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Review

Assessment of genomic and non-genomic molecular indicators for the development of steroid resistance in dermatoses of various etiologies

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ABSTRACT

Resistance to systemic glucocorticosteroids in various dermatological conditions represents a serious clinical problem, often leading to treatment failure and exacerbation of the disease. The purpose of the review is to determine the relationships between association of genomic and non-genomic molecular factors and steroid resistance development in dermatoses of various etiologies. Genomic factors, including glucocorticoid receptor polymorphisms and changes in steroid metabolizing enzymes, may alter patient sensitivity to systemic glucocorticosteroids. All authors individually carried out a search of the available literature through PubMed, ScienceDirect, Wiley Online Library, Google Scholar, Cochrane Library, and MeSH using such key words "glucocorticoid receptor," and "glucocorticoid resistance," and "macrophage migration inhibitory factor," and "P-glycoprotein," and "polymorphism NR3C1," and "systemic lupus erythematosus," and "bullous pemphigoid," and "pemphigus vulgaris," and "atopic dermatitis."

Out of 23 analyzed sources, 8 studies were selected that describe various genomic and nongenomic factors potentially influencing the development of steroid resistance in a vast variety of skin conditions including pemphigus, bullous pemphigoid, atopic dermatitis, nummular eczema, localized neurodermatitis, lichen planus, and cutaneous and systemic lupus erythematosus.

We found that the mechanisms of steroid insensitivity were thoroughly studied in patients with systemic lupus erythematosus, including its cutaneous manifestations. Moreover, they differ in all these diseases. Meanwhile, the mechanisms underlying steroid resistance in other dermatological diseases are currently not fully understood. It is of a paramount importance to investigate mechanisms of steroid insensitivity and develop a panel of biomarkers which could predict steroid resistance in advance to optimize therapy of these conditions.

Keywords: systemic glucocorticoids; glucocorticoid receptors; steroid resistance; sensitivity to glucocorticoids.

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Научный обзор

Оценка влияния геномных и негеномных молекулярных механизмов на развитие стероидной резистентности при дерматозах различной этиологии. Систематический обзор

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АННОТАЦИЯ

Устойчивость к системным глюкокортикоидам при различных дерматологических заболеваниях представляет серьёзную клиническую проблему, обусловливающую неэффективность лечения и обострение заболевания. Геномные факторы, включая полиморфизм глюкокортикоидных рецепторов и изменения ферментов метаболизма стероидов, способны изменять чувствительность пациентов к системным глюкокортикоидам.

Авторами обзора выполнен анализ влияния геномных и негеномных молекулярных механизмов на развитие стероидной резистентности у дерматологических больных, для чего в базах данных доказательной медицины (PubMed, ScienceDirect, Wiley Online Library, Google Scholar, Cochrane Library и MeSH) осуществлялся поиск опубликованной литературы по указанной тематике. Поиск исследований проводился по таким ключевым словам, как «glucocorticoid receptor», «glucocorticoid resistance», «macrophage migration inhibitory factor», «P-glycoprotein», «polymorphism NR3C1», «systemic lupus erythematosus», «bullous pemphigoid», «pemphigus vulgaris», «atopic dermatitis». Из 23 проанализированных источников было выбрано 8 исследований, описывающих различные геномные и негеномные факторы, которые потенциально могут влиять на формирование стероидной резистентности у пациентов с такими заболеваниями, как пузырчатка, буллёзный пемфигоид, атопический дерматит, нумулярная экзема, ограниченный нейродермит, красный плоский лишай, кожная форма системной красной волчанки.

Проведённая нами поисково-аналитическая работа позволила установить, что патогенез стероидной резистентности наиболее подробно изучен только для системной красной волчанки, в том числе с кожными проявлениями, при этом механизмы формирования стероидной резистентности при других дерматологических заболеваниях в настоящее время до конца не изучены. Кроме того, следует отметить, что механизмы её формирования при этих заболеваниях отличались. Исследование новых механизмов развития стероидной резистентности, а также разработка универсальных биомаркеров стероидной резистентности позволит усовершенствовать и оптимизировать терапию рассматриваемых дерматозов в будущем.

Ключевые слова: системные глюкокортикоиды; глюкокортикоидный рецептор; стероидная резистентность; чувствительность к глюкокортикоидам.

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ABSTRACT

The most widely used anti-inflammatory drugs in dermatology are systemic glucocorticosteroids (SGCs) [1]. SGCs are steroid hormones that affect a variety of physiological processes in the body, including glucose and fatty acid metabolism, inflammatory and immune responses, behavior, and the functioning of the central nervous system, the gastrointestinal tract, and the reproductive system [2].

SGCs are mediated by glucocorticoid receptors (GRs) [3], which belong to the nuclear receptor superfamily, as do receptors for mineralocorticoids, thyroid and sex hormones, vitamin D, and retinoic acid [4]. When binding to SGCs in the cytoplasm, GRs increase or decrease the transcription of target genes involved in metabolism and stress and inflammatory responses. The member 1 gene of group C of subgroup 3 (*NR3C1*) encoding GR is located on chromosome 5q31 [5]. The GR gene comprises nine exons, with exon 1 forming the 5'-untranslated region (5'-UTR), exon 2 forming the N-terminal domain (NTD), exons 3 and 4 forming the DNA-binding domain (DBD), and exons 5 to 9 forming the C-terminal ligand-binding domain (LBD) [6]. The promoter regions of the GR gene contain binding sites for several transcription factors, including nuclear factor kappa B (NF-kB), activating protein-1 (AP-1), and GR itself. These promoters contain several GC boxes and lack characteristic TATA and CAAT boxes [4]. Thirteen alternative variants of exon 1 were identified, resulting in different levels of expression of GR isoforms in cells and tissues due to differential usage [7].

Multiple GR isoforms are known to be produced as a result of alternative splicing and the use of eight different translation initiation sites [7]. Exons 1 and 9 of the GR gene are alternatively spliced [4]. Splicing of exon 9 of the immature messenger ribonucleic acid (mRNA) of GR results in the formation of two distinct mRNAs: the GR α-isoform and the GR β-isoform [4]. Both GR isoforms are identical up to amino acid 727; however, the GR α-isoform contains 50 additional amino acids, whereas the GR β-isoform contains 15 non-homologous amino acids [8]. The β-isoform cannot bind to SGCs, but has a dominant negative effect on the α-isoform, competing for binding sites and forming α/β heterodimers [7]. In the absence of ligand, GR localizes to the cytoplasm and binds to heat shock proteins (HSP90, HSP70, and HSP40) [5], Hip, Bag-1, Hop, CHIP, p23, immunophilins of the FK506 binding protein family (FKBP51 and FKBP52), and protein phosphatase 5 [2].

INFLUENCE OF MOLECULAR MECHANISMS ON THE DEVELOPMENT OF STEROID RESISTANCE

Genomic mechanisms

Upon binding to SGCs, the receptor undergoes a conformational change, disengages from chaperone proteins, and enters the cell nucleus [4]. In the nucleus, GR suppresses the expression of pro-inflammatory genes or enhances the expression of anti-inflammatory genes [9]. This is facilitated by the binding of GR to the glucocorticoid regulation element (GRE) of the promoter region of a glucocorticoid-sensitive gene, or by the interaction between DNA-bound GR and a transcription coactivator [10]. Negative GRE (nGRE) mediates glucocorticoid-dependent repression of specific genes [11]. The principal anti-inflammatory effect of SGCs is attributable to the protein-protein interaction between GR and transcription factors that modulate the expression of pro-inflammatory genes, such as AP-1 and NF-kB [4]. Target genes include the majority of inflammatory mediators, including chemokines, cytokines, growth factors, and their receptors [9]. Genes that are activated by SGCs encode for β2-adrenergic receptors and anti-inflammatory receptors, secretory leukoprotease inhibitor, and mitogen-activated protein kinase phosphatase 1 (MKP1) [10].

Non-genomic mechanisms

In addition to the classical genomic action of SGCs, there is a non-genomic mechanism that does not involve changes in gene expression and causes a rapid cellular response [11]. The rapid effects of SGCs include the following: inhibition of adrenocorticotropic hormone release from the pituitary gland, increase in the frequency of excitatory postsynaptic potentials in the hippocampus, cardioprotective effect on patients experienced a myocardial infarction or stroke, and immunomodulatory effects associated with disruption of T-cell receptor signaling [12].

Despite the availability and efficacy of SGCs in the treatment of inflammatory diseases, some patients do not respond even to high doses of SGCs [13]. Resistance to high-dose SGCs was described in inflammatory diseases such as bronchial asthma and chronic obstructive pulmonary disease [14], rheumatoid arthritis [15], and ulcerative colitis [16]. This resistance poses a substantial challenge in the management of various dermatological conditions, including pemphigus vulgaris (PV), systemic lupus erythematosus (SLE), eczema,

bullous pemphigoid (BP), atopic dermatitis (AD), lichen planus (LP), and localized neurodermatitis (LN) [22].

The study analyzed the influence of various molecular mechanisms on the development of steroid resistance (SR) in dermatological patients using PubMed, ScienceDirect, Wiley Online Library, Google Scholar, Cochrane Library, and MeSH databases. The following keywords were used: "glucocorticoid receptor," "glucocorticoid resistance," "macrophage migration inhibitory factor," "P-glycoprotein," "NR3C1 polymorphism," "systemic lupus erythematosus," "bullous pemphigoid," "pemphigus vulgaris," and "atopic dermatitis". A total of 23 papers were analyzed, of which eight papers were included in the study (Fig. 1) [3, 17, 22–27].

BULLOUS DERMATOSES

P-glycoprotein levels in peripheral blood mononuclear cells in pemphigus

P-glycoprotein (P-gp) is a protein that facilitates the transport of various drugs into the cell through the cell membrane [28]. The overexpression of this protein is associated with multidrug resistance, which refers to the ability of cells to resist the effects of multiple drugs used in chemotherapy, HIV, and parasitic infections [29]. Consequently, increased P-gp expression on peripheral blood lymphocytes may result in the efflux of SGCs, thereby contributing to the development of steroid resistance mechanisms [26].

Fuente et al. [23] investigated the expression of P-gp in mononuclear cells of resistant (n=8) and sensitive to therapy patients with pemphigus (n=12) using flow cytometry and real-time polymerase chain reaction (PCR). A subsequent comparison of P-gp expression levels before and after treatment in both study groups revealed no statistically significant differences (see Appendix 1). Based on these findings, the authors concluded that P-gp does not play a role in the pathogenesis of resistance to SGCs.

Expression of the α- and β-isoforms of the glucocorticoid receptor in bullous pemphigoid

Kubin et al. [3] evaluated the expression of GR α- and β-isoforms in patients with BP by real-time quantitative PCR (qPCR), as well as the effect of SGC therapy on this expression. Sixteen patients with BP (study group) before SGC therapy and 17 patients with non-melanoma skin cancer (control group) participated in the study. The mRNA expression of the GR α-isoform was detected in all investigated and control samples, while the GR β-isoform was detected only in 13 patients with BP and 12 participants of the control group (see Appendix 1). Interestingly, when immunoblotting was used, increased expression of the GR β-isoform was observed in only four out of six patients with BP, which may be due to differences in sensitivity of the methods. Furthermore, the GR α-isoform expression on Days 5 and 14 of prednisolone treatment exhibited variability. On Day 60, the GR α-isoform expression increased in nine patients, decreased in four patients, and remained at the pretreatment level in one patient. The authors found that the GR β-isoform expression was activated in the early stages of SGC therapy, remained elevated on Day 60 of prednisolone treatment in five patients, decreased in seven patients, and returned to baseline in one patient (see Appendix 1). Thus, the GR isoform expression in BP patients changed during SGC therapy. However, a statistically significant correlation between the GR expression and prolonged use of SGCs was not observed. Nonetheless, the increase of the GR β-isoform on Day 5 of therapy in the majority of patients offers valuable insights for subsequent research. This study is limited by the small sample size. Furthermore, no correlation was identified between the expression of GR isoforms and the disease activity marker (BP180).

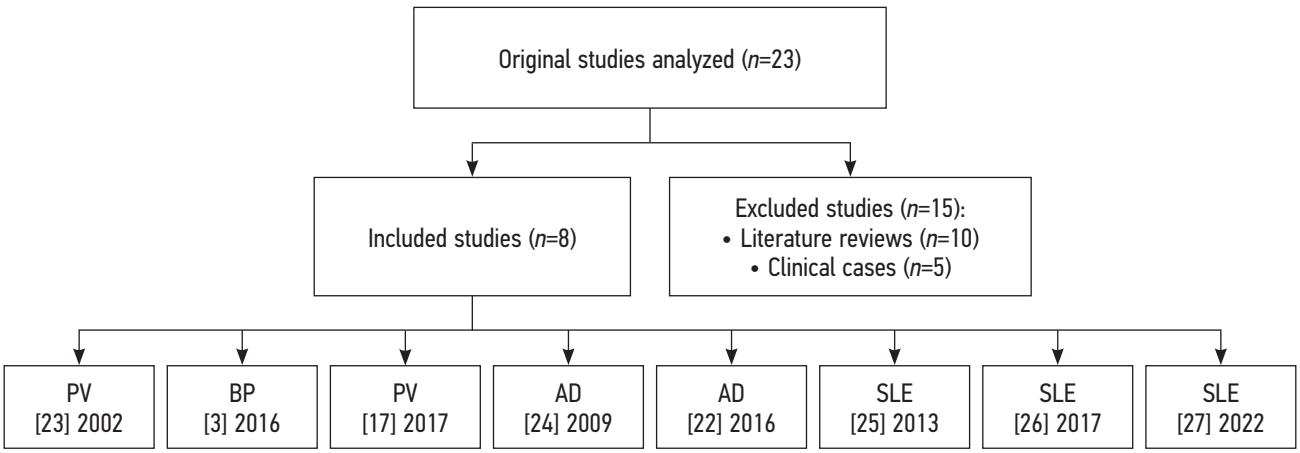

Fig. 1. Selected scientific literature for further analysis. PV: pemphigus vulgaris; BP: bullous pemphigoid; AD: atopic dermatitis; SLE: systemic lupus erythematosus.

Given the ongoing debates surrounding the role of the increased GR β-isoform expression in the development of SR, it is hypothesized that genetic mechanisms, particularly the presence of various polymorphisms in the *NR3C1* gene encoding GR, contribute significantly to its development. For example, Fang et al. [17] studied single nucleotide polymorphisms (SNPs) of GR in 94 patients with pemphigus and 100 healthy donors. The results revealed that the SNPs such as rs11745958C/T (OR=8.95), rs17 209237A/G (OR=4.07) and rs33388A/T (OR=0.45), and rs7701443A/G (OR=0.51), increased and decreased, respectively, the risk of developing SR in patients with pemphigus. All patients received prednisolone 0.50–0.75 mg/kg daily. Patients were divided into two groups: those exhibiting steroid resistance (SR+; *n*=64) and those exhibiting steroid sensitivity (SR–; *n*=30). Genotyping of SNPs at five sites in the coding region of the *NR3C1* gene was performed by mass spectrometry (see Appendix 1).

ALLERGIC DERMATOSES

Expression of the β-isoform of the glucocorticoid receptor in lymphocytes of patients with severe atopic dermatitis resistant to topical steroids

Hägg et al. [24] investigated the mRNA and protein expression of GR α- and β-isoforms in lymphocytes of patients with AD (*n*=23) before and after treatment with topical SGCs using PCR and Western blotting. The study included patients with mild (*n*=10) and severe (*n*=13) AD. Disease severity and treatment efficacy were determined using the Eczema Area and Severity Index (EASI). The study indicated the expression of GR α-isoform mRNA in all patients and control subjects. GR β-isoform mRNA was detected in 4 of 11 (36%) patients in the control group, in 5 of 10 (50%) patients with mild AD, and in 11 of 13 (85%) patients with severe AD (see Appendix 1). The frequency of the GR β-isoform mRNA expression was higher in patients with severe AD: 85% vs. 50% in patients with mild AD and 36% in controls (*p*=0.033).

Western blot analysis supported these findings, confirming the presence of GR α-isoform protein in all study participants, including the control group. In contrast, GR β-isoform protein was not detected in the control group (see Appendix 1).

Changes in the expression of the major GR isoforms after topical GCS therapy were determined in patients with severe AD using qPCR. Four out of 13 patients had no significant clinical response to treatment (EASI score decreased by <8%). Following a two-week period, a significant increase in the GR β-isoform mRNA expression was detected in these insensitive patients. The remaining nine patients had a good or very good response to local treatment (EASI score decreased by 48%±9% and 87%±4%, respectively), whereas the GR β-isoform mRNA expression increased slightly (0–2 to 9-fold, respectively).

In addition, the authors examined the quantitative change in the levels of GR protein isoforms during two weeks of therapy using Western blotting of samples from two patients with severe AD who did not respond to GCS therapy. In patient No. 8, the GR β-isoform was present before and after treatment; the GR β-isoform expression increased 2-fold during therapy, whereas GR α-isoform expression did not change. In patient No. 12, only the GR α-isoform expression was detected before treatment; the GR β-isoform expression was detected during therapy, whereas the GR α-isoform expression increased 5-fold over time.

Accordingly, the researchers were able to assess the increased expression of the GR β-isoform in lymphocytes of patients with AD during GCS therapy and associated it with insensitivity to the therapy in 4 out of 13 patients with severe AD. The results provide further insight into the mechanisms of SR. The GR β-isoform expression in patients with inflammatory skin diseases may be considered as a potential marker of resistance to SGCs and serve as a basis for repeated tests.

Expression of α- and β-isoforms of the glucocorticoid receptor in atopic dermatitis, nummular eczema, and localized neurodermatitis

Kubin et al. [22] evaluated the expression of GR α- and β-isoforms in lymphocytes, neutrophils, and keratinocytes of affected skin areas of patients with AD (*n*=8), LP (*n*=10), nummular eczema (NE) (*n*=9), and LN (*n*=11) using immunohistochemical analysis (see Appendix 1). Notably, the authors detected the GR α-isoform expression in the nuclei and cytoplasm of keratinocytes and lymphocytes in the affected skin of the patients for the first time. The strongest nuclear staining of the GR α-isoform in keratinocytes was observed in skin biopsy specimens of patients with LP. The second disease by the content of GR nuclear α-isoform staining was NE, whereas keratinocytes from AD patients exhibited the lowest nuclear staining of the GR α-isoform (see Appendix 1). A direct correlation between the nuclear expression of GR α- and β-isoforms in keratinocytes was observed in all patients (*p*=0.538 and *p*=0.000414, respectively). Furthermore, the GR β-isoform was also detected in the cytoplasm and nuclei of cells (see Appendix 1). In contrast to the GR α-isoform, which was observed in low amounts in neutrophils in LP, NE, and undetectable in LN, the GR β-isoform exhibited strong cytoplasmic staining in all samples.

The second part of the study evaluated the effect of SGC therapy on the GR α- and β-isoform expression in 13 patients with severe AD. Disease activity and treatment efficacy were assessed by the EASI. The study found that three patients

exhibited no response to therapy (EASI <7%), five cases demonstrated a moderate response (EASI 17.4%–37.4%), and five patients exhibited an adequate response to therapy (EASI 46.8%–70%). The expression levels of GR α- and β-isoforms were evaluated prior to treatment and on Days 3 and 14 from the start of therapy by analyzing peripheral blood mononuclear samples using qPCR. On Day 3, there was an increase in the GR α-isoform expression in five patients, a decrease in seven patients, and no changes in one patient. On Day 14, the GR α-isoform expression continued to decrease in four patients. The expression levels of GR β-isoforms on Day 3 exhibited an increase in eight patients and a decrease in five patients. On Day 14, the increase in expression persisted in four out of eight patients, while the decrease was observed in only one patient (see Appendix 1). Interestingly, in two patients with AD, a direct correlation was observed between the lack of response to SGC therapy and increased expression of the GR β-isoform. Notably, these patients exhibited concurrent decreased expression of the GR α-isoform.

The researchers quantitatively analyzed the expression levels of GR α-isoform mRNA and GR β-isoform mRNA in response to prednisolone treatment. Their findings revealed a statistically non-significant decrease in mean GR α-isoform mRNA levels (p=0.735) and a concomitant increase in mean GR β-isoform mRNA levels (p=0.191). These observations, while not reaching statistical significance, warrant further consideration in subsequent studies.

In addition to PCR, western blotting was used to confirm the expression of GR α- and β-isoforms (see Appendix 1).

However, the authors did not provide data on immunohistochemical staining of skin biopsy specimens.

The influence of the GR isoform expression on sensitivity to SGCs remains poorly understood. However, the findings of decreased mean mRNA levels of the GR-α isoform in combination with increased mean mRNA levels of the GR-beta isoform, as well as the finding of a direct relationship between receptor concentration and resistance to SGCs in a small proportion of the patients, make an important contribution to the study of this problem.

Due to the study's limitations, including the duration of therapy, the duration of patient follow-up, and a small sample size, the findings should be tested in a larger sample of patients with prolonged follow-up periods.

SYSTEMIC LUPUS ERYTHEMATOSUS

SLE is an autoimmune disease with a wide variety of clinical manifestations, including lesions of many organs, especially the skin [30]. According to Yell et al. [31], skin lesions occur in more than 70% of SLE cases and may be the first symptom of the disease.

Melo et al. [25] proposed that the level of NF-kB expression impacts sensitivity to SGCs in patients with SLE. The study encompassed patients in remission (n=9) and healthy individuals (control group; n=10). The authors performed loading tests, including oral dexamethasone suppression test (DST) and very low-dose intravenous dexamethasone suppression test (VLD-IV-DST), to determine the level of sensitivity to SGCs. GR α-isoform and NF-kB mRNA levels were measured by qPCR. Sensitivity to SGCs was assessed by the percentage of cortisol reduction after the VLD-IV-DST (F, %) and the degree of cortisol suppression (FOr, %) after the DST. The study revealed no statistically significant association between the expression of the GR α-isoform, NF-kB, and SR, as assessed by F, % after VLD-IV-DST and FOr, %, respectively (see Appendix 1).

Serum P-glycoprotein levels in patients with systemic lupus erythematosus

Perez-Guerrero et al. [26] evaluated the relationship between P-gp levels and the activity of SLE after SGC therapy. The study used the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and included patients (n=93) with active (SLEDAI ⩾3) and inactive (SLEDAI <3) forms of the disease, as well as a healthy control group (n=43). Serum P-gp levels were measured using an enzyme-linked immunosorbent assay (ELISA). The results indicated that patients with active SLE exhibited higher P-gp levels after treatment in comparison to patients with inactive disease (p=0.018), as well as higher levels than in the control group (p=0.011) (see Appendix 1). Furthermore, a correlation was identified between serum P-gp levels, the degree of disease activity, as defined by SLEDAI (r=26; p=0.01), Mex-SLEDAI (the Mexican version of SLEDAI scale; r=0.32; p=0.002), SLICC/ACR (Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; r=0.47; p <0.01), and prednisolone dosage (r=0.33; p=0.001) (see Appendix 1).

Evaluation of the association between macrophage migration inhibitory factor and P-glycoprotein levels in steroid-resistant patients with systemic lupus erythematosus

Macrophage migration inhibitory factor (MIF) is a cytokine that inhibits the suppression of pro-inflammatory cytokine secretion activated by macrophages. The effect of MIF is mediated by SGCs [32].

Beltrán-Ramírez et al. [27] evaluated the relationship between the levels of MIF and P-gp and SR in patients with SLE (n=188). Sensitivity to SGCs was evaluated using the SLEDAI. The steroid-sensitive group (n=98) included patients with SLEDAI 3, and the SR group (n=90) included patients with SLEDAI 4. The serum levels of MIF and P-gp were then measured by ELISA. The results showed that the SR group had higher MIF levels compared to the steroid-sensitive group (p <0.001). Similarly, the SR group had higher P-gp levels compared to the steroid-sensitive group (p <0.001) (see Appendix 1).

Serum MIF levels demonstrated a positive correlation with P-gp levels. Furthermore, serum P-gp levels were found to be associated with GCS dosage, indicating that higher prednisolone dosages were associated with higher P-gp levels. However, no such relationship was observed between drug dosage and MIF levels.

The present study sought to ascertain the threshold levels of MIF and P-gp that corresponded to the absence of response to SGCs in patients. The findings revealed that serum P-gp levels exceeding 15.22 ng/mL were the major contributing factor to SR. Additionally, MIF levels higher than 15.75 ng/mL emerged as a risk factor for SR, particularly in patients who exhibited low P-gp levels (see Appendix 1).

RISK FACTORS FOR STEROID RESISTANCE IN DERMATOSES OF VARIOUS ETIOLOGIES

This review presents the main known mechanisms of SR in dermatological patients. According to the analyzed sources, genetic factors, especially the polymorphism of the *NR3C1* gene encoding GR, are the main contributors to its development in patients with bullous dermatoses. However, this mechanism is not universal for the formation of SR. For example, Xuan et al. [33] found no association between the *NR3C1* gene polymorphism and sensitivity to SGCs in thrombocytopenic purpura. Additionally, the role of P-gp in the pathogenesis of SR in patients with PV was not substantiated. The relationship between the GR β-isoform expression and a marker of BP activity (BP180) was not confirmed. However, the role of the GR β-isoform is important in the development of SR, since a rapid increase in the GR β-isoform expression was observed in the early stages of treatment of patients with BP [3].

In contrast, in inflammatory diseases such as rheumatoid arthritis [34] and ulcerative colitis [35], the expression of GR α- and β-isoforms plays an important role in the efficacy of SGC therapy. The search for SR factors in allergic dermatoses remains relevant. The authors of two studies found a correlation between the increase in the average concentration of the GR β-isoform and the lack of therapeutic effect in several patients. The result obtained is likely attributable to the inherent limitations concerning the duration of the follow-up period, the duration of therapy, and the number of patients included in the study. Currently, the effect of the increased β-isoform expression on the development of SR in allergodermatoses has not been demonstrated. This represents a promising area for future research.

In addition, the mechanism of resistance to SGCs at the receptor level was investigated in bullous dermatoses. For example, an increased level of P-gp expression on peripheral blood lymphocytes in pemphigus was observed, which promoted an increased outflow of SGCs from the cell [26].

The pathogenesis of SR in SLE, particularly in relation to cutaneous lesions, was the subject of extensive research. Increased activity of P-gp and MIF was detected in patients who do not respond to SGC therapy. The concentration of P-gp was shown to correlate with the severity of the disease and the dosage of SGCs. This suggests that high levels of P-gp and MIF may serve as reliable risk factors for SR in SLE with cutaneous lesions.

CONCLUSION

A review of the literature on the influence of genomic and non-genomic molecular mechanisms on the development of SR in dermatological patients reveals several conclusions. Currently, there are no universal biomarkers for SR, and the mechanisms of its formation in various dermatological diseases remain to be fully elucidated. A more in-depth study of these mechanisms is therefore essential for the development of a strategy for overcoming SR and for the timely selection of optimal personalized therapy for a variety of dermatoses.

ADDITIONAL INFORMATION

Supplement 1. Mechanisms of steroid resistance formation.
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