EXPLORING MULTIFACTOR-MEDIATED DYSFUNCTIONAL MODULES IN PSORIATIC AND PREDICTING POTENTIAL DRUG TARGETS

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ABSTRACT

Psoriasis is a chronic inflammatory skin disease that is long-lasting and prone to recurrence, seriously affecting the health and mental state of patients. However, we still know very little about its pathogenesis and treatment. Therefore, this study explores the psoriasis dysfunction module mediated by multiple regulators to predict its potential drug and drug targets. In this work, we identified 23 dysfunctional modules based on the co-expression of potential pathogenic genes and functional and KEGG pathway enrichment. Further, by deciphering the regulators of these dysfunctional modules, we revealed a series of genes (including CDK1, UBE2N and MAPK8, etc.), ncRNAs (including miR-92a-3p, miR-146a-5p, etc.) and transcription factors (including TP53, RELA, NFKB1, STAT1, etc.) may be involved in the pathogenesis of psoriasis. Finally, based on these multifactor-mediated dysfunctional modules, we predicted potential drugs for the treatment of psoriasis (including copper, polaprezinc, zinc, etc.), which have significant regulatory effects on dysfunction and may have pharmacological or toxicological effects for psoriasis. We observed the effects of these drugs on the module genes and predicted the potential drug targets of these drugs (including S100A2, S100A4, APP, etc.). These potential drugs and targets provide a valuable reference for drug developers to conduct drug re-positioning and new drug development. In summary, the strategy for exploring the multifactor mediated dysfunction modules provides a new way to discover the underlying pathogenesis of psoriasis and its treatment strategies, which can also be widely applied to other disease research.

Keywords: *Psoriasis, WGCNA, drug, regulated network, pathogenesis.*

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Introduction

Psoriasis is an inflammatory immune-mediated skin disease with potential pathogenic effects of systemic complications such as arthritis, depression, inflammatory bowel disease and cardiovascular disease[1, 2]. It not only has a serious impact on the patient's physical and mental health and quality of life, but also caused a worldwide social and economic burden[3, 4]. Therefore, research on the pathogenesis and treatment mechanism of psoriasis is urgent. Fortunately, many biologists and medical researchers have invested in the exploration of psoriasis pathogenesis, physiological processes and treatments, and have achieved some results. For example, Ammar M et al. followed a 10-year genome scanning to track more than a dozen sites of several candidate genes of psoriasis "PSORS"[5]. In addition, more and more studies have shown that the pathogenesis of psoriasis is complex and involves a variety of biological mechanisms, such as immunization with interleukin (IL-12, IL-17, IL-23) and chronic inflammation[6, 7].Therefore, antibody drugs targeting these cytokines have become a new method for the treatment of psoriasis[6-8]. On the other hand, biologists have also identified a series

of psoriasis-related signaling pathways that affect a variety of physiological processes and mediate disease. Skarmoutsou E et al. found that in the skin of patients with psoriasis, the mRNA and protein levels of NOTCH1, NOTCH2, JAGGED1 and HES1 in the Notch pathway are significantly up-regulated, affecting cell proliferation, differentiation, and development of immune cells. Function[9]. In addition, the Wnt/β-catenin signaling pathway is inhibited by progranulin protein (PGRN) in the skin of patients and promotes keratinogenesis and autophagy[10, 11]. Other potential effects of immune-associated signaling pathways such as the TGFbeta/Smads pathway, the c-Jun N-terminal kinase (JNK)-phospho-c-JUN (ser63/73) pathway on psoriasis are also widely accepted[12, 13]. However, a comprehensive understanding of the basic mechanisms and key molecular targets of psoriasis remains to be explored.

After decades of intensive research, the progression of psoriasis is primarily related to 550 key molecules. However, the underlying pathogenesis of psoriasis should include factors that are multifactorial and multi-biological, such as changes in gene expression, transcriptional or post-transcriptional regulatory abnormalities, genetic factors, and even microbial infections[14]. Therefore, the complex pathogenesis of psoriasis should be analyzed at the global level rather than on a single factor. Moreover, this comprehensive exploration is important and necessary to obtain a comprehensive and accurate understanding of the psoriasis mechanism.

Therefore, in order to explore the complex pathogenesis of psoriasis, global and integrated network approaches should be encouraged to increase the likelihood of identifying potential molecular targets. In order to solve this problem more properly, we have introduced a multidimensional integration strategy based on gene expression profiling, protein-protein interaction (PPI) and transcriptional and post-transcriptional regulatory data to identify biologically significant dysfunction modules in complex pathogenic mechanisms. Reveal potential molecular targets by deciphering the internal drive genes of these dysfunctional modules. In addition, based on these multifactor mediated dysfunction modules, we predicted potential drugs and targets for the treatment of psoriasis. In summary, our comprehensive strategy not only provides new insights into the underlying pathogenesis and treatment mechanisms of psoriasis, but also provides a new way of thinking for other disease research.

Materials and methods

Data resources

In this experiment, whole blood samples of 3 normal people and 9 psoriasis patients were collected. Gene expression microarray datasets (GSE53552[58]) were downloaded from the NCBI Gene Expression Omnibus (GEO) database[59], including 50 psoriasis-injured skin samples of 25 patients.

In addition, psoriasis-related genes were curated from NCBI Gene database[60] and OMIM database[61]. For explored the relationships between psoriasis-related genes, protein-protein interactions in human were curated form STRING database[62], with score >900.

PCR array

These whole blood samples were incubated and centrifuged at room temperature. After sufficient lysis, we obtained the total RNA of sample and reverse-transcribed it into cDNA. Finally, a quantitative PCR experiment was performed. These experimental steps followed the guidelines of Urumqi Yingjie Leading Biotechnology Co., Ltd. and ensured that all samples were treated the same. All experiments were informed and agreed by all volunteers.

Identified co-expression modules

To explore the synergistic expression of these potential pathogenic genes in psoriasis, we performed weighted gene co-expression network analysis (WGCNA)[63] to analyze the gene expression profile of psoriasis-related genes and identify gene co-expression modules. Unlike general clustering methods, the WGCNA clustering criteria are biologically significant. It takes the nth power of the gene expression correlation coefficient, so that the distribution of the correlation coefficient values gradually conforms to the scale-free distribution. Then, based on cohesion, a hierarchical clustering tree is constructed by correlation coefficients between genes. Genes with similar patterns are grouped into the same branch, and different branches of the cluster tree represent different gene modules. Therefore, the results obtained by this method have higher credibility.

Functional and pathway enrichment analysis

The Clusterprofiler package of R[64] was performed for GO functional enrichment (pvalueCutoff=0.01, qvalueCutoff=0.01) and KEGG pathway enrichment (pvalueCutoff=0.05,

qvalueCutoff=0.2) for all functional modules. In addition, we used BinGO application[65] in Cytoscape[66] for functional analysis of the integrated module network.

Prediction of pivot regulators and potential drugs for dysfunction modules

The transcription and post-transcriptional regulation of genes are often driven by transcription factors (TFs) and non-coding RNAs (ncRNAs), which often mediate disease. To explore regulators of co-expression modules, we used the ncRNA-mRNA interaction pairs with score >= 0.5 in the RAID v2.0 database[67] and all human transcription factor-target data in the TRRUST v2 database[68] as a background set for pivot analysis. Pivot analysis refers to finding a regulators with at least two interactions with a module, and the significance of the interactions between the driver and the module is signiciant according to the hypergeometric test (P value<0.01), which identified as pivot regulator.

Similarly, prediction of potential drugs was performed, based on the drug-target data in the Drugbank database[69].

Results

Co-expression of psoriasis-related genes in pathogenic processes

Biomedical scientists have conducted a series of studies on psoriasis and acquired many genes that may regulate psoriasis. However, the regulatory mechanisms of these genes and the inter-gene synergy are not clear. Therefore, we have conducted in-depth research on this. First, a total of 550 psoriasis-related genes were included in multiple databases. Second, based on human protein-protein interaction data, we collected the interactors of these psoriasis-related genes. Combining the two gene sets, we obtained 4577 genes that potentially regulate psoriasis. Observing the expression of these genes in skin samples of 50 psoriasis patients, we identified 24 co-expression modules (Figure 1). Considering the module with the highest number of genes (2129 genes) may mean that the cohesive force is weak, and the phenomenon of synergistic expression is not obvious. Therefore, it was removed in the next study. Finally, we obtained 23 modules, which were identified as functional modules. These functional modules may be involved in different functions and pathways, representing different regulatory mechanisms that mediate the development and progression of psoriasis.

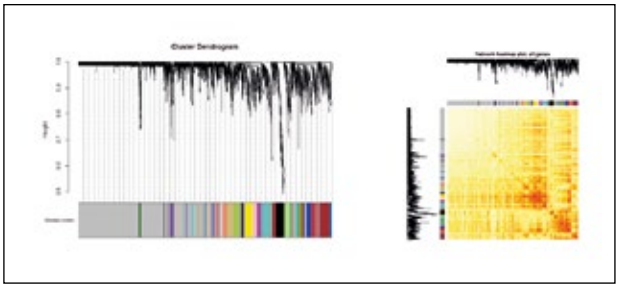

Figure 1: Co-expression of psoriasis-related genes in patient samples.

A. Clustering into 13 modules based on differential gene co-expression relationships. One color represents a module. B. Heat map of the expression of the module gene in the sample. The expression of 13 modules in 13 disease samples was shown to be significantly consistent.

Dysfunctional modules characterizing the pathogenesis of psoriasis

Studying the functions and pathways involved in genes is an important means of identifying their pathogenesis. In order to study the possible dysfunction resulting from module genes disorder, we performed functional and KEGG pathway enrichment analysis for each module. The results indicate that most of the functional modules (except modules 8, 12, 18) are involved in proven psoriasis-related functions and pathways, cell proliferation and apoptosis, cell cycle regulation, protein catabolism, immune system supervision and so on (Figure 2).

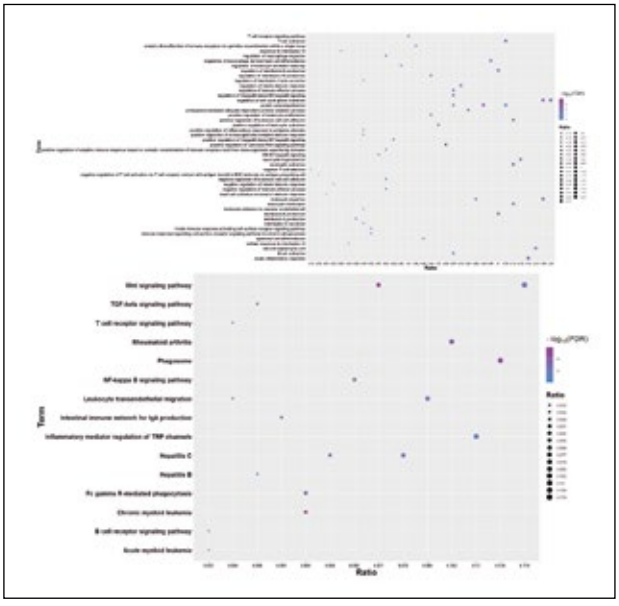

Figure 2: Functions and pathways the psoriasis dysfunction modules involved in.

A. GO function enrichment analysis. The deeper the color, the stronger the enrichment. The larger the circle, the greater the proportion of the gene in the module that accounts for the GO function. B. KEGG pathway enrichment analysis. The deeper the color, the stronger the enrichment. The larger the circle, the greater the proportion of the gene in the KEGG pathway entry.

Therefore, these 20 modules were identified as psoriasis-related dysfunction modules. Module genes can regulate a range of functions and pathways, and the dysfunction of modules is likely to be an important cause of disease. A function network was build based on the interaction relationships between modules (Figure 3), which may represent a global dysfunctional mechanism for psoriasis.

The dysfunction of genes in the module triggers dysfunction of the module, leading to the occurrence and progression of the disease. Based on the interactions of module genes, genes with the highest connectivity in each module were screened (Figure 4) and these genes were thought to have an active regulatory role in the module which identified as an internal drive gene for the psoriasis dysfunction module. We obtained 31 internal drive genes from twenty dysfunction modules, including CDK1, UBE2N, RAC1 and so on. They involved in skin keratinization, apoptosis, autoimmunity and so on. More importantly, in order to verify the scientific nature of the dysfunction module characterizing the pathogenesis of psoriasis, we conducted experimental validation. In the PCR array experiment on patients with psoriasis, we identified significantly differentially expressed genes in modules. And MAPK8, STAT1 and CDKN1B played an important role in the module, which were also considered to be potential promoters of psoriasis. Significant dysregulation of the modul genes in the patient activates the dysfunction module and ultimately induces psoriasis, which strongly supports the scientific nature of the dysfunction module theory.

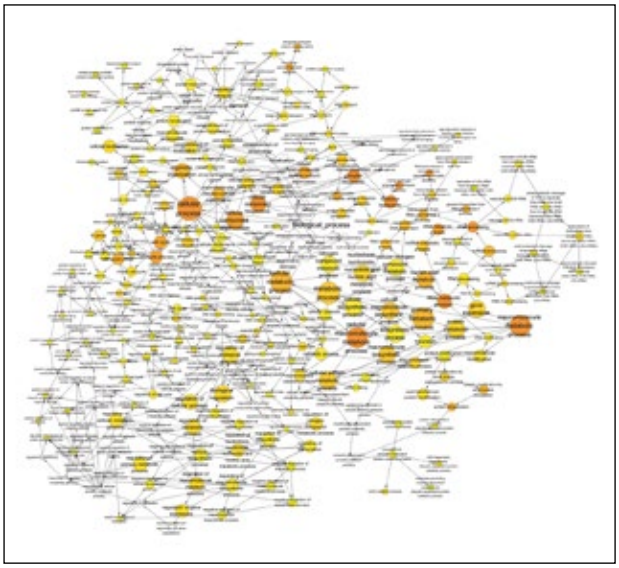

Figure 3: Functional network of dysfunctional modules. *The deeper the color, the stronger the enrichment. The larger the circle, the greater the proportion of the module genes.*

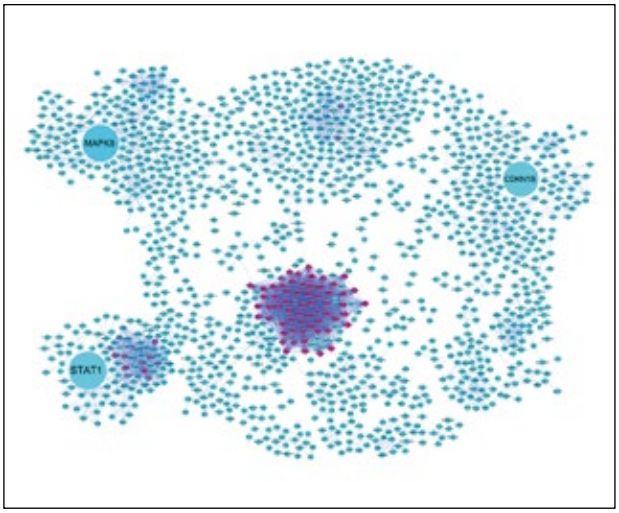

Figure 4: Interaction network of module genes. *The deeper the node color (red), the greater the connectivity and the stronger the adjustment capability.*

Identified pivot regulators for dysfunctional modules

The transcription and post-transcriptional regulation of genes has long been recognized as a key factor regulating the occurrence and development of diseases, Therefore, we performed a pivot analysis on the module based on the regulatory relationships between the transcription factors/ncRNAs and genes. The results (Figure 5) indicated that a total of 74 pivot transcription factors with 103 TF-module regulation pairs. Statistical analysis of these TF-module regulation pairs revealed that the tumor suppressor gene TP53 significantly regulated five dysfunctional modules, which had potential effects on maintaining immune system homeostasis and regulating psoriatic arthritis (PsA). RelA, as an important component of nuclear factor-κB (NF-κB), is involved in the regulation of pro-inflammatory gene activity. It had a significant regulatory effect on the four dysfunction modules and was highly likely to be involved in the dysfunctional mechanism of psoriasis. Transcription factors such as HIF1A, NFKB1, SP1 and STAT1 were recognized to regulate three dysfunction modules, and also played an important role in the pathogenesis of psoriasis.

These transcription factors which had significant regulatory effects on multiple dysfunction modules, had been identified as core transcription factors of psoriasis. In addition, observation of the expression of these transcription factors in patients with psoriasis in the PCR array experiment revealed that STAT1 and CREB5 were significantly differentially expressed. This may represent a key transcription factor for the onset of psoriasis patients involved in

the experiment. For post-transcriptional regulations, we identified 1341 pivot ncRNAs with 2331 ncRNA-module target pairs (Figure 5).

These ncRNAs are involved in various physiological processes such as cell proliferation, cycle progression, apoptosis, invasion, angiogenesis, and cancer development. In addition, statistical analysis of the results found that miR-92a-3p has a significant regulatory effect on 9 dysfunctional modules and played an important role in the function of modules. MiR-146a-5p, miR-15b-5p and miR-200c-3p were identified as important regulatory factors in 8 dysfunction modules and may be potential pathogenic factors for psoriasis. Other ncRNAs also exhibited significant modulation of dysfunction modules and contributed significantly to the pathogenesis of psoriasis.

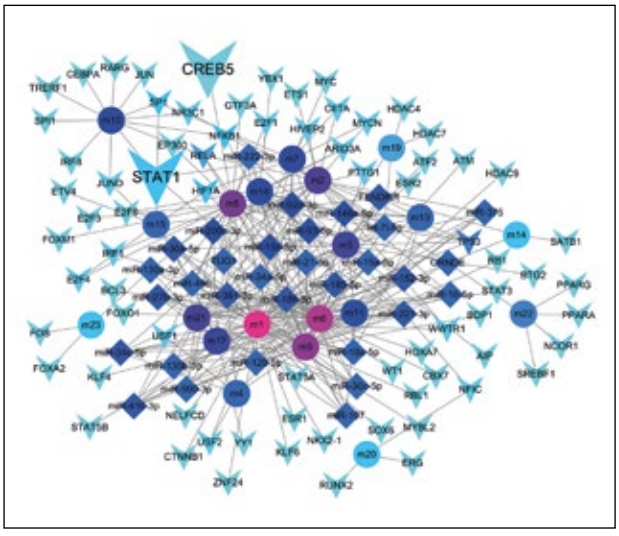

Figure 5: Regulation of non-coding RNAs and TFs to dysfunction modules.
The circle represents the potential pathogenic module, the diamond represents the ncRNAs and the arrow shape represents the transcription factor. The color from red to blue to cyan represents the connectivity of the nodes from large to small. Arrows with relatively large node sizes represent experimentally validated transcription factors.

Potential drugs for the treatment of psoriasis and their targets

The ultimate goal of an in-depth study of the pathogenesis of psoriasis is to explore its potential therapeutic mechanisms for clinical and drug development. To this end, we based on this multifactor mediated dysfunction module for potential drug prediction. Based on the drug-target interactions, we predicted 212 drug-module interaction pairs for 190 drugs (Figure 6). These drugs had significant pharmacological effects on dysfunction modules and were potential drugs for the treatment of psoriasis, providing a valuable reference for drug developers to reposition drugs. We observered that copper can play a regulatory role by targeting four dysfunction modules. Targets for copper included CDK1, UBE2N and RAC1, etc., which were distributed throughout modules 2, 7, 8, and 14, respectively.

In addition, Polaprezinc (zinc L-carnosine complex) had a significant regulatory effect on three dysfunction modules, involving a variety of inflammation, fibrosis and lesions. Other 16 drugs, such as Zinc, Aripiprazole, and Quetiapine, were targeted to regulate two dysfunction modules, which had potential regulatory effects on various physiological processes of psoriasis. The exploration of disease treatment mechanism is the common goal of biologists and medical scientists, and the prediction of psoriasis potential drugs and their drug targets in this study lays a theoretical foundation for their further exploration.

Figure 6: Potential therapeutic mechanisms of drugs for psoriasis.
The red circle represents the module. The blue circle represents a potential drug that has a regulatory effect on the module.

Discussion

Psoriasis is a recognized multifactor, multi-cascade, multiple disorders, chronic inflammatory skin disease. In recent years, the exploration of psoriasis has focused on certain genes or proteins, as well as related signaling pathways, and has achieved certain results. However, the global regulation of these genes, proteins, and signaling pathways in psoriasis remains unclear. To gain a deeper understanding of the pathogenesis of psoriasis, we should explore the underlying mechanisms and key targets from a global perspective, based on integrated strategies, rather than studying individual components. Therefore, we have established multidimensional integration methods based on gene expression data, protein–protein interaction networks data,

transcriptional and post-transcriptional regulation data, and drug-module interactions. In order to fully explore the mechanism of the potential pathogenic genes of psoriasis, we first integrated these potential pathogenic genes and their interaction genes, and observed their synergistic expression behavior in disease skin samples.

Thus, we obtained 23 co-expression modules and identified 20 dysfunction modules based on their participating functions and pathways. Among them, up to 11 modules were significantly involved in proteasome-mediated ubiquitin-dependent protein catabolism, while 10 modules significantly enriched the biological process of protein mulit-ubiquitination. This indicates that ubiquitination of proteins plays an important role in the pathogenesis of psoriasis. The ubiquitin system plays a key role in autoimmune diseases such as psoriasis and rheumatoid arthritis[15]. This was confirmed in the study of Lin B, which highlighted the potential physiological role and the complexity of regulating innate immunity in inflammation and host antiviral responses when take the RNF114 as E3 ubiquitin ligase[16]. In addition, in a wide range of skin diseases (including psoriasis), endogenous catabolism of proteins is significantly increased, leading to various complications such as hypoalbuminemia in patients[17]. Thus, protein multi-ubiquitination plays an important role in the occurrence and development of psoriasis. This also confirmed the scientific nature of 20 dysfunction modules which characterize the underlying pathogenesis of psoriasis. On the other hand, the biological processes regulating the phase transition of the cell cycle and the mitotic cell cycle are significantly enriched in the 10 dysfunction modules. Studies have shown that the increase in epidermal cell proliferation in active lesions of psoriasis is mainly caused by the recruitment or recurrence of two types of non-circulating cells (G1 or G2 phase of the cell cycle)[18]. Therefore, cell cycle regulation is a potential target for the treatment of psoriasis in the clinic[19, 20]. These functions and pathways involved in the modular gene produce a comprehensive network effect that comprehensively regulates the pathogenesis of psoriasis.

Subsequently, we identified factors that regulate these dysfunction modules, including endogenous genes (including CDK1, UBE2N, RAC1, and MAPK8), ncRNA (including miR-92a-3p, miR-146a-5p, etc.) and transcription factors (including TP53, RELA, NFKB1, HIF1A and STAT1, etc.). The internal drive gene refers to the most active genes interacting with other genes in each dysfunction module. These genes often have characteristics that affect the overall situation and have a significant regulatory effect on the module. Among them, the increase of Tyr15 phosphorylation of CDK1 is related to the proliferation of human epidermal keratinocytes and the arrest of cell cycle S phase, which can reduce the damage caused by psoriasis, reduce the thickness of epidermis, and form the expression of spine and PCNA[21]. Secondly, the ubiquitin-conjugating enzyme E2N (UBE2N) is mainly involved in the ubiquitin-related NF-κB signaling pathway (involving innate immunity, pro-inflammatory cytokines and antigen receptors), and PUVA induced keratinocyte p53-dependent apoptosis[22-24] in the pathogenesis of psoriasis. Ras-related C3 botulinum toxin substrate 1(RAC1) is considered to be a key mediator of epidermal dysfunction and plays an important role between the imbalance and homeostasis of psoriatic skin(including barrier function, wound healing and inflammatory response)[25, 26]. Other endogenous genes such as RBX1, RBCK1, and POLR2A are also involved in different degrees in the ubiquitin system, TNF/NF-κB pathway, and p53 signaling, and other immune-related systems and pathways[27-30]. In addition, MAPK8 and other genes have been experimentally verified in this study and are reliable psoriasis-driven genes. MAPK8 (JNK) is regulated by p63 and keratinocyte growth factor, which mediates the differentiation of epithelial cells, which may be a potential pathological mechanism of psoriasis[31]. On the other hand, miR-92a-3p is considered to be specifically targeted to inflammation-related signaling pathways such as CDH1 / β-Catenin and Notch-1 / Akt, and may be one of the potential mechanisms of psoriasis[32].While miR-146a-5p is thought to inhibit IL-17-mediated skin inflammation (including psoriasis), reduce epidermal proliferation and regulate neutrophil infiltration, and relate to susceptibility to autoimmune diseases and psoriatic arthritis Comorbidity[33-35].

In addition, in the regulation of transcription factors, the tumor suppressor gene TP53 is considered to be a susceptibility gene for autoimmune diseases such as rheumatoid arthritis, and it has been found to significantly regulate five dysfunction modules in the study, which has potential function in pathogenesis of psoriasis. Therefore it is used as an apoptotic marker for the treatment of psoriasis with anti-tumor necrosis factor alpha (infliximab)[36, 37]. Also, nuclear factor-κB (NF-κB) that RELA binding

to NFκB1 or NFκB2 is a transcription factor that regulates the activity of pro-inflammatory genes and is considered to be indispensable in the pathogenesis of psoriasis[38, 39]. Hypoxia-inducible factor 1-alpha (HIF-1α) is involved in angiogenesis, inflammation, and regulation of keratinocyte proliferation, and is therefore identified as a potential therapeutic diagnostic marker and new target which can control inflammatory activity in psoriatic lesions[40-42]. Finally, expression and activity of STAT1 is increased in pathological psoriasis skin, and promotes IL-17A expression tegather with STAT3, ultimately promoting autoimmune symptoms[43, 44].

An in-depth study of the pathogenesis of the disease is to scientifically formulate treatment strategies for the disease and design effective treatments. In order to realize the research value of the dysfunction module, we tried to predict the drugs that have a regulatory effect on the psoriatic dysfunction module, which has potential pharmacological or toxicological effects on psoriasis. According to statistical analysis, it was found that copper has a significant regulatory effect on four dysfunction modules, resulting in extremely strong regulatory efficacy.

A number of studies have shown that serum ceruloplasmin activity and copper levels in patients with psoriasis are significantly higher than normal, and have a potential role in promoting the progression of psoriasis[45, 46]. It can be seen that copper has toxic effect for psoriasis and is very harmful. Therefore, reducing the amount of copper and ceruloplasmin activity has become a potential strategy for the treatment of psoriasis[47, 48]. In addition, the prediction results of drug targets show that copper mainly activates the psoriasis dysfunction module by regulating S100A2, S100A4, APP and other genes and has a toxic effect on psoriasis. As a mediator of calcium-related signal transduction, S100 protein responds to changes in subcellular distribution caused by extracellular stimulation in the epidermis, thereby regulating psoriasis, wound healing, skin cancer, inflammation, cellular stress and other epidermal states[49].

In particular, the expression of transfer-promoting protein S100A4 is significantly up-regulated in the psoriatic dermis cell and is more prominent than other S100 proteins, possibly having a positive effect on the pathogenesis of psoriasis[50]. In addition, the amyloid-βprecursor protein(APP) acts as a target for synergistic induction of IFNα/ Wnt5a , which is up-regulated differently in psoriasis and regulates epidermal differentiation[51]. These potential drug targets are the main mechanisms of psoriasis in which copper plays a toxic role. On the other hand, Polaprezinc, which has significant efficacy in inflammatory diseases such as radiation mucositis and oral mucositis, was found to be able to mediate three dysfunction modules in this study, and may also have potential therapeutic effects on psoriasis, but have not been reported[52, 53].

In addition, 15 drugs such as Zinc, Aripiprazole, Quetiapine, and Diethylstilbestrol were identified to have significant regulatory effects on two dysfunction modules. First, zinc therapy has long been used to treat psoriasis, which has a significant regulatory effect on neutrophil chemotaxis, interleukins and antioxidant enzymes, and is a potential supplement to local intervention treatment in psoriasis[54, 55]. Secondly, the antipsychotic drugs Aripiprazole and Quetiapine may activate the dysfunction module to induce a side effect mechanism of psoriasis, which subtly explains the results of Bujor CE et al.[56]. Then, diethylstilbestrol is a commonly used experimental reagent for inducing psoriasis, and its mechanism has been explained in this study[57]. Finally, other drugs predicted in this study have different degrees of regulation of dysfunction modules and are potential drugs for treating or activating psoriasis. These results provide a valuable reference for drug developers to perform drug relocation and identify drug side effects.

In summary, our work provides comprehensive and in-depth insights into the pathogenesis of psoriasis. The multi-factor mediated dysfunction module not only greatly characterizes the molecular mechanism of psoriasis, but also lays a theoretical foundation for predicting potential drugs for psoriasis. With the increasing diversification of high-throughput data, the multidimensional integration strategy of dysfunction modules help to clarify the underlying biological mechanisms and therapeutic mechanisms of disease in a global and in-depth perspective.

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