. Indeed, murine MIF was first cloned from activated anterior pituitary cells [6] and a model soon emerged by which MIF, whether released from the neuroendocrine system or the immune system, acts in concert with circulating glucocorticoids to regulate the magnitude of the host inflammatory response [7]. Mice genetically deficient in MIF have an alteration in their MIF–glucocorticoid axis and lower glucocorticoid levels, which probably accounts for their developmental defect in alveolar surfactant production and lung maturation [8].

Prior experimental studies have also revealed mechanisms by which MIF counter-regulates the immunosuppressive action of glucocorticoids; these mechanisms

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include suppression of glucocorticoid-induced expression of I κ B α , which is a cytosolic inhibitor of NF- κ B [9], and suppression of glucocorticoid-induced mitogen-activated protein kinase phosphatase [10,11], which inactivates the strongly proinflammatory ERK1/2, JNK, and p38 mitogen-activated protein kinase signaling pathways. Wang and colleagues investigated MIF-dependent pathways in two clinically defined cohorts of steroid-sensitive and steroid-resistant SLE patients. First, they observed increased MIF levels in the steroid-unresponsive patients. Because these subjects may also have more severe underlying disease, this finding would be expected [12]. A closer study of peripheral blood monocyte responses, however, revealed higher cytosolic MIF content and higher intranuclear NF- κ B levels in the steroid-resistant group. Experimental reduction of MIF expression in turn increased the cytosolic expression of the NF- κ B inhibitor, I κ B. Conversely, exogenous MIF addition reduced glucocorticoid-induced expression of cytosolic I κ B and increased NF- κ B expression in the steroid-sensitive patients.

Obtaining such functional data in a significant number of clinically defined human subjects is no simple task, as those engaged in studies of human immunologic pathways can attest. One should also appreciate that this MIF-regulated pathway is unlikely to explain all features of glucocorticoid insensitivity; for instance, there is recent evidence that glucocorticoids do not affect NF- κ B activation within plasmacytoid dendritic cells, which may be important initiators of inflammation in SLE [13]. Nevertheless, by providing mechanistic information in human cells and validating one pathway suggested by *in vitro* studies, Wang and colleagues' results have important implications. Their data suggest that differences in MIF expression may be an intrinsic feature of an individual's immune response, a conclusion also supported by a recent study showing significant associations between SLE clinical severity and commonly occurring, high-expression *MIF* alleles [14]. Circulating or cytosolic MIF also may be a useful biomarker for steroid resistance. Wang and colleagues further show inhibition of MIF-dependent upregulation of I κ B by anti-MIF, which is now undergoing clinical evaluation [15]. One may thus envision the contribution of high-expression *MIF* alleles to the development of steroid resistance and the realistic possibility of a pharmacogenomic approach to this problem based on the utilization of MIF antagonists.

Abbreviations

I κ B, NF- κ B inhibitor; MIF, macrophage migration inhibitory factor; NF, nuclear factor; SLE, systemic lupus erythematosus.

Competing interests

RB is an inventor on patents describing the potential therapeutic utility of MIF inhibition.

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