Research progress and perspective in metabolism and metabolomics of psoriasis

Ni Lian, Li-Qing Shi, Zhi-Min Hao, Min Chen

Department of Dermatology, Hospital for Skin Diseases (Institute of Dermatology), Chinese Academy of Medical Sciences & Peking Union Medical Collage, Nanjing, Jiangsu 210042, China.

Abstract

Psoriasis is considered a systemic disease associated with metabolic abnormalities, and it is important to understand the mechanisms by which metabolism affects pathophysiological processes both holistically and systematically. Metabolites are closely related to disease phenotypes, especially in systemic diseases under multifactorial modulation. The emergence of metabolomics has provided information regarding metabolite changes in lesions and circulation and deepened our understanding of the association between metabolic reprogramming and psoriasis. Metabolomics has great potential for the development of effective biomarkers for clinical diagnosis, therapeutic monitoring, prediction of the efficacy of psoriasis management, and further discovery of new metabolism-based therapeutic targets.

Keywords: Psoriasis; Metabolism; Metabolomics; Biomarkers

Introduction

Psoriasis is currently considered a chronic, inflammatory, systemic, and autoimmune skin disease.[1] Previously, studies focusing on the inflammatory immune response have been centered around T lymphocytes, and very little research has been conducted regarding the link between metabolism and psoriasis. Metabolic abnormalities affect the disease process in terms of occurrence, development, efficacy, and prognosis, while the inflammatory cascade of psoriasis can also affect metabolism in the body.[2] Even if metabolic disorders do not drive disease progression significantly, the effects of the disease could still trigger profound changes in metabolism.[3]

The application of various "-omics" techniques (such as genomics and proteomics technologies) has led to significant breakthroughs in the study of the pathogenesis of psoriasis in terms of inflammation, immunity, and inheritance.[4,5] With the emergence of metabolomics, major progress has been made regarding the close relationship between psoriasis and metabolic reprogramming. Previously, the application of metabolomics in dermatology was mainly focused in specific biomarkers for melanoma,[6] basal cell carcinoma,[7] and porphyrin disease.[8] However, metabolomics has great potential and is a promising tool in the research and clinical applications in psoriasis. Many studies have found that there are close connections between metabolic syndrome and the pathogenesis, outcome, and treatment of psoriasis.[1-3] In addition, recent studies have identified many metabolic diseases as comorbidities of psoriasis, including obesity, diabetes, and atherosclerosis.[9-11] Furthermore, in contrast to genomics and proteomics, metabolomics can also reveal the effects of exogenous factors, such as diet, environment, and the microbiome.[12]

In summary, the metabolome represents the ultimate apex of gene expression, epigenetics, protein function, and environmental influences[13] because metabolites may reflect the biochemical processes that occur in a particular phenotype directly. Moreover, the combination of genomics, proteomics, and metabolomics could further enable a comprehensive understanding of psoriasis in terms of systems biology [Figure 1].

Metabolomics analysis was first based on metabolic profiling using gas chromatography-mass spectrometry (GC-MS), a technique widely used in laboratory diagnosis and clinical examinations.[14] The advent of high-performance liquid chromatography and nuclear magnetic resonance (NMR) technologies has allowed the further

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Correspondence to: Min Chen, Department of Dermatology, Hospital for Skin Diseases (Institute of Dermatology), Chinese Academy of Medical Sciences & Peking Union Medical Collage, Nanjing, Jiangsu 210042, China
E-Mail: drchenmin@126.com

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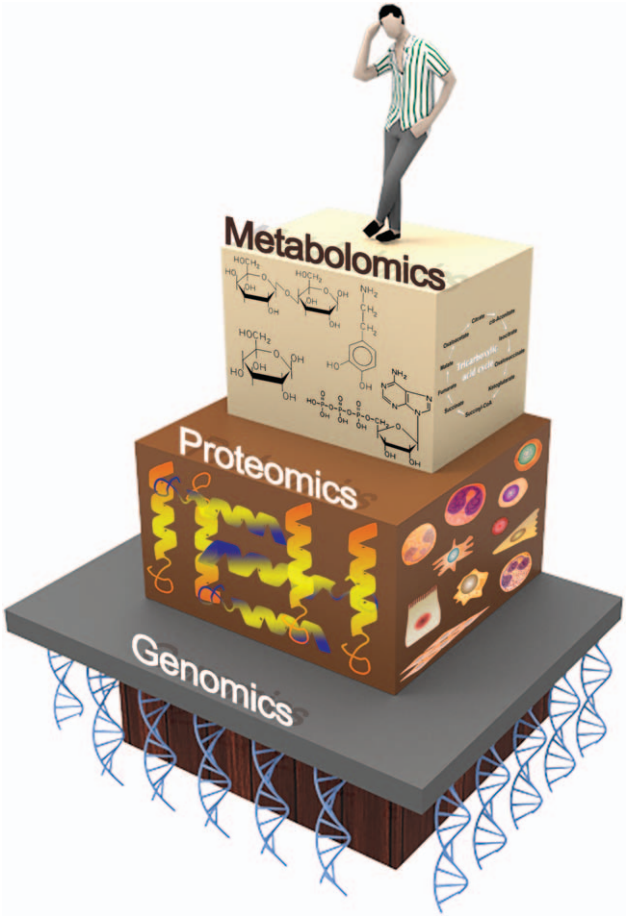

Figure 1: Combination of genomics, proteomics, and metabolomics can further enable a comprehensive and holistic understanding of psoriasis.

exploration of how drugs are metabolized in the body.[15-17] Nowadays, liquid chromatography-MS technology has revolutionized metabolomics analyses, leading to the discovery of new biomarkers.[18] Therefore, our understanding of systems biology is deepening, and the recognition of diseases is becoming more holistic.

Metabolomics is a new branch of systems biology that follows genomics, proteomics, and transcriptomics.[4,18,19] The advantages are as follows: (1) subtle changes at the gene and protein expression levels may be amplified at the metabolite level; (2) there is no need to establish a large database of expression sequence tags or carry out extensive whole-genome sequencing; (3) it is now generally accepted that metabolites can effectively reflect the phenotype and state of an organism, and that metabolites can be not only functional and signaling molecules but also biomarkers; and (4) the number of metabolite species is theoretically much smaller than the number of gene and protein species. Although great progress has been made in metabolomics research, there remain shortcomings that need to be addressed.

Metabolic changes and biomarkers of patients with psoriasis

Metabolomics studies using skin lesion samples may provide the most direct and intuitive metabolic changes in local areas. The advantage is that this may promote the integration of metabolite information with local pathological changes, local inflammatory immune responses, and cell proliferation. Moreover, it may play an important role in the discovery of new topical therapeutic targets and the evaluation of the efficacy of existing topical drugs.[20,21] However, psoriasis is a systemic disease, and its metabolic changes are not only local but also systemic. Metabolomics based on peripheral blood can provide an overall picture of how psoriasis affects metabolic pathways in the body. Although it can be difficult to determine the specific cause or final result of the pathogenesis of psoriasis, the utilization of blood samples has particular advantages in that it may contribute to the development of a holistic view of the relationship between psoriasis and metabolism. Urine is also a useful sample for metabolomics research. Its advantages lie mainly in convenience of access, non-invasive collection, and abundant content of *in vivo* metabolites and non-cellular products.[20] However, few metabolomics studies involving psoriasis have adopted urine as a sample source.

To date, some studies have used metabolomics techniques for the analysis of peripheral blood, skin lesions, and urine in patients with psoriasis to determine changes in carbohydrates, lipids, amino acids, and nucleotides. These four molecular classes are not only independent of each other but also interconnected. Nutrient metabolism not only affects the supply of energy for cell proliferation but is also involved in a variety of inflammatory and immune processes in the body. We summarized data into four categories (glucose metabolism [Supplementary Table 1, http://links.lww.com/CM9/A392], lipid metabolism [Supplementary Table 2, http://links.lww.com/CM9/A392], amino acid metabolism [Supplementary Table 3, http://links.lww.com/CM9/A392], and nucleotide metabolism [Supplementary Table 4, http://links.lww.com/CM9/A392]) to demonstrate the overall metabolic network.

Glucose metabolism

The association of psoriasis with abnormal glucose metabolism has been identified in previous epidemiological studies and clinical observations.[22] The presence of insulin resistance as well as the abnormal function of glucose transporter (GLUT) proteins has been confirmed in patients with psoriasis, and several genetic psoriasis susceptibility motifs (PSORS, PSORS2, PSORS3, and PSORS4) have been found to be associated with susceptibility loci in multiple metabolic diseases, including type 2 diabetes.[23] However, the mechanism by which glucose metabolism (including the tricarboxylic acid cycle, anaerobic glycolysis, gluconeogenesis, and oxidative respiratory chain) is involved in the regulation of psoriasis remains to be further studied.

In a metabolomics study using NMR spectroscopy, Sitter *et al*[21] identified a decrease in glucose levels in psoriatic lesions that may be related to the need to consume more glucose for energy supply when the epidermis over-proliferates.[21] Supplementary Table 1, http://links.lww.com/CM9/A392 shows that levels of glucose metabolism-related metabolites are always decreased in psoriatic

lesions or psoriasis-like inflammation samples. Anaerobic glycolysis may permanently be in a state of overconsumption in lesions. Moreover, reduced levels of the substrates and products of anaerobic enzymes (such as myoinositol and lactic acid) have been detected.[21,24] It has been hypothesized that the reduction of lactic acid in local lesions may be due to metabolic changes in sweat glands and keratinocytes or the obstruction of sweat ducts.[24]

Alonso *et al*[25] applied proton NMR technology to analyze urine metabolites from patients with psoriasis as well as patients with several autoimmune diseases, such as systemic lupus erythematosus, rheumatoid arthritis (RA), coeliac disease, and ulcerative colitis. Compared with healthy controls, patients with psoriasis were found to have lower levels of citrate, alanine, and methylsuccinate.[25] The authors also performed a subsequent clustering analysis of metabolites. The profile of psoriasis (together with psoriatic arthritis) was different to that of RA, which may be beneficial for differential diagnosis in the future.[25]

In contrast with the metabolites detected in lesions and urine, the levels of the substances involved in glucose metabolic circulation in peripheral blood demonstrated an increasing trend. Multivariate analyses showed a higher level of α-ketoglutaric acid, lactic acid, aspartic acid, and glutamic acid in patients with psoriasis.[24,26,27] All these acids could be mobilized into the peripheral circulation due to the increased energy requirements associated with rapid protein synthesis and cytokine production under cellular hyperproliferation. In addition, α-ketoglutarate participates in the synthesis of proline in downstream reactions, which is one of the main raw materials for the synthesis of skin collagen. In contrast, peripheral circulating lactate levels are significantly elevated, presumably relating to the provision of a favorable microenvironment for keratinocyte proliferation. In the context of the inflammatory environment and high oxidative stress, asparagine can spontaneously deamidate and decompose to aspartate in circulation.[20] Branched-chain amino acids (BCAAs) may be involved in worsening insulin resistance.[28-30] Furthermore, high intake of BCAAs in a high-fat diet may interfere with the normal physiological abilities of insulin in the body.[28]

Lipid metabolism

Excess free fatty acids in the circulation can produce cytotoxic effects on pancreatic β-cells, disrupting their normal physiological function and leading to insulin resistance, further affecting the vasodilatory function and disrupting the vascular endothelial system.[31-33] Adipocytes under prolonged hypoxic conditions can secrete multiple inflammation-associated cytokines (eg, interleukin 6 [IL-6], tumor necrosis factor alpha [TNF-α], and plasminogen activator inhibitor-1) to trigger a range of inflammatory responses.[10] Lipids are not only the main components that constitute the structure of the bilayer cell membrane, they are also involved in regulating various biological processes, such as cell proliferation, apoptosis, and inflammation.[20] Therefore, some lipid metabolites may be potential biomarkers. It is currently thought that the major alterations in lipid metabolites may occur mainly through increased lipid synthesis, impaired lipolysis, and excessive activation of the fatty acid β-oxidation pathway.

A non-targeted lipidomic study based on ultra-performance liquid chromatography-MS/MS analyzing plasma from patients with psoriasis, with validation occurring via enzyme-linked immunosorbent assay, revealed that the levels of glycerophospholipid pathway metabolites significantly changed (higher lysophosphatidic acid [LPA], lysophosphatidylcholine [LPC], and phosphatidic acid levels, and lower phosphatidylinositol and phosphatidyl choline levels).[34]

Hemolipophosphate family members act as receptor-active mediators in cell proliferation, differentiation, and apoptosis.[35] LPA and LPC are thought to be inflammatory lipids associated with multiple immune-mediated diseases.[36-38] LPC exerts proinflammatory effects in inflammatory cells through different signaling pathways (eg, nuclear factor kappa B, protein kinase C, and extracellular-signal-regulated kinase pathways). Furthermore, LPC induces the expression of cyclooxygenase-2, a key proinflammatory mediator.[39] LPA promotes cell growth, differentiation, and mastocyte proliferation during inflammation [40,41] and is not only involved in constituting the skeletal structure of the cell membrane, but also acts as a secondary messenger mediating downstream signaling pathways.[42-44]

In the serum lipid metabolites of patients with psoriasis, unsaturated fatty acids show an overall decreasing trend. Serum levels of crotonic acid, 2-hydroxysebacic acid, and 13-octadecenoic acid also decrease.[27] Unsaturated fatty acids not only prevent thrombosis by reducing platelet aggregation and blood viscosity, but also improve the lipid profile (increasing high-density lipoprotein cholesterol, but reducing serum triglycerides and total and low-density lipoprotein cholesterol). Besides, unsaturated fatty acids may indirectly contribute to the occurrence of chronic inflammation through their negative effects on the lipid profile and blood vessels.[45,46]

Studies have also confirmed the upregulation of lipid peroxidation and reduction of antioxidant markers (such as glutathione) in plasma. Elevated levels of azelaic acid (the final product of linoleic acid after peroxidation decomposition) have been observed in blood samples.[27,35] However, there remains controversy regarding whether hydroxynonenal and malondialdehyde can be used as biomarkers for psoriasis, as very different results have emerged from different studies.[47,48]

In psoriatic lesions, the levels of unsaturated fatty acids differ significantly. Of these, all products of lipoxygenase (LOX) are abundant and involve monohydroxy derivatives from arachidonic acid (5-, 8-, 9-, 11-, 12-, and 15-hydroxyeicosatetraenoic acid [HETE]) and linoleic acid (9- and 13-hydroxyoctadecadienoic acid [HODE]).[35] These lipids have specific physiological functions in the epidermis. For example, 13-HODE is thought to have anti-inflammatory effects and the ability to maintain normal keratinogenic cell proliferation.[49,50] 9-HODE promotes

the release of inflammatory cytokines.[35,51] However, the amount of 13-HODE produced by the psoriatic epidermis is not sufficient to inhibit the hyperproliferation of keratinocytes. Similarly, 12-HETE is a proinflammatory chemotactic agent,[52] whereas 15-HETE reduces inflammatory cell infiltration. However, 15-HETE is higher in psoriatic lesions than 12-HETE.[35] LOX oxidation products are further oxidized to produce epoxides, such as epoxy octadecadienoic acid and epoxy eicosatrienoic acid. These epoxides may promote neutrophil infiltration and inflammation.[53,54]

Choline not only provides the energy needed for cell growth and division but is also involved in the synthesis of bioactive lipids. Elevated choline levels in psoriatic lesions may indicate the local hyperproliferation of epidermal cells.[21,24] Taurine is abundant in inflammatory cells, such as leukocytes, and is also abundant in local inflammatory lesions and oxidative stress tissues.[21,55-57] LPC has elevated levels in both lesions and serum and is presumably involved locally in the induction of lymphocyte and macrophage migration as well as increased production of proinflammatory cytokines.[34,58]

The level of tetranor-12(S)-HETE is elevated, whereas that of 12(S)-HETE is reduced in the urine of patients with psoriasis. 12(S)-HETE is involved in the regulation of skin homeostasis and affects the growth and differentiation of keratinocytes. Dermatologic inflammation may also accelerate beta-oxidation.[59]

Amino acid metabolism

The importance of amino acids and their metabolites lies in providing the raw material for cellular protein biosynthesis, forming cytoskeletons, and participating in a variety of bioactive reactions. Glutamine and asparagine levels are lower in patients with psoriasis than in those without. However, levels of alpha-ketoglutarate are higher in patients with psoriasis vulgaris but lower in those with psoriatic arthritis. This suggests that glutamine consumption may increase due to overactive immune cell proliferation. However, the decrease in asparagine is due to spontaneous deamidation and catabolism in an inflammatory, oxidative stress environment. α-Ketoglutarate is involved in the synthesis of proline, a major substrate for collagen synthesis, and in the oxidative supply of the tricarboxylic acid cycle as a citric acid cycle intermediate.[60] Therefore, levels of alpha-ketoglutarate are elevated in patients with psoriasis but reduced in those with psoriatic arthritis, presumably due to the excessive proliferation of keratinocytes and decreased collagen synthesis.

At the same time, patients with psoriasis have more active urea circulation. During the development of psoriasis, which is characterized by the hyperproliferation of keratinocytes, the increased demand for polyamines may prompt the release of the three intermediates of the urea cycle (arginine, ornithine, and citrulline) into the peripheral circulation.[27,61] Phenylalanine is a raw material that takes part in synthesizing adrenaline, thyroxine, and melanin in the body. Since the accelerated metabolism caused by psoriasis is not only manifested in the skin but also in systemic metabolism, it is believed that the elevated plasma levels of phenylalanine in patients with psoriasis may be related to increased demand for synthetic neurotransmitters and hormones.[27] Keratinization of the epidermis requires scaffold and supporting proteins (eg, small proline-rich protein). Additionally, the main amino acids involved in the synthesis of human collagen 1α are glycine and proline. Although dermal collagen is not obviously thickened, there are indications of a higher collagen conversion rate in patients with psoriasis.[61,62]

BCAAs are involved in extrahepatic oxidative metabolism (mainly in muscle). BCAAs include leucine (a ketogenic amino acid), valine (a glycosylated amino acid), and isoleucine (a glycosylated and ketogenic amino acid). BCAAs affect metabolism in the following ways: (1) promoting the release of insulin, insulin-like growth factor-1, and growth hormone (pro-synthesis); (2) regulating the metabolism of other amino acids, especially aromatic amino acids; and (3) participating in cellular peroxidative damage resistance.[25,63,64] BCAA levels are elevated in the plasma of patients with diabetes and cardiovascular disease[65-68] and also in patients with psoriasis.[27,69-71] Considering the link between psoriasis and its systemic metabolic comorbidities, the metabolism of BCAAs in patients with psoriasis deserves further exploration. Interestingly, BCAAs activate the mammalian target of rapamycin (mTOR), an atypical serine/threonine kinase that promotes cell proliferation, survival, protein synthesis, and the growth and proliferation of epithelial cells. This allows BCAAs to play an important role in tumor therapy as a potential therapeutic agent.[64,72]

In addition, significant alterations in homocysteine metabolism have been detected in plasma, and homocysteine is an independent risk factor for cardiovascular events.[73,74] Elevated plasma homocysteine levels in patients with psoriasis are presumed to be related to induced oxidative stress and vascular endothelial inflammation.[75] Homocysteine causes the accumulation of asymmetrical dimethyl arginine (ADMA; a potent endogenous nitric oxide synthase [NOS] inhibitor). The inhibitory effect of ADMA on cutaneous NOS reduces epidermal nitric oxide (NO), thereby promoting the hyperproliferation of keratinocytes. This inhibitory effect on endothelial NOS may lead to increased cardiovascular risk in patients with psoriasis.[75-78]

Psoriasis is characterized by hyperactive keratinocyte proliferation and by an increased demand for glutamine to adapt to higher protein synthesis rates and to promote more glutamate mobilization locally.[24,26]

Tryptophan and phenylalanine are essential amino acids that cannot be synthesized *in vivo*. The production and accumulation of proinflammatory cytokines, such as interferon gamma (IFN-Y) and TNF-α, in psoriatic inflammatory lesions could stimulate the synthesis of tetrahydrobiopterin, which, as an important cofactor with phenylalanine, promotes the synthesis of neurotransmitters. This may drive the matching-quantity phenylalanine to be moved locally.[79] In addition, the phenylalanine-tyrosine pathway is involved in the production of increased

melanin in the inflammatory context, which may explain the local accumulation of phenylalanine in inflammatory lesions.[80]

The metabolism of the urea cycle in lesions is different to that in the peripheral circulation. In lesions, the level of ornithine, as a substrate for polyamine synthesis, increases with the increase in demand. Meanwhile, the increased ornithine level upregulates the activity of arginidase, leading to an excessive consumption of arginine as a substrate.[81,82] At this point, citrulline levels are also reduced, and this decrease is most pronounced in the hyperproliferating epidermis.[24] Moreover, arginidase-1 can compete with inducible NOS (iNOS) for arginine, further reducing the levels of this amino acid in skin lesions; at the same time, arginase-1 inhibits iNOS synthesis of NO, further promoting epidermal proliferation.[81]

Nucleotide metabolism

Because the epidermis of patients with psoriasis is rapidly proliferating and differentiating, alterations in nucleotide metabolism in the peripheral circulation are mainly manifested in reduced levels of metabolites (ie, aspartic acid, glutamine, hypoxanthine, pseudouridine, inosine, guanosine, cystine, cysteine, and phosphoric acid) due to increasing demand for raw materials, and in product accumulation due to hypercatabolism of purines and pyrimidines.[26,27,35,61,62,83]

In nucleotide metabolism, one carbon unit is synthesized and transferred. Serine, glycine, histidine, and tryptophan are sources of carbon units required for purine and pyrimidine synthesis. Elevated levels of these amino acids in patients with psoriasis may be associated with overactive cell proliferation. The one-carbon unit metabolism inhibitor methotrexate can block DNA synthesis by inhibiting the cycle of the one-carbon unit transporter tetrahydrofolate.[84-86] The methionine cycle provides methyl groups, where S-adenosylmethionine is the direct donor and N_5-CH_3-FH_4 is the indirect donor. Methyl groups are involved in the methylation of DNA, RNA, and histones, which regulate gene expression at the epigenetic level and influence disease phenotypes. Methyl groups are also involved in other metabolic pathways, such as lipid synthesis and protein synthesis pathways.[87] Reduced levels of methionine in the peripheral blood of patients with psoriasis may be associated with an increasing demand for raw materials in the activation of the methionine cycle.[83] Physiological functions of cystine and cysteine include the production of active sulfate (3′-phosphoadenosine 5′-phosphosulfate), which is involved in biological transformation, and the production of glutathione, which is involved in detoxification and antioxidant reactions *in vivo*, which may also be associated with psoriasis-induced inflammation and oxidative stress. Furthermore, since methionine is converted into cystine and cysteine, it cannot be synthesized *in vivo*, which further reduces its levels.[84,87]

Role of metabolites in the pathogenesis of psoriasis

Psoriasis is an inflammatory skin disease centered on T cell immunity. Metabolic abnormalities in patients with psoriasis may also have an impact on the inflammatory immune response. The association between metabolites and psoriasis is not limited to energy generation, storage, and transmission, or to the synthesis and assembly of the cytoskeleton and its components, but is also reflected in the activation of several genes and the regulation of their expression. This association is also detected in the regulation of components of diverse signal transduction pathways.[88,89]

Survival, activation, and proliferation of T cells

Different from T effector (Teff) cells, T memory (Tm) cells do not absorb extracellular palmitate but initiate de novo synthesis of fatty acids instead.[90] Moreover, the fatty acid catabolism algebraic approach differs for different T cell subtypes, with Tm cells utilizing lysosomal acidic lipase (LAL)-dependent fatty acid β-oxidation. The loss of LAL activity only reduces the survival rate of Tm cells and does not affect Teff cells.[90] It also provides useful information regarding the importance of fatty acid metabolism in producing immune memory.

Fatty acids also regulate the activation of immune cells and binding to specific receptors. The activation of T cell receptors is accompanied by the upregulation of genes related to the fatty acid and cholesterol biosynthesis process regulated by sterol regulatory element binding protein.[91]

After stimulation by IFN and toll-like receptor 7 (TLR7) ligands, spermidines are reduced and metabolism shifts from oxidative phosphorylation to glycolysis. Supplementation with arginine inhibits glycolysis both *in vivo* and *in vitro*, prevents IFN-induced dendritic cell (DC) overactivation, and reduces inflammation.[92]

Differentiation of T cells

Short- and medium-chain fatty acids can affect the differentiation of T helper ($CD4^+$) cells in T helper type 1 (Th1) and Th17 cells by downregulating histone deacetylase activity and activating the mTOR pathway.[93] Fatty acids and their metabolites activate different cell signal transduction pathways by binding peroxisome proliferator-activated receptors (PPARs), which are important for the differentiation of several T cell subsets,[94] particularly in the regulation of $CD4^+$ cell differentiation in Th17 or T regulatory (Treg) cells.[95] In addition, PPARs are critical for the activity of adipose tissue-associated Treg cells.[96]

Teff and Treg cells exhibit different metabolic preferences during differentiation, with Teff cells preferring glycolytic action, whereas Treg cells are more dependent on lipid oxidation.[97]

Migration of immune-associated cells

Direct exposure to palmitate leads to a change in the differentiation of $CD4^+$ cells, resulting in an abnormal expansion of the proinflammatory effector and memory lymphocyte population in patients with obesity.[98] These

abnormal T lymphocytes migrate to non-lymphoid inflammatory sites and maintain chronic inflammation for a long time.

Unsaturated fatty acids (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) can reduce the number of effector and memory $CD4^+$ cells, prevent T cell polarization and ras-related C3 botulinum toxin substrate 1 activation, and inhibit the migration of $CD4^+$ cells to the inflammation sites.[99] Besides, EPA and DHA increase the infiltration of $CD4^+$ and cytotoxic T cells in the skin under ultraviolet exposure.[100]

In addition, sphingol-1-phosphate (S1P) is associated with T cell migration. Each of the five different S1P receptors plays a unique role in proliferation, convergence, efflux, and transportation. S1P receptor 1 (S1PR1) can downregulate iNOS signals and enhance the formation of anti-inflammatory phenotypes in macrophages. S1PR2 and S1PR3 are necessary for macrophage recruitment.[101] Moreover, S1P can inhibit 12-O-tetradecanoylphorbol 13-acetate-induced T cell proliferation.[102,103] One of the unique pathological manifestations of psoriasis is the aggregation of neutrophils in the epidermis (namely, Munro microabscesses). Ceramides can monitor neutrophil function by inhibiting superoxide production, particularly controlling the response to TNF-α, and can block respiratory bursts in neutrophils caused by N-formylmethionine-leucyl-phenylalanine stimulation.[104,105]

Influence on the inflammation-associated signaling pathway

LPC can activate transcription factors through a combination of G protein-coupled receptors and TLRs. LPC may then increase the expression of target genes to activate inflammatory signaling pathways and increase inflammatory factor release. In addition, LPC is involved in inducing apoptosis and promoting reactive oxygen species production to enhance oxidative stress.[58,106]

Ceramide plays an important role in DC activation. First, it induces DC apoptosis by downregulating survival signaling pathways, such as NF-κB and protein kinase B (PKB).[106] In addition, ceramides may participate in the induction of DC maturation and promote the production of major histocompatibility complex class I molecules and the secretion of proinflammatory cytokines, such as IL-12 and TNF-α.[107] Moreover, S1P has anti-inflammatory effects by reducing the production of IL-12 and IL-23 by the shared p40 subunit in DCs, thereby inhibiting DC crosstalk with activated keratinogenic cells.[108]

Excess circulating amino acids may stimulate the mTOR/S6 kinase (S6K) pathway and inhibit serine phosphorylation of insulin receptor substrate 1, resulting in impaired glucose tolerance and inhibition of insulin-mediated gluconeogenesis.[109] Insulin resistance plays an inducing and exacerbating role in the chronic inflammatory state of psoriasis. The increased levels of circulating amino acids observed by metabolomics suggest that the mTOR/S6K pathway may contribute to the development and maintenance of chronic inflammation.[110]

In addition, short-chain fatty acids have therapeutic potential for psoriasis. Topical application of short-chain fatty acids reduces imiquimod-induced inflammation by downregulating IL-17 and inducing the transcription of IL-10 and forkhead box P3. Short-chain fatty acids can also normalize the reduced Treg inhibitory activity in peripheral blood isolated from patients with psoriasis and reduce the number of Tregs in psoriatic lesions.[111]

Effects of metabolite transporters

Transporters are proteins responsible for transporting metabolic substrates across cell membranes, which can affect metabolite levels, metabolic balance, and immunity. Transportation-mediated uptake, utilization, and catabolism of metabolites can greatly affect the function, balance, activation, and differentiation of immune cells.[112] Immune metabolism is essential for immunity and immune responses, and metabolite transporter proteins may be suitable targets for regulating the metabolic phenotype of immune cells.

GLUT1 is the major GLUT in T cells and plays a regulatory role in their activation and differentiation.[113] The transport of glucose via GLUT1 is considered to be a rate-limiting step in the glucose metabolism of T cells. T cell activation leads to increased energy demand, and GLUT1 and GLUT3 mediate increased glucose uptake, thereby enhancing glycolysis to maintain T cell activation and promote differentiation.[112] In addition, GLUT can influence the selection of T cell differentiation profiles. Transgenic expression of GLUT1 promotes the activation of T cells and the generation of memory phenotype-like T cells that are prone to activation.[97]

In addition to glucose metabolism, T cells use glutamine breakdown to meet their considerable energy and biosynthetic needs. The expression of glutamine transporter protein and glutamine catabolic components induces T cell activation via an MYC-dependent pathway.[114]

Increased expression of L-type amino acid transporter 1 (LAT1) was detected in keratinocytes and lymphocytes in psoriatic lesions. Inhibition of LAT1 prevents the proliferation of human gammadelta T cells and inhibits the secretion of IL-17. In addition, inhibition of LAT1 effectively controls IL-23- and IL-1β-induced phosphatidylinositol 3-kinase/PKB/mTOR activation.[115]

Limitations and expectations

Potential for clinical application

Rapid developments in metabolomics have upended the traditional view of metabolites as simply energy sources. Indeed, metabolites can act as signaling molecules, immunomodulators, and stress sensors, and play an important role in the onset and development of psoriasis. Metabolomics not only provides a more unified and holistic understanding of physiological metabolism and pathophysiology, but also demonstrates new potential for

clinical applications in psoriasis (eg, diagnosis, treatment, and prognosis).

The increased levels of amino acids in the urea cycle (ornithine, arginine, and citrulline) and collagen synthesis (proline and hydroxyproline) in serum, and glutamate and choline in psoriatic lesions are considered to be associated with the severity of psoriasis.[21,61] Moreover, hydroxyproline may be a new indicator of psoriatic arthritis.[61]

Sitter *et al*[21] compared metabolite profiles between patients with normal skin, psoriatic lesions, and lesions treated with external corticosteroids. After topical treatment with corticosteroids, glucose, inositol, glycerophosphate choline, and glycine levels increased in the lesions, while choline levels decreased. The levels of metabolites were comparable to those of the normal control, which demonstrated its good therapeutic effect.

Plasma concentrations of glutamine, threonine, ornithine, arginine, methionine, glycine, citrulline, and proline in patients with psoriasis can reach normal levels in healthy individuals after etanercept treatment, reversing most of the circulating metabolite trends.[61] Kapoor *et al*[116] analyzed different changes in the urinary metabolic profile of patients with psoriatic arthritis and rheumatoid arthritis (RA) treated with infliximab or etanercept. The levels of citrate and lactate in the urine of patients treated with infliximab were elevated, whereas patients receiving etanercept therapy had elevated choline and creatine levels. The elevated choline levels suggest that etanercept may regulate lipid metabolism *in vivo*.[116] Although both infliximab and etanercept have been considered primary targets of TNF-α, the differences in this study suggest that there may still exist a different mechanism between the two biological agents in terms of their effects. The results of a study by Madsen *et al*[83] suggest that psoriasis and RA have unique metabolite profiles, although they share common inflammatory cytokines and signal transduction pathways. Metabolomics is of great clinical value for psoriasis diagnosis and treatment, including its application in developing individualized therapeutic plans and predicting efficacy.

Recently, non-targeted metabolomics has shown that (R)-salbutamol can alleviate psoriasis-like inflammation by affecting three different metabolic pathways, including glycerophospholipid, sphingolipid, and arachidonic acid metabolism, modulating Th17 and Treg responses, which may provide new directions for developing treatments.[117] Oral dimethyl fumarate (DMF) has been approved by the European Union for the treatment of psoriasis. DMF post-inhibits NF-κB through glutathione depletion and converts the involved cytokines from the Th1/Th17 proinflammatory to the Th2 anti-inflammatory mode.[118]

The type of fatty acid substrate determines the direction of T cell differentiation and can be used to develop clinical interventions aimed at controlling the pathogenicity of abnormal T cells under inflammatory conditions.[119] This is crucial for the balance between Th17 and Treg cells. PPAR stimulation may be a suitable strategy for blocking the Th17 pathway.[120,121]

Limitations

Currently, the challenges of metabolomics research can be summarized in several points.[122-127] (1) Compound identification: the poor and slow identification of metabolites (ie, low number of annotated metabolites) is a pivotal problem that cannot be ignored. The complexity of biological samples and metabolites means metabolomics places high demands on the sensitivity, resolution, dynamic range, and flux size of analytical techniques. Therefore, in-depth studies must rely on evolving analytical techniques. (2) Expansion of the metabolome space: this is mainly reflected in inadequate coverage (ie, low sensitivity and matrix effects). The development of metabolomics is somewhat constrained by the continued lack of functional metabolite databases and uniform common research standards for metabolomics. (3) The link between metabolomics data and biomedicine is easily confused. Some metabolites are often associated with different types of diseases, which can create confusion and mistrust of metabolomics data and hinder the development of metabolomics in other fields. (4) Some biomarkers are generic for inflammation-related diseases. Research should focus on exploring biomarkers specific for psoriasis. (5) The clinical application of metabolomics still requires validation by orthogonal analysis techniques.

Future integrated "-omics" approaches

Understanding the effects of metabolism alterations on patients with psoriasis at a holistic level requires the integration of metabolomics and other "-omics," such as proteomics and genomics.[69,128] The integration of high precision, high throughput "-omics" techniques and bioinformatics allows the consideration of genetic, environmental, inflammatory, diet, immune, and microbial influences on the disease process at multiple levels.[129,130] New models have been developed, such as mergeomics,[131,132] which aims to integrate multidimensional data for exploring meaningful biological pathways and signal networks,[133] and skinomics, which uses microarrays as the primary technical means.[134] These new algorithms and models emphasize the concept of "systematic" and "holistic" in psoriasis research.[12,135]

The efficacy and safety of targeted biomarker-based treatments have been well established, and metabolomics may assist with developing new therapeutic targets.[131,136-138] The correlation between psoriatic disease severity and metabolite level suggests that metabolic changes may reflect the trajectory of disease progression, indicating an important role in monitoring and predicting efficacy.[61] In addition, metabolomics continues to evolve with the emergence of new technologies. At present, metabolites can be analyzed in single cells.[139] In addition, metabolic pathways can be monitored with stable isotope tracers to further clarify metabolic networks in disease.[140,141]

Conclusions

There is currently a growing interest in the use of metabolomics techniques in developing treatments for

psoriasis. The levels of metabolites in body fluids or skin tissues are considered to reflect the functional state of the cells, providing markers for assessing disease activity and predicting disease progression. Metabolomics has great potential for assisting in the understanding of altered cellular functions, exploring complex signaling pathways, and discovering emerging drug targets. In addition, psoriasis is a genetically related, multifactorial, and systemic autoimmune disease. As each patient's genetic information and metabolic profile are different, strategies for integrating metabolomics with other technologies may be beneficial for developing individualized therapies. Metabolomics provides in-depth information regarding the association between metabolic state and disease, providing strong support for developing individualized management plans for patients with psoriasis. As metabolomics technology continues to evolve and our understanding of metabolic disorders also deepens, it is reasonable to expect that more diagnostic and therapeutic targets will emerge and be translated into clinical practice.

Conflicts of interest

None.

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