Psoriasis: Targets and Therapy

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REVIEW

Research Progress on Glycolysis Mechanism of Psoriasis

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Abstract: Psoriasis is a chronic inflammatory disease with a complex pathogenesis. Hyperplasia of glycolytic-dependent epidermal keratinocytes (KCs) is a new hallmark of psoriasis pathogenesis. Meanwhile, immune cells undergo metabolic reprogramming similar to KCs. Glycolysis provides energy for the proliferation of KCs, while it also releases lactic acid to facilitate the differentiation of immune cells. In turn, differentiated immune cells further promote KCs glycolysis by releasing inflammatory factors, thus forming an immunometabolism loop. The interaction between immune response and metabolic pathways jointly promotes the sustained proliferation of KCs and the secretion of various inflammatory factors by immune cells. Understanding the role of glycolysis in immunometabolism of psoriasis may provide new ideas for non-immunosuppressive treatment of psoriasis. This article aims to review the role of glycolysis in the pathogenesis of psoriasis and attempts to summarize the key enzymes and regulatory factors involved in psoriasis glycolysis, as well as their interactions. Finally, we discuss the pharmacological modulators of glycolysis in psoriasis.

Keywords: psoriasis, keratinocytes, glycolysis, metabolic reprogramming, immunometabolism

Introduction

Psoriasis is a systemic disease associated with metabolic abnormalities.[1] The crosstalk between keratinocytes (KCs) and immune cells has always been considered an indispensable factor in initiating and maintaining the state of psoriasis disease.[2–4] The latest research indicates that the metabolic energy supply pathway of KCs in psoriasis experiences alterations, which are characterized by increased glycolysis.[5] Meanwhile, the incorporation of metabolic syndrome improves the process of glucose metabolism reprogramming in KCs within the skin lesions of psoriasis patients. On the one hand, glycolysis is the primary source of energy required for the proliferation of KCs;[6] on the other hand, glycolysis further promotes the inflammatory cascade of KCs by stimulating immune cells activation. Under the interaction of immune inflammation and metabolic disorders, the proliferation of KCs continues to intensify, leading to the deterioration of the disease.

Decoding the metabolic commonalities between immune cells and KCs and correcting immune metabolic imbalances, is of great significance for the creation and study of new medications for psoriasis. This article aims to review the function of glycolysis in the pathogenesis of psoriasis. Additionally, it will discuss the enzymes, key regulatory factors and related pharmacological modulators involved in psoriasis glycolysis, aiming to explore new opportunities for the diagnosis and treatment of psoriasis.

Glycolytic Metabolism

Glucose breakdown metabolism is the most important way for organisms to obtain energy. There are three primary pathways for the oxidation and decomposition of glucose in living organisms: anaerobic oxidation (also known as glycolysis), oxidative phosphorylation, and pentose phosphate. Six carbon glucose molecules are catalyzed by various key enzymes to

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decompose into two molecules of pyruvic acid. When there is adequate oxygen supply, pyruvate primarily enters the mitochondria and undergoes complete oxidation to carbon dioxide and water through the tricarboxylic acid (TCA) cycle. When there is insufficient oxygen supply or impaired oxygen utilization, pyruvate is further catalyzed to lactate. Typically, normal cells primarily derive energy through the process of aerobic respiration. However, evidence has emerged implicating glycolysis as significant pathogenic characteristic in several illnesses, including autoimmune diseases[7] and cancer.[8] The availability of enough energy within a relatively short time is essential for cancer cells. Consequently, unlike normal cells, cancer cells preferentially get energy via glycolysis to support their accelerated growth, even under oxygen-rich conditions. This phenomenon is referred to as the "Warburg effect".[9] Immune cells and cancer cells have similarities in their requirement for adequate metabolic flux and bioenergetics to facilitate macromolecule synthesis, as well as cell growth and expansion.[10] Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease primarily impacting joints and extra-articular tissues.[11] In inflammatory joints, hypoxia modifies cellular bioenergetics by inducing mitochondrial dysfunction and facilitating a switch to the glycolytic pathway.[12] Lactate, a metabolic intermediate produced during glycolysis, facilitates cancer progression through various mechanisms, including the maintenance of metabolic symbiosis, serving as a substrate for the TCA cycle, suppressing the immune system and et al.[13] Meanwhile, it can regulate immune responses and sustain persistent chronic inflammation in RA joints.[14]

Psoriasis and Glycolytic Metabolic Disorders

Although psoriasis is a benign illness, the pathological phenomenon of rapid proliferation of KCs is similar to that of cancer cells. On the one hand, cell proliferation leads to an increase in both oxygen demand and supply. On the other hand, the pathological phenomenon of epidermal spinous layer hyperplasia further exacerbates hypoxia, resulting in hypoxia in the local lesions of psoriasis. As the oxygen content decreases, the energy generation of KCs transitions from oxidative phosphorylation to oxygen-independent glycolysis pathways.[15] While psoriasis glycolysis and cancer have certain similarities, they also differ somewhat. Compared to KCs, cancer cells usually exhibit higher rates of aerobic glycolysis. Apart from variations in glycolysis rates, it can also rely on whether the body regulates it autonomously. In normal tissues, cells receive growth factor signals from the body to utilize nutrients for growth.[16] However, one function of oncogenic pathways is to promote cell-autonomous nutrient uptake and program proliferative metabolism.[17]

Research shows that the glucose uptake and glycolytic energy supply of psoriatic KCs are significantly enhanced.[18] Psoriatic lesions exhibit heightened requirements for glucose uptake and metabolism in comparison to healthy persons.[19] Patients with psoriasis exhibit increased glycolysis and amino acid metabolism activity, as indicated by the systems metabolomics technique.[20] In addition, positron emission tomography/Computed Tomography imaging demonstrates a correlation between the cutaneous [18F]-fluorodeoxyglucose uptake and clinically apparent psoriatic lesions.[21] In the GSE85034 dataset, an additional study indicated a positive association between the severity of psoriasis and the scores of glycolysis gene signatures.[22]

In addition, immune cells infiltrated locally in psoriasis lesions also exhibit enhanced glycolysis. Skin lesions from psoriasis models show increased levels of macrophage glycolysis.[23] In comparison with healthy controls, the glycolytic metabolic activity of $CD4^{+}$T cells in the serum of patients with psoriasis[24] and immunosuppressive cells (such as regulatory T cells)[25] in local skin lesions are upregulated. There is a correlation between disease severity and C-X-C motif chemokine receptor 4 (CXCR4) ^{hi} neutrophils in both the peripheral blood and inflamed psoriatic skin, when compared to healthy controls. $CXCR4^{hi}$ neutrophils show a metabolic shift towards glycolysis along with heightened pro-inflammatory functions.[26]

Overall, glycolysis is a distinct feature in the pathogenesis of psoriasis. Psoriasis KCs and immune cells both undergo metabolic reprogramming, relying mostly on glycolysis for glucose metabolism to maintain or complete their self-accelerating life processes. Therefore, it is imperative to comprehend the fundamental mechanism of glycolysis in psoriasis.

Role of Glycolysis in Psoriasis

Regulating KCs Proliferation and Differentiation

The nutrients and energy required for biosynthesis are provided by cellular metabolism to support cell proliferation and growth. Studies suggest that the rate of cell proliferation is correlated with metabolic characteristics and activity.[27] Cells that are rapidly proliferating tend to use glucose as a synthetic substrate for bioenergy. Recent investigations have found that enhanced glycolysis promotes glucose uptake and cell proliferation in KCs.[28] The increase of peroxisome proliferator-activated receptors δ induces anaerobic glycolysis, which is a beneficial metabolic pathway for maintaining KCs proliferation due of it is a significant source of adenosine triphosphate (ATP).[6] In psoriatic, dermal-derived mesenchymal stem cells (DMSCs) enhance glycolysis and proliferation in HaCaT cells while decreasing cell junctions.[29] Interleukin (IL)-27 promotes glycolytic enzyme expression, mitochondrial activity, and mitochondrial fusion, all of which contribute to the maintenance of KCs proliferation.[30]

In addition to cell proliferation, the inhibition of glycolysis had an impact on HaCaT cells differentiation and inflammatory mediator secretion.[5] Uridine phosphorylase-1 enhances cell viability and cell-cycle progression in human epidermal KCs by regulating the glycolytic pathway, according to research by Xiao et al.[31] These studies indicate that glycolysis plays an important role in regulating the proliferation and differentiation of KCs.

Regulating Immune Cell Differentiation

An excellent review published in 2007 proposed that psoriasis exists a "KCs response phase" triggered by the immunological response and inflammation of the skin.[27] Currently, the comprehension of psoriasis's pathophysiology still follows this perspective. The differentiation of naïve $CD4^+$T cells into T helper type (Th) 17 cells is essential for the development of psoriasis.[32]

It is widely recognized that inflammation has the potential to regulate both local and systemic metabolism and vice versa.[33] Metabolic reprogramming refers to modifying various metabolic processes and regulating the function and phenotype of immune cells to meet the regulation and execution of immune functions.[34] Von Meyenn et al[35] described in detail the role of T cell metabolic reprogramming in inflammatory skin diseases. In psoriatic epidermis, metabolic and nutrient sensing pathways might regulate the activation and differentiation of immune cells and KCs.[18] Cyclin-dependent kinase 7 regulates glycolytic metabolism through the activated protein kinase B (Akt)/mammalian target of rapamycin (mTOR)/hypoxia-inducible factor-1α(HIF-1α) pathway, which in turn modulates $CD4^+$Tcell activation and Th17/Th1 cell differentiation, and so contributes to the pathogenesis of psoriasis.[24] CD147/basigin serves as a molecular marker that is associated with high proliferation and low differentiation of KCs, as well as a susceptibility gene for psoriasis. CD147 is significantly upregulated in the peripheral blood of psoriasis patients compared to healthy individuals.[36] The naïve CD4 +T cells of CD147-deficient mice demonstrated a diminished capacity to differentiate into Th17 cells.[37] By controlling T cell glycolysis and inducing Th17 cell differentiation, CD147 is believed to have a role in the development of psoriasis.[38]

Metabolic reprogramming can affect the fate of T cells. Meanwhile, regulating the metabolic state of T cells can also orchestrate their immune function.[39–41] Immunometabolism is the interaction between the immune cells and metabolic processes in physiological or pathological conditions.[42] It primarily investigates the relationship between the functioning of immune cells and the pathways of intracellular energy metabolism, along with their regulatory effects on diseases.[43] Research has shown that immune metabolic disorders are closely associated with the pathogenesis of psoriasis.[44] Lysophosphatidylcholine (LPC) is a kind of glycerophospholipid and a precursor of lysophosphatidic acid (LPA). LPC abundance is significant in relation to the glycolytic activity in the imiquimod (IMQ)-induced psoriasis-like dermatitis model.[45] On the one hand, LPC activates KCs and directly promotes Th1 differentiation through glycolysis, which enhances the IMQ-induced psoriatic mouse model. On the other hand, LPC indirectly promoted Th17 differentiation by stimulating the release of IL-1β in the coculture system of KCs and T cells.[45] This metabolic circuit is a novel finding regarding the immune metabolic interaction mechanism in psoriasis. Consequently, the interaction between metabolic pathways and immune cells may jointly lead to abnormal inflammation in psoriasis.

Key Enzymes of Glycolysis in Psoriasis

Glycolysis is the initial stage of glucose catabolism, which is comprised of ten enzyme processes. Glucose transporter (GLUT)s enable the transportation of glucose across a plasma membrane. Hexokinase (HK), phosphofructokinase (PFK), and pyruvate kinases (PKs) catalyze three irreversible processes. The increase in glycolysis rate is intricately linked to the increase or heightened activity of key glycolytic enzymes. Here, we mainly discuss the role of GLUTs and enzymes that control the glycolysis rate in psoriasis.

GLUTs

The first stage of cellular energy metabolism involves the passage of glucose molecules through the lipid bilayer of the cell membrane with the help of transport proteins, achieving cellular uptake of glucose. In humans, fourteen distinct GLUTs have been discovered.[46] GLUT1–4 and GLUT14 have been extensively studied and are classified together.[47]

GLUT1 is a glucose transporter protein that is embedded in the cell membrane, which functions to transport glucose along a concentration gradient. GLUT1 is the sole significant hexose transporter expressed in epidermal KCs, in contrast to numerous other tissues.[48] GLUT1 expression is increased in psoriatic epidermis and is positively associated with disease severity,[49,50] acanthosis degree, and the percentage of Ki-67 expression,[51] suggesting that GLUT-1 could potentially be a target for addressing aberrant hyperproliferation in psoriasis. In vitro studies also showed Research has shown that the administration of exogenous IL-6, IL-17, IL-23 and IL-36 to HaCaT cells leads to an increase in the expression of GLUT1.[52] Huang et al[53] found that GLUT1 in mouse KCs of the control group had a distribution within the cytoplasm, however in the IMQ group, it was significantly enriched on the cellular membrane, indicating that GLUT1 was highly activated and could potentially facilitate glucose uptake in hyperproliferative KCs. Evidence from single-cell RNA sequencing demonstrated that GLUT1 and mono-carboxylate transporters 1(MCT1) expression levels rose in psoriasis-related undifferentiated KCs, increasing in glucose and lactate uptake.[54] This metabolic shift contributes to the pathophysiology of psoriasis by promoting cell proliferation through the glycolytic pathway and supporting cell differentiation via the TCA cycle. Psoriatic plaques and UV-induced hyperplasia both show elevated GLUT1 expression, which is consistent with its role in stimulating the proliferation of KCs.[55,56] CD147 is a newly discovered companion of GLUT1 in KCs. According to recent research, CD147 increases glucose uptake by interacting with GLUT1.[57] This leads to an increase in glycolytic activity and worsens inflammation in psoriasis. KCs that were deficient in GLUT1 displayed metabolic disorders, oxidative stress, as well as impaired proliferation.[48] The inhibition of GLUT1-mediated glucose uptake, according to Cibrian et al,[18] may serve as a new approach to regulate the proliferation of KCs, while also having immunoregulatory effects on proinflammatory cytokines. Psoriatic KCs reprogram the metabolism and proliferation of DMSCs by upregulating the expression levels of GLUT1 in DMSCs.[58] mRNA of GLUT1, HK2, and vascular endothelial cell differentiation were increased in psoriatic DMSCs, indicating that vascular differentiation and local vascular abnormalities in psoriasis patients were impacted by the aberrant glucose metabolism level of DMSCs.[59] Thus, it was hypothesized that the disrupted glucose metabolism in DMSCs may affect their proliferation ability, leading to the pathophysiological development of psoriasis. Overall, GLUT1 is involved in the pathogenesis of psoriasis by promoting epidermal hyperproliferation, inflammation and angiogenesis.[50]

Lysophosphatidylcholine acyltransferase 1 (LPCAT1) is a member of the lysophosphatidylcholine acyltransferase family, which can regulate the stability of biofilm structures and signal transduction.[60] Research has shown that LPCAT1 regulates the activity of GLUT3 in KCs by nuclear transcription factor kappa B (NF-κB)/signal transducer and activator of transcription 3 signaling, leading to increased glycolysis of KCs and promoting proliferative and proinflammatory effects. LPCAT1 inhibition in animal experiments resulted in a decrease in the infiltration of neutrophils and T cells in skin lesions, a reduction in epidermal hyperplasia, and alleviation of skin inflammation in IMQ-treated mice.[61] The pro-inflammatory cytokines interferon gamma and tumor necrosis factor function in conjunction to swiftly induce GLUT4 to translocate to the plasma membrane.[15] This process triggers intracellular signaling that relies on activated monophosphate protein kinase, thus enhancing the glucose uptake and glycolytic capability in KCs.

HK

HK is situated on the outer membrane of mitochondria and serves as the first rate-limiting enzyme in glycolysis. It has the capacity to phosphorylate glucose into 6-phosphate glucose, an irreversible reaction that consumes energy. Four isoforms of HK, namely HK1-4, have been discovered in mammals, with HK2 being the most active isoform in this family.[62] In comparison to healthy individuals, psoriasis patients showed an increase in the expression of HK2. In addition, increased IL-23 expression in dendritic cells and psoriasis-like inflammatory responses are linked to metabolic adaptation of glycolysis through HK activity.[63]

6-Phosphofructo-2-Kinase/Fructose-2,6-Biphosphatase 3(PFKFB3)

PFK-1 controls cellular glycolytic flux by converting the initial fructose-6-phosphate committed during glycolysis into fructose-1,6-bisphosphate(F1,6BP). PFKFBs is the most powerful allosteric activator of the enzyme PFK-1. PFKFB3 is a key regulator of glycolytic metabolism in proliferative human KCs, which are responsible for sustaining the hyperproliferative and poorly differentiated phenotype of psoriatic epidermis.[64]

PKM2

PKs, a homotetrameric enzyme, catalyses the final and rate-limiting step of the glycolytic process. It transfers the high-energy phosphate from phosphoenolpyruvate to two molecules of adenosine diphosphate, resulting in the production of two molecules of ATP and pyruvate. There are four isoforms of PKs, specifically L, R, M1, and M2. Among these, the PKM2 tetramer primarily controls the glycolytic process.[65] There is a positive correlation between the degree of KCs proliferation and the expression level of PKM2.[66] Aerobic glycolysis and KCs proliferation were aided by PKM2 expression and nuclear translocation in the epidermis of psoriasis patients.[67] Overexpression of PKM2 enhanced the glycolytic metabolism of KCs, and knockdown of PKM2 decreased the proliferation and glycolysis of KCs.[68] Research has shown that the mechanism by which PKM2 affects KCs is mainly to regulate the NF-κB transcriptional signaling downstream of IL-17 receptor in KCs, thereby initiating cutaneous psoriatic inflammation.[69] Meanwhile, silent information regulator 2 alleviates psoriasiform cutaneous inflammation by inhibiting the PKM2/signal transducer and activator of the transcription 3 (STAT3) pathway.[70]

Lactate Dehydrogenase (LDH)

Lactate is the predominant byproduct of glycolytic metabolism, and its level is significantly elevated in the epidermis of psoriasis lesions.[71,72] Lactate produced by "glycolytic" cells can serve as a carbon source for "non-glycolytic" cells.[73] Research has found that lactate induces type 17 immune responses.[74] IL-17 stimulates the production of HIF-1α in the epithelial cells, leading to increased glycolysis in psoriasis. In turn, lactate produced by glycolysis stimulates γδ T cells to maintain the production of IL-17, thereby forming a feedback loop that perpetuates psoriasis.[74] Inhibiting lactate synthesis or transport can protect mice from IMQ-induced inflammation and restrain γδ T17 cells.[74] Recent research indicates that the psoriatic skin disorder is a result of the crosstalk between the epidermis and macrophages that is mediated by lactate.[75] The production of lactate is increased as a result of enhanced glycolysis in the epidermis. Increasing lactate levels may activate the NF-κB pathway, which polarizes macrophages into an M2-like fate; this might worsen the inflammation associated with psoriasis.[75]

LDH is responsible for the conversion of pyruvate to lactate.[76] The elevated level of serum LDH in psoriasis is indicative of the increased respiratory activity of T cells. A relationship was seen between clinical improvement and serum LDH level in psoriasis patients who received apremilast treatment.[77] Through nuclear translocation and phosphorylation, cytoskeletal protein keratin 17 stimulates the transcription of LDHA, resulting in increased glycolysis and proliferation of KCs in vitro.[78]

Others

The expression of phosphoglycerate mutase 1 (PGAM1) was elevated in the lesional KCs of psoriasis patients, as determined by proteomic profiling.[79] The LPA-induced aerobic glycolysis was markedly reduced when PGAM1 was

knocked down in HaCaT cells.[80] Aryl hydrocarbon receptor modulates and controls the differentiation of KCs by downregulating the expression of GLUT1 and the glycolytic enzyme, enolase 1, hence inhibiting glycolysis.[81] Fructose-1,6-bisphosphatase (FBP1) is a rate-limiting gluconeogenic enzyme that catalyzes the hydrolysis of fructose-1,6-bisphosphate to fructose-6-phosphate. Research has shown that the expression of FBP1 was significantly decreased in human psoriatic lesions and skin of the IMQ mouse psoriasis model.[82] FBP1 deficiency enhances the inflammatory infiltration and epidermal hyperplasia in animal models of psoriasis through glycolysis and acetyl-CoA-dependent mechanisms.[82]

Key Regulatory Factors of Glycolysis

The immune inflammatory response in psoriasis is further exacerbated by the elevated metabolic demand of epithelial cells. Meanwhile, immune cells or inflammatory cells infiltrating psoriasis lesions also exhibit similar metabolic reprogramming phenomena similar to KCs. Therefore, cellular metabolic reprogramming centered on glycolysis is the key to the pathogenesis of psoriasis. Nevertheless, the uptake of glucose from the environment and its intracellular metabolism is a strictly regulated process. This process is influenced by the crosstalk between growth signals and metabolic pathways. In this study, we primarily explore the involvement of the mTOR and HIF-1α signaling pathways, as well as protein post-translational modifications, in the regulation of glycolysis. See Figure 1 for a comprised overview of the interplay between glycolytic enzymes and key regulatory factors in psoriasis.

mTOR

mTOR, the master sensor of nutrients and growth factors, plays a critical role in the extracellular nutrient status triggers and the promotion of cell differentiation and proliferation. High-glucose and high-fat culture intensified glucose metabolism reprogramming in psoriasiform KCs partially through the Akt/mTOR pathway, indicating that the reprogramming of glucose metabolism in KCs contributes to heightened psoriatic inflammation in metabolic syndrome.[5] LPA promotes the expression of PGAM1 through the Akt/mTOR/HIF-1 α/LPA receptor (LPAR)1 axis, thereby increasing aerobic glycolysis in psoriasis.[80] In addition, mTORC1 regulates the differentiation of peripheral γδ T cells into γδ T17 cells by mechanisms that involve glycolysis.[83]

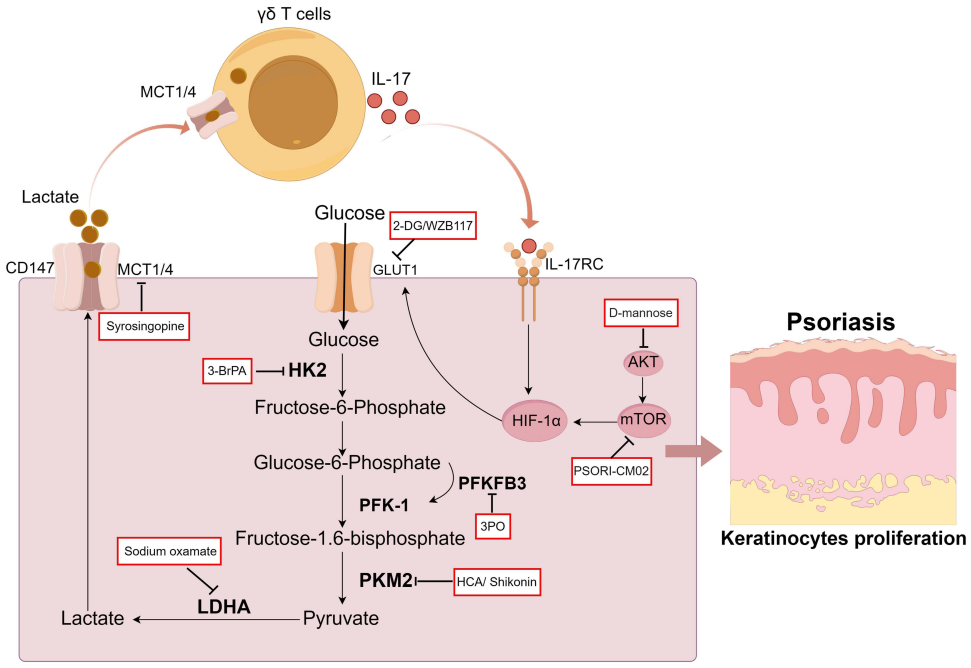

Figure 1 An interplay between glycolytic enzymes and key regulatory factors in psoriasis. Enzymes are indicated in bold. Key regulatory factors are indicated in pink. Pharmacological modulators of the glycolysis process are represented by red boxes. Created by Figdraw (www.figdraw.com).

HIF-1α

The transcription factor HIF-1 α can adjust to hypoxic environments and trigger the transcription of genes that are downstream of its action. Typically, HaCaT cells do not express HIF-1 α unless they are stimulated by hypoxia or inflammatory signals.[68] Overexpression of HIF-1α stimulates the proliferation of KCs while suppressing their terminal differentiation.[84] Another important role that HIF-1 α plays in psoriasis is enhancing glycolysis in HaCaT cells through increasing the expression of CD147 and GLUT1.[85] The epidermal metabolic reprogramming mediated by HIF1a is crucial to the pathogenesis of psoriasis.[74]

The mouse model of psoriasis can be alleviated by suppressing the activation of HIF-1α and impeding the associated glycolysis. In addition, research has shown that suppressing the p21/HIF-1α/GLUT1 signaling pathway in myeloid-derived suppressor cells can decrease glycolysis, leading to a reduction in Th17 cell infiltration and the alleviation of psoriatic dermatitis in mice.[86] The γδ T cells from the skin-draining lymph node of psoriatic mice exhibited increased expression of p-HIF-1α and upregulated genes linked with glycolysis.[87] Depletion of epidermal HIF-1α or its downstream target, GLUT1, effectively suppressed mouse dermatitis caused by IMQ.[88] Meanwhile, it significantly reduced hypervascularization, hyperinnervation, and the type 17 immune response, which is mostly driven by γδ T cells, in the skin of mice.

Others

In addition to the above regulatory factors, glycolysis can also be impeded by post-translational modifications of glycolytic enzymes. MicroRNAs are short non-coding RNAs composed of approximately 22 nucleotides. By specific complementary binding to their target messenger RNAs, they regulate gene expression at the posttranscriptional level. MiR-155 may enhance the glycolysis of psoriatic mesenchymal stem cells, hence stimulating the proliferation of psoriatic mesenchymal stem cells.[89] The m6A modification is the process of methylating the nitrogen atom at the sixth site of adenine in RNA molecules. IL-6 stimulates methyltransferase-like protein 14 in HaCaT cells, resulting in m6A methylation of triple domain protein 27. This methylation enhances the stability of triple domain protein 27 and facilitates its activation, ultimately leading to the activation of STAT3 and promoting enhanced viability, glycolysis, and inflammation in HaCaT cells.[90]

Pharmacological Modulators of Glycolysis in Psoriasis

The current treatment approaches for psoriasis mainly depends on the severity and type, patient preferences, and whether there are comorbidities. Conventional therapies for psoriasis include corticosteroids, vitamin D analogs, calcineurin inhibitors, phototherapy, methotrexate, cyclosporine, acitretin, and apremilast.[91] Conventional therapies for psoriasis including corticosteroids, vitamin D analogs, calcineurin inhibitors, phototherapy, methotrexate, cyclosporine, acitretin, and apremilast. Immunometabolism is a field that has recently attracted a lot of attention due to evidence linking immunological activation in psoriasis. According to Subudhi and Konieczny et al[74] hold that the metabolic coordination between skin epithelium and type 17 immunity sustains chronic skin inflammation in psoriasis. The regulation of immunometabolism has significant promise as a treatment for psoriasis. Modulating glycolysis can modulate immune cell-mediated chronic inflammation of psoriasis.[92] A new method for treating psoriasis is to regulate the flow and direction of glycolytic substrates to rectify immunometabolism imbalances. Recent research indicate that therapeutic drugs aimed against glycolysis-related molecules provide potential therapeutic efficacy in psoriasis, as demonstrated in in vitro and in vivo investigations. A summary of pharmacological modulators of glycolysis in psoriasis is shown in Table 1.

2-deoxy-D-glucose (2-DG), a glycolysis inhibitor, is a possible therapeutic target in Th-17-dependent disorders, such as psoriasis. By suppressing GLUT1 expression in KCs, 2-DG was able to alleviate the psoriatic lesions in in vivo animal model.[53] In mouse primary KCs, 2-DG can reduce the production of proinflammatory molecules generated by IL-17A.[57] The pharmacological inhibition of GLUT1 with the agent WZB117 led to a reduction in the inflammatory response in skin biopsies from psoriasis patients and decreased hyperplasia in psoriasis animal models.[48] The proliferation and glycolysis of M5-stimulated HaCaT cells were greatly reduced by the HK2 inhibitor 3-bromopyruvate (3-BrPA). Meanwhile, the topical administration of 3-BrPA demonstrated significant therapeutic efficacy in an IMQ mouse

Table 1 Pharmacological Modulators of Glycolysis and Their Putative Therapeutic Application in Psoriasis

Metabolic Target	Pharmacological Intervention	Cellular Effect	Psoriatic Phenotype Effect	References
GLUT1	2-DG	Glycolysis inhibition	Skin thickness reduction and improved skin lesions in mice	[53, 57]
	WZB117	Glucose uptake inhibition	Decreased inflammation in human skin biopsies and reduced hyperplasia in mice	[48]
HK	3-BrPA	Glycolysis inhibition	Inhibition of HaCaT cells proliferation in vitro and alleviation epidermal thickening in mice	[93]
PFKFB3	3PO	Glucose uptake inhibition	Inhibition of KCs proliferation and promote differentiation	[64, 94, 95]
PKM2	HCA	Glucose inhibition	Suppression of T cell activation and Th17 cell differentiation in vitro, alleviation psoriatic phenotype in mice	[96]
	Shikonin	Glucose inhibition	Inhibited KCs proliferation in mice	[97]
LDHA	Sodium oxamate	Glucose inhibition	Limited epithelial thickness and cutaneous T cell numbers in mice	[74]
MCT1/4	Syrosingopine	Glucose inhibition	Limited epithelial thickness and cutaneous T cell numbers in mice	[74]
mTOR/ HIF-1a	D-mannose	Glucose inhibition	Suppressed γδ T cell reaction	[87]
mTOR/HK2	PSORI-CM02	Glucose inhibition	Inhibition of KCs proliferation in mice	[98]
HIF-1a, HK	Resveratrol	Glucose inhibition	Decreased macrophages infiltration in mice	[23]

model, decreasing the PASI score and mitigating epidermal thickening.[93] A small molecule antagonist of PFKFB3, 3-(3-pyridinyl)-1-(4-pyridinyl)-2-propen-1-one (3PO), inhibits the proliferation of KCs in the epidermis and promote differentiation.[64] After treating the skin of mice with IMQ, researchers found that 3PO prevented the development of a psoriasis-like dermatitis.[94] Furthermore, 3PO can efficiently prevent the synthesis of fructose-2,6-diphosphate, uptake of 2- [1–14 C]-deoxy-D-glucose, production of lactate and activation of T cells.[95] 2′-Hydroxycinnamaldehyde (HCA), the active component isolated from the stem bark of Cinnamomum cassia. Studies have demonstrated that HCA inhibited PKM2 and STAT3 signaling, leading to the suppression of T cell activation, the differentiation of Th17 cells, and the hyperproliferation of KCs, hence alleviating IMQ-induced psoriasiform inflammation.[96] Through blocking PKM2 in KCs, shikonin alleviates psoriasis-like skin lesions in mice induced by IMQ.[97] Treated mice with either sodium oxamate (LDHA inhibitor) or syrosingopine (inhibitor of lactate transporters MCT1 and MCT4) during the course of IMQ treatment can reduce epithelial thickness and the quantity of cutaneous T cells.[74]

D-mannose, a hexose sugar, could alleviate experimental psoriasis by suppressing γδT cells via inhibition of glycolysis and AKT/mTOR/HIF-1a signaling.[87] PSORI-CM02, a traditional Chinese medicine formula, has an anti-proliferative effect on psoriatic KCs, by inhibiting the mTOR/HK2/glycolysis axis.[98] Resveratrol alleviated psoriasis symptoms by suppressing macrophages infiltration and glycolysis.[23]

The above pharmacological modulators have shown therapeutic effects on psoriasis in vivo or in vitro. However, similar to cancer treatment, the inhibition of glycolysis can impede tumor development, but with various side effects. The biggest problem related to glycolysis-based therapies is the systemic adverse effects caused by the unexpected involvement of off-target cells. In addition to KCs, glycolytic enzymes may also predominate in the metabolism of other cells inside the body. Inhibitors that selectively target KCs glycolysis should be developed to effectively mitigate the pathological evolution of psoriasis without compromising the function of other cells.

Conclusion

Psoriasis is an immune-mediated inflammatory skin disease. It is commonly accepted that the crosstalk between hyperproliferative KCs and activated inflammatory cells plays a significant role in the progression of psoriasis. Nevertheless, new evidence indicates that metabolic disorders of KCs and immune cells maintains psoriasis chronic skin inflammation. Due to the rapid proliferation and high energy demand of KCs, the supply of glycolytic energy in psoriasis lesions increases. Immune cells undergo metabolic reprogramming similar to KCs. The glycolysis pathway releases lactate to promote immune cell differentiation. In turn, differentiated immune cells further promote KCs glycolysis by releasing inflammatory factors, thereby forming an immunometabolism circuit. Disease circuits are fed by inflammation-driven epithelial glycolytic programs, which intrinsically modulate epithelial behavior and extrinsically enhance immunoreaction. Therefore, immune metabolic interaction is the intrinsic basis for the excessive proliferation of KCs and the abnormal differentiation of immune cells. A promising strategy for the treatment of psoriasis is to establish a metabolic-centered immune regulatory network. Targeting this network should be able to break the immune metabolic circuit, inhibit immune cell glycolysis, reprogram pro-inflammatory cell metabolism to a normal state, and ultimately achieve non-immunosuppressive therapy for psoriasis. Overall, continued research in this field may lead to the development of new diagnostic and therapeutic opportunities for a range of diseases.

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Disclosure

The authors declare no conflicts of interests in this work.

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