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Review article

Molecular mechanisms of glucocorticoid resistance in systemic lupus erythematosus: A review

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ABSTRACT

The treatment of systemic lupus erythematosus (SLE) with glucocorticoids (GCs) is quite effective; however, GC resistance or insensitivity is a major barrier to the treatment of SLE. Therefore, it is necessary to identify the underlying mechanisms that lead to GC resistance. Much evidence shows that the mechanism of GC resistance is very complicated. GC receptor is involved in the main mechanism of GC resistance and was illustrated by a lot of literature. Therefore, this paper focuses on the GC resistance mechanisms of non-glucocorticoids receptor, including P-gp, MIF, TLR9, and Th17 cells. These molecular mechanisms may help diagnose GC resistance and provide an alternative treatment strategy to reverse GC resistance by blocking the underlying mechanisms.

1. Introduction

Systemic lupus erythematosus (SLE) is a classic autoimmune disease that is characterized by the presence of autoreactive T cells as well as hyperactive B cells that produce autoantibodies, which has varied clinical manifestations and involves multiple systems and organs [1]. Glucocorticoids (GCs) have broad-spectrum anti-inflammatory and immunomodulatory effects on the host immune response. Therefore, GCs are the most effective anti-inflammatory drugs available for SLE [2]. Nevertheless, a few patients with SLE respond poorly or not at all to GCs, a condition known as GC resistance [3]. In this case, increasing the amount of GCs cannot reduce the activity of the disease [4]. GC resistance not only prevents exogenous glucocorticoid therapy from achieving the desired effect, but the condition also precludes the patient's endogenous GC from functioning correctly. As a result, GCs do not bring any benefits to these patients and actually cause serious side effects. Meanwhile, GC resistance is an important barrier to effective treatment and leads to substantial medical expenditures [5]. Therefore, it is of great significance to review the mechanisms of GC resistance to prevent or reduce the occurrence of GC resistance.

The mechanism of GC resistance is very complicated. GC resistance may be due to disease itself, genetic or various epigenetic mechanisms regulating expression of GC receptors and various enzymes metabolizing GCs [6]. The majority of research on the molecular mechanism of GC resistance has been on asthma [5]. Meanwhile, more recent studies have focused on SLE. Experts have demonstrated the role of the GR level in GC resistance [7–9], and some studies have pointed out that structural changes to the GC receptor are related to GC resistance; these changes reduce the GC/receptor complex [10] and affect the pharmacological effects of GCs. In recent years, several factors have been implicated in GC resistance in SLE, including p-glycoprotein, macrophage migration inhibitory factor, Th17 cells, toll-like receptor 9. Understanding these mechanisms is vital for providing an alternative treatment strategy to reverse GC resistance by blocking its underlying mechanisms in SLE.

2. The molecular mechanisms of GC resistance in SLE

2.1. P-glycoprotein

P-glycoprotein (P-gp) is a 170-kDa glycoprotein product of *MDR-1*, a multidrug resistance gene. It is a member of the ATP-binding cassette transporter superfamily [11]. As a drug efflux pump, P-gp transports numerous drugs out of cells (including antibiotics and cytotoxins). P-gp over-expression or hyper-function has been proposed as a possible mechanism of drug resistance in patients with autoimmune disorders. It is widely present in various tissues, including in epithelial cells of the kidney, liver, and intestine, and in endothelial cells in the brain and placenta [12]. Peripheral blood T- and B-lymphocytes also express modest levels of P-gp [13]. Notably, P-gp expression is increased in the

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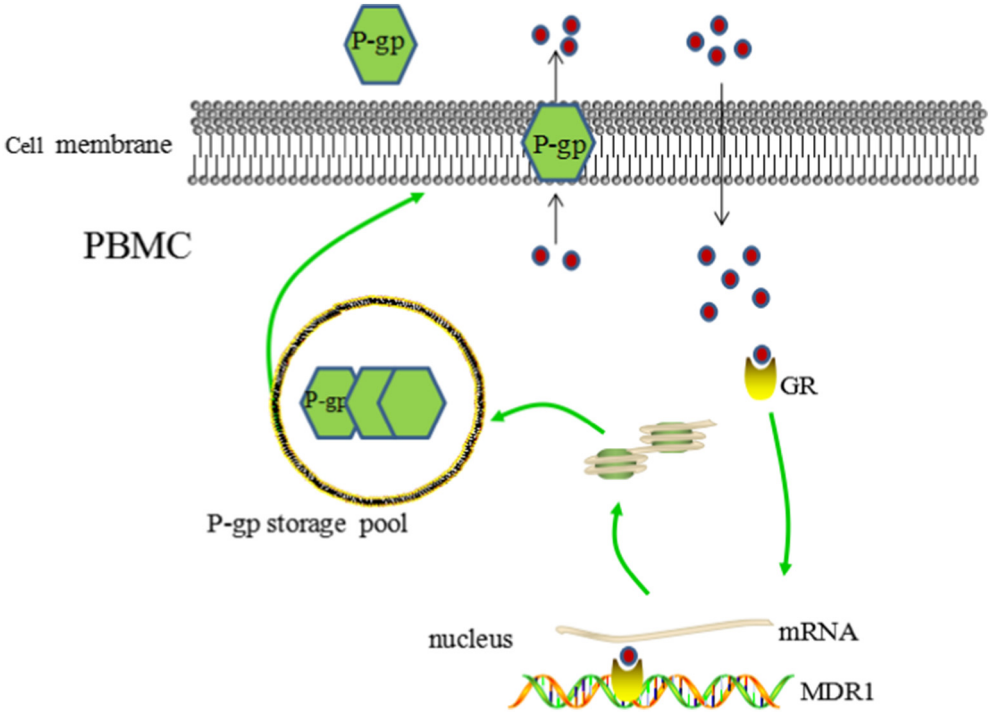

Fig. 1. P-gp-dependent GC resistance in SLE.
P-gp acts as a drug efflux pump that transports GCs out of the cell and reduces the GC concentration in the cell.

peripheral blood lymphocytes (PBMCs) of patients with SLE, and extremely high levels of P-gp have also been found in patients with highly active SLE [14]. P-gp levels and disease activity can be significantly reduced with intensive treatments of methylprednisolone or plasmapheresis [15]. The results of these studies indicate that P-gp overexpression is related to GC resistance. The mechanism is that a large amount of P-gp constantly pushes GCs out of the cell, thwarting the normal function of intracellular hormones. This specific mechanism is illustrated in Fig. 1.

To investigate the correlation between P-gp expression and GC resistance, one study monitored 30 healthy subjects and 60 SLE patients who had received systemic GC treatment for more than 6 months. SLE patients were subclassified into those with active or severely active disease, according to the SLE Disease Activity Index (SLEDAI). P-gp expression in the PBMCs was significantly higher in SLE patients than in healthy controls, and a positive correlation between disease activity. Further, a significant increase in P-gp expression was observed in the severely active compared to the active SLE group [16]. This suggests that elevated levels of P-gp lead to poor disease control by systemic GC therapy. A similar study investigated the effect of GCs on P-gp levels in patients with SLE [17]. After 3 months of therapy, SLE patients were divided into GC resistance and GC-sensitive groups. The two groups were then differentiated based on P-gp expression in PBMCs. The expression of P-gp did not change in the GC-resistant group, but it decreased significantly in the GC-sensitive group. In addition, the same pattern of P-gp expression was also found in serum [14]. Therefore, persistent overexpression and activity of P-gp may be associated with poor response to GCs. P-gp may be a promising indicator of GC-resistance and may assist in using GCs correctly.

2.2. Macrophage migration inhibitory factor

Macrophage migration inhibitory factor (MIF) is an inflammatory cytokine that actively participates in multiple stages of the inflammatory response [18]. There are many MIF proteins in monocytes and macrophages, which regulate endocrine activities in these cells [19]. TNF-α and IFN-γ can stimulate macrophages to release MIF [20]. MIF has also been pointed out to counter-regulate GC-induced expression of MAPK phosphatase-1 (MKP-1), which suppresses the secretion of pro-inflammatory cytokine by GCs signal. MIF also can prevent GC-induced MKP-1 expression [21]. MIF-deficient macrophages show increased sensitivity to GCs following lipopolysaccharides (LPS) stimulation, with higher levels of MKP-1 expression [21] (Fig. 2). MIF can induce macrophages and activated T cells to produce other proinflammatory factors, including TNF-α, IL-1β, IL-2, IL-6, NO, COX-2, and some metalloproteinases, eventually leading to increased inflammation and organ injury in SLE [20,22,23]. The mechanisms suggest MIF impairs GC sensitivity.

MIF is associated with the pathogenesis of SLE [24], MIF concentrations were positively associated with SLE disease damage (SLICC/ACR index) [25]. MIF in PBMCs and its serum concentration were significantly increased in SLE and correlated directly with SLE disease activity [26]. The urine MIF/Cr ratio not only differentiates active disease from inactive or no disease, but it also correlates with the activity indices of renal pathology in patients with lupus nephritis [27]. Some studies have found that MIF was higher in serum and PBMCs in the GC-resistant group than in the GCs-sensitive or health groups [28,29]. Compared with the GC-sensitive group, the NF-κB level was significantly higher in the GC-resistant group, and the level of κB1 was lower. After silencing the MIF gene, the level of κB1 increased. Similarly, when PBMCs from the GC-sensitive group were treated with a recombinant MIF protein, the levels of NF-κB increased and κB1 decreased [30]. These results suggest that MIF may play an important role by affecting amplification of the NF-κB/κB1 signal cascade and indicate that MIF is a potential therapeutic target for sensitive regulation factor of GR [31] (Fig. 2). In addition, low levels of GRα and HSP90 mRNA and a high level of MIF protein are associated with GC resistance. MIF may play a key role in the development of GC resistance by down-regulating HSP90 and destabilizing the balance of HSP90/GRα in SLE patients [7,32]. These data suggest that MIF is important for the development of GC resistance in SLE. Fig. 3 shows the detailed mechanism of MIF.