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The Influence of Tissue-Specific Glucocorticoid System on the Inflammatory Microenviroment: A Mini-Review

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Abstract

Glucocorticoids have been belonged to the most widely and commonly used immune modulatory drugs in autoimmune and inflammatory conditions. The anti-inflammatory and immune suppressant mechanisms have been described. However, the glucocorticoids have paracrine and autocrine manner, acting at local tissue level and that is called as "tissue-specific" glucocorticoids. Those have a significant role in the development of inflammation. The glucocorticoid receptors, the sensitivity for glucocorticoids and the hypothalamic-pituitary-adrenal (HPA) axis are associated strongly in the development, treatment and outcome of the inflammatory diseases. Dysregulation of the immune system and the endogenous glucocorticoid system may contribute to the pathogenesis of chronic autoimmune and inflammatory diseases.

Keywords: Glucocorticoids; Tissue-specific autoimmunity; Microenviroment

Abbreviations:

CBG: Cortisol Binding Globulin; HSD11B1: 11β-Hydroxisteroid Dehydrogenase Enzymes Type 1; HSD11B2: 11β-Hydroxisteroid Dehydrogenase Enzymes Type 2; GCR: Glucocorticoid Receptors; CS: Corticosteroid; GRE: Glucocorticoid Response Elements

Introduction

Glucocorticoids (GCs) are the most commonly described and deeply observed anti-inflammatory agents in the treatment of inflammatory and autoimmune diseases. Due to their immune modulatory effect, decreased endogenous GC level or reduced GC sensitivity might play a significant role in the inflammatory mechanisms and the development of autoimmune diseases [1]. Rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and inflammatory bowel diseases (IBD) are chronic inflammatory diseases with largely unknown aetiology and frequently treated by GCs [2]. The glucocorticoid response is regulated at multiple steps, such as endogenous GCs, glucocorticoid receptors (GRs) hypothalamic-pituitary-adrenal (HPA) axis and inflammatory cytokines. Endogenous GC functions depend on the bioavailability (serum cortisol concentration, the level of glucocorticoid binding globuline) and the activity of GCs, the tissue resistance or sensitivity to GCs, the activity of 11β-hydroxysteroid dehydrogenase enzyme (HSD11B) and glucocorticoid receptors (GRs) [3]. The systemic and local concentration of GCs, their binding to polymorphic GRs can decrease or increase the development of inflammatory diseases. The number of GRs in chronic diseases are usually lower than in healthy controls [4]. The glucocorticoid receptor alpha (GRα) isoform initiate the classical glucocorticoid pathway while the glucocorticoid receptor betas (GRβ) inhibit the GRα. Therefore, GRα is eligible in the anti-inflammatory mechanisms, otherwise the GRβ has a pro-inflammatory effect. In systemic lupus erythaematosus (SLE) some data described the decreased expression of GRα and the increased level of GRβ. These alterations can contribute in the corticosteroid resistency and in the patomechanism of SLE, overall. In this short review, we discuss the impact of the glucocorticoid system on the inflammatory microenvironment and dysregulation of the immune system.

Anti-inflammatory effect of endogenous glucocorticoids

Physiologically, the endogenous GC, such as the therapeutic GC has anti-inflammatory effect. In both type of GC regulate the hypothalamic-pituitary-adrenal (HPA) axis. The most common impact of GCs on inflammation is led by genomic pathways. GCs bind to cytosolic glucocorticoid receptors (GRs) and translocate into the nucleus, bind to the glucocorticoid response elements (GRE) and can modify the inflammation by transactivation and transrepression [4] (Figure 1). The molecular mechanisms of GCs are complex as GRs, binding to special sequences on deoxyribonucleic acid (DNA), may modify the function of various transcription factors, such as NF-κB and activating protein-1 (AP1) and suppress pro-inflammatory gene promoters. The less-known, non-genomic mechanisms can be carried out by interpolation of GCs into cell membranes and modification mitochondrial functions [5]. Recently, researchers hypothesised that both mechanisms can regulate cell and tissue functions. Although the genomic pathway is thought to be more important regarding inflammation, more rapid functions by inhibition of calcium and sodium cycling through the plasma membrane are carried out by membrane-bound glucocorticoid receptors (mGRS) [6]. There is a major role of GC influence on T regulatory (Treg) cells generation. GC influence on T regulatory (Treg) cells generation. T regulatory (Treg) cells are characterized by the transcription factor FOXP3, also. The loss of balance immune responses and peripheral tolerance against antigens

and allergens may lead to autoimmune or inflammatory mechanism. These process can be therapeutically controlled by GCs. Karagiannidis et al. described that glucocorticoid treatment include immunosuppressive and anti-inflammatory effect and also promotes or initiates differentiation toward Treg cells by a FOXP3-dependent mechanism [7].

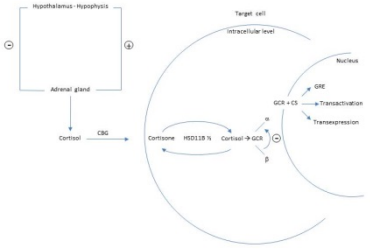

Figure 1: Inflammation by transactivation and transrepression.

Regards to the anti-inflammatory mechanisms, it is very important GCs can regulate both the innate and adaptive immune system. Naive T cells can differentiate into Th1, Th2 and Th17 cells. Th2 cells are increased by IL-4 and IL-5 and inhibit Th1 differentiation. Naive $CD4^+$ cells modify into Th17 cells by IL-17, IL-21 and IL-22. T-cells are also regulated by IL-6, IL-23, IL-21, IL-1β and TGFβ. Although, the effects of GCs on the Th17 development are unknown, it seems that GCs likely inhibit Th17 polarization by suppression IL-23 on dendritic cells (DCs). DCs are crucial in the activation of Th cells, and increased by IL-10, IL-6, and TNFα [8,9]. Flammer et al. and others also observed that several cytokines (IL-10, IL-6, TNFα) and pathogens are GCs-sensitive. Toll-like receptor 2 (TLR2) is activated by bacterial lipoprotein and results secretion of IL-10, IL-6 and TNFα [10]. Some studies have shown that GCs can suppress Th1 cells indirectly via DCs and decrease cytokine levels [11].

Behind the classic pro-inflammatory cytokines - such as tumor-necrosis factor- α (TNFα), IL-6, IL-1β-there is a strong association between autoimmunity and dysregulation of interferon-γ (IFNγ). IFN can be induced by viral and autoimmune effects, leads to IFN regulatory factor (IRF) 3, NF-κB and AP1 and induce transcription of IFN. The early, pro-inflammatory cytokines, type I IFN β and α1, induced by IRF3/NF-κB pathways. IFN molecules binding to their receptors can effect in an auto- or paracrine manner. This manner managed by phosphorylation, heterodimerization, and nuclear translocation of signal transducer and activator of transcription (STAT) proteins [12,13]. Flammer et al have discussed that GC therapy can suppress a third transcription factor, i.e. interferon regulatory factor (IRF9) and STAT2 heterotrimeric complex, known as ISGF3, finally the IFN expression. However, the exact mechanism is not totally known, and it could be regulated by direct or indirect ways. They also emphasized that the main source of IFN-production, the plasmocytoid dendritic cells (pDC) are induced by TLR7/9 activation, therefore the blockade of this persistency and pDCs can normalize ISG expression.

Taking all together, the relationship of GRs, GCs, NF-κB and IRF pathways can regulate the IFN gene expression [10,13].

Response to glucocorticoids in autoimmune disorders

Glucocorticoids still remains the first choice of therapy in autoimmune disorders. However the benefits of GCs, there are some patients who do not respond well to GCs or the long-term GCs therapy can result several side-effects [14]. Several mechanisms can lead to the glucocorticoid-resistance [15].

Among the chronic disorders, the patients with systemic lupus erythaematosus (SLE) usually expect rapid and good response from anti-inflammatory effects of GCs. The two isoforms of glucocorticoid receptors (GRs) recognized as GCRα and GCRβ. GCs do not bind to GCRβ, which inhibits the GCRα- glucocorticoid complex and consequent the GCs action. In SLE patients increased GCRβ and decreased GCRα expressions have been detected in peripheral blood mononuclear cells (PBMCs), T-cells and monocytes as well. The dysregulation of the GRs can correlate with the disease activity. Furthermore, there are other pathways of GC-resistance such as alteration of the GC entering into nucleus, interaction with other cytokines and modification of the GRs [16].

In rheumatoid arthritis (RA) low active cortisol level has been measured, resulted by failure of type-1 11β-hydroxysteroid dehydrogenase enzyme (HSD11B). This phenomenon could basically contribute to the pathomechanism of RA [17]. Van Osten et al. have shown that in rheumatoid arthritis (RA), GC sensitivity is determined by acquired and genetic factors. They have found that GR polymorphisms correlated with GC sensitivity and leads lower risk of developing RA. These prominent polymorphisms are the minor alleles of the N363 S and BclI. Otherwise, the minor alleles of the ER22/2EK and 9β polymorphisms can have relatively great tendency to GC resistance. However the cytokines, which can modulate the acquired GC-resistance, the genetic factors involve the GR polymorphisms and the variants of activity of the HPA axis. van Oosten et al also have shown that GR polymorphisms in RA can associate with age and sex as ER22/23EK in elderly men expected a better survival. Moreover, ER22/23EK polymorphisms and GC-resistance could lead a severe and early onset of RA, significant higher number of patients with this polymorphisms are a candidate for biological therapy [18].

Similar to RA, physicians can expect that GCs are effective in ankylosing spondylitis (AS), as well. There are some research about GC-resistance in AS and demonstrated that GRβ mRNA expression was significantly increased in the PBMCs in patients with AS [19]. Chang-Keun Lee et al. have shown that there were not strong correlation between the ESR and CRP and the GRβ messenger ribonucleotid acid (mRNA) level. This phenomenon was also detected in RA patients, DAS28 did not correlate with the expression of GRβ mRNA, also. Therefore, the systemic inflammation in RA and AS do not induce GRβ mRNA expression in the PBMCs [20].

In autoimmune hepatitis (AIH) - like in RA and AS - some paper have reported that increased GRβ in PBMCs in response to TNFα and IL-1 was measured. There are some controversies about the GRβ levels and disease activity, as Hasain et al. suggested that the TNFα and IL-1 were found correlated with disease activity. Contrary, Rai et al. did not confirm this strong association [21].

The micro-environmental background in inflammatory bowel diseases (IBD) plays a significant role regarding disease activity, outcome and response to therapy.

However, some studies suggest that most glucocorticoid resistance in peripheral leukocytes do not compare responder patients and non-

responders [22]. Flood et al. have demonstrated that there is not significant difference in GRs mRNA expression in patients with ulcerative colitis (UC) resistant or sensitive to GCs. Although, Honda et al. reported that increased GRβ-specific mRNA expression was detected patients with steroid-resistant UC contrary to steroid-responsive patients. These results suggest that beside the GRs diversity, the relative GC-resistance depends on the T-lymphocytes, the local microenvironment and the inflammatory cytokines. Moreover, researchers strongly emphasise the fact, that GC-resistance may be determined genetically, but the microenvironment, GR diversity and the multidrug protein 1 (MDR-1) can modify the responsiveness [23].

Disease heterogeneity is also a main cause of GC-resistance in IBD. Farrell et al. focused on genetic factors associated with various disease phenotypes may lead to the different response to GC therapy. They showed higher incidence of perinuclear anti-neutrophil cytoplasmic antibody in steroid refractory UC. Among Crohn-disease (CD) patients the mutations of nucleotide-binding oligomerization domain-containing protein 2 (NOD2) gene result strong binding to bacterial endotoxin and therefore significant increased nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and TNFα production. So, researches on all the GRs, NOD2, MDR1 gene polymorphisms and the microenvironmental space can be prominent targets to help us to understand GC-resistance in IBD [24].

Summary

There are increasing evidences about the effects of exogenous and endogenous glucocorticoids in autoimmune and chronic inflammatory diseases [2]. Glucocorticoids can suppress the inflammatory process, but the local microenvironment, the tissue-specific system can also modify the response to GCs [1,2] There are several mechanisms,-for example the extracellular and intracellular conditions, alteration of genetic factors- may contribute to the phenomenon that some patients do not respond well to GC therapy [10] Understanding to these mechanisms may result to specify the patients who are not the proper candidates to GC therapy or we can dosage the GCs, precisely or avoid the side effect, well before.

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