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Role of Th1/Th2 imbalance mediated by T cell glycolytic rate-limiting enzymes hexokinase 2, phosphofructokinase-1, and pyruvate kinase M2 in oral lichen planus

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ABSTRACT

Background: We aimed to explore the role of T helper cell 1 (Th1)/Th2 imbalance mediated by T cell glycolytic rate-limiting enzymes hexokinase 2 (HK2), phosphofructokinase-1 (PEK1) and pyruvate kinase M2 (PKM2) in oral lichen planus (OLP).

Methods: A total of 120 OLP patients treated in our hospital and 120 volunteers undergoing extraction of impacted teeth between January 2023 and January 2024 were recruited as study and control groups, respectively. The expressions of HK2, PEK1, PKM2, Th1 cytokine interferon-γ (IFN-γ) and Th2 cytokine interleukin-4 (IL-4) in the oral mucosa were measured. Analyses were conducted on the correlations of HK2, PEK1, and PKM2 with the Th1/Th2 cytokines IFN-γ and IL-4 as well as their diagnostic values for OLP.

Results: Higher expressions of HK2, PEK1 and PKM2, increased mRNA expression of IL-4 and a reduced mRNA expression of IFN-γ were detected in the oral mucosa of OLP patients with erosion, severe lymphocyte infiltration and severe liquefaction degeneration of basal cells ($P<0.05$). According to receiver operating characteristic curves, the diagnostic efficiency of the combination of T cell glycolytic rate-limiting enzymes (HK2, PEK1 and PKM2) with Th1/Th2 cytokines (IFN-γ and IL-4) was higher than that of any single indicator.

Conclusions: Increased expressions of T cell glycolytic rate-limiting enzymes HK2, PEK1 and PKM2 and obvious Th1/Th2 imbalance are found in the oral mucosa of OLP patients, being associated with the basic pathological changes.

Keywords: enzyme, glycolysis, imbalance, oral lichen planus, T helper cell

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INTRODUCTION

Oral lichen planus (OLP), as a chronic inflammatory disease of the oral mucosa mediated by immune responses, is usually characterized by banded infiltration of T lymphocytes in lamina propria or destruction of basal cells. OLP frequently occurs in middle-aged people [1,2]. It is classified into non-erosive and erosive OLP based on clinical manifestations. The former usually displays no obvious symptoms, whereas the latter is often accompanied by various degrees of eating-induced irritating pain or spontaneous pain. OLP has a malignant transformation rate of as high as 1.0-3.0% [3]. Currently, OLP is diagnosed based on clinical and histopathological changes together with typical linea alba on the cheek in most cases, but its specific pathogenesis remains unclear.

OLP is induced by various factors like stress, anxiety, mechanochemical stimulation, habits of smoking and drinking, and endocrine and immune network abnormalities, especially immune response disorders mediated by T cells in immunity [4,5]. Upon activation, T cells shift their metabolic processes toward glycolysis, even in the presence of ample oxygen, a phenomenon known as the Warburg effect [6]. This metabolic switch provides the necessary energy and biosynthetic precursors for rapid cell proliferation and effector functions, driving the differentiation of T cells into distinct subsets, such as T helper cell 1 (Th1) and Th2 [7]. In the context of OLP, a chronic inflammatory disease with autoimmune features, this shift towards glycolysis may play a pivotal role in driving the Th1/Th2 imbalance observed in affected patients [8]. Similar metabolic shifts are seen in other au-

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toimmune diseases, such as rheumatoid arthritis, where aberrant T-cell activation and differentiation are central to disease pathology [9]. In these conditions, increased glycolytic activity not only sustains the inflammatory response but also enhances the survival and function of pathogenic T-cell populations. Understanding these parallels may offer new insights into the metabolic underpinnings of OLP and provide a rationale for targeting glycolytic pathways as a potential therapeutic strategy [10].

Glycolytic metabolism plays a key role in the activation of T cells and is associated with the proliferation and differentiation of T cells [11]. In the case of raised expression of glycolytic metabolic enzymes, the differentiation into Th1 and Th2 cells is accelerated, and the secretion of Th1/Th2 cytokines interferon-γ (IFN-γ) and interleukin 4 (IL-4) is enhanced. As a result, OLP occurs. Acting as T cell glycolytic rate-limiting enzymes, hexokinase 2 (HK2), phosphofructokinase-1 (PEK1) and pyruvate kinase M2 (PKM2) are crucial factors for regulating the metabolic rate of glycolysis. However, their mechanisms of action in Th1/Th2 imbalance are still largely unknown [12].

In this study, therefore, the correlations of HK2, PEK1 and PKM2 with Th1/Th2 imbalance in the oral mucosa of OLP patients were analyzed, rendering references for the diagnosis and treatment of OLP in clinical practice.

METHODS

Clinical data

A study group including 120 OLP patients treated in our hospital from January 2023 to January 2024 was set up. The study group consisted of 68 males and 52 females aged 35-68 years old, (47.65±5.31) years old on average. In terms of the disease type, there were 65 and 55 cases of erosive and non-erosive OLP, respectively.

The following inclusive criteria were employed: 1) patients diagnosed with OLP based on clinical manifestations (with linea alba on the oral mucosa, irritating pain and burning pain when eating stimulating food, and no skin damage) and histopathological examination (with blurred basement membrane, liquefaction degeneration of basal cells, and gathering of massive lymphocytes in the lamina propria under a histopathological microscope), and 2) those who were diagnosed for the first time, had not received any disease treatment, and had no history of immunotherapy in the past 3 months.

The exclusion criteria involved: 1) patients with diseases possibly posing an impact on glycolytic metabolism such as diabetes mellitus and hypertension, 2) those with oral submucosal fibrosis, chronic discoid lupus erythematosus, oral leukoplakia, and other oral diseases potentially affecting the immune system, 3) those with malignant tumors, 4) those with severe damage or failure of vital organs, 5) those with a history of oral diseases, 6) those with periodontitis, gingivitis or other oral mucosal diseases during oral examination, 7) those who had used glucocorticoids, antibiotics or other drugs in the past 3 months, or 8) those with mental or communication disorders.

Besides, 120 volunteers receiving the extraction of impacted teeth in our hospital in the same period were enrolled as a control group, including 63 males and 57 females aged 35-69 years old, with a mean of (48.13±5.77) years old. The subjects in the control group had normal physical examination results, no history of oral diseases, no injury or inflammation in the oral mucosa, and no diseases affecting glycolytic metabolism and immune function. In addition, their oral mucosa samples collected during the extraction of impacted teeth were proven to be normal. No differences of statistical significance were found between the two groups in terms of general data like gender and age ($P>0.05$).

All subjects voluntarily participated in this study and signed the informed consent form on the acquisition and use of the mucosa, and such acquisition and use were approved by the ethics committee of Children's Hospital of Nanjing Medical University on January 6th, 2023 (approval No. CHNMU202301002).

Sampling of mucosa

The oral mucosa was removed during the histopathological examination in the study group and during the extraction of impacted teeth in the control group, respectively. Next, the oral mucosa samples were divided into three portions, with one fixed in 10% formaldehyde solution for histopathological observation, one used for immunohistochemistry, and one stored in a refrigerator at -80°C for real-time quantitative polymerase chain reaction (qPCR).

Histopathological observation

The oral mucosa samples fixed in formaldehyde solution (Sigma-Aldrich, St. Louis, MO, USA, Cat. No. HT501128) were taken out, embedded in paraffin and stained with hematoxylin-eosin. Finally, the pathological scoring of OLP was completed (Table 1) [13].

Table 1. Pathological scoring criteria

Grade	Degree of lymphocyte infiltration	Degree of basal cell liquefaction degeneration
Mild	Shallow infiltration with low density	Cellular edema
Moderate	Shallow infiltration with high density or deep infiltration with low density	Cellular edema or liquefaction
Severe	Deep infiltration with high density	Presence of cracks between the epithelium and connective tissue

Immunohistochemistry

The positive expression rates of HK2, PEK1 and PKM2 in the oral mucosa were measured through immunohistochemistry. In brief, the oral mucosa samples were routinely sliced, deparaffinized, incubated with 3%H2O2 deionized water at ambient temperature, and rinsed 3 times with PBS, 5 min/time. Then they were completely soaked in citrate buffer for 3 min, followed by natural cooling for tissue antigen thermal repair. Next, the samples were blocked with 5% BSA solution and incubated overnight with primary antibodies against HK2 (Abcam, Cambridge, UK, Cat. No. ab104836, diluted at 1: 300), PFK-1 (Cell Signaling Technology, Danvers, MA, USA, Cat. No. 8164, diluted at 1:100) and PKM2 (Abcam, Cambridge, UK, Cat. No. ab137852, diluted at 1:150), and then with HRP-labeled secondary antibodies (Abcam, Cambridge, UK, Cat. No. ab654321, diluted at 1:1000). Afterwards, they were stained with DAB (Vector Laboratories, Burlingame, CA, USA, Cat. No. SK-4100), counterstained with hematoxylin (Sigma-Aldrich, Cat. No. HHS16), transparentized and mounted. Finally, the expressions of HK2, PFK-1 and PKM2 were observed using Eclipse E200 microscope (Nikon, Tokyo, Japan). Positive cells referred to those with yellow or brownish-yellow granules in the cytoplasm or nucleus. Next, the positive expression intensity of HK2, PFK-1 and PKM2 was further determined based on the percentage of positive cells and the staining intensity of cells. In terms of staining intensity, uncolored, light yellow, yellow and brownish yellow were scored 0 point, 1 point, 2 points, and 3 points, respectively. As to the percentage of positive cells, ≤5%, 6-25%, 26-50% and ≥51% were scored 0 point, 1 point, 2 points, and 3 points, respectively. The product of the two of <2 points, 2-3 points, 4-9 points, and 10-12 points suggested negative, weakly positive, moderately positive, and strongly positive, respectively. Two pathologists independently scored the percentage and staining intensity, and the average score was used. Discrepancies between the scores were resolved by a third pathologist. The calculated Cohen's kappa value was 0.85, indicating excellent agreement between the two pathologists.

Real-time qPCR

The expressions of HK2, PEK1, and PKM2 as well as Th1/Th2 cytokines IFN-γ and IL-4 in the oral mucosa were measured by real-time qPCR. Specifically, total RNA was extracted using Trizol reagent (Thermo Fisher Scientific, Waltham, MA, USA, Cat. No. 15596026), followed by reverse transcription into cDNA. Next, real-time qPCR was conducted on ABI 7500 PCR system (Applied Biosystems, USA) using a reaction system composed of 7.5 μL of 2× qPCR mix (Applied Biosystems, USA, Cat. No. 4367659), 1.5 μL of forward and reverse primers, 2.0 μL of reverse transcription products and 4.0 μL of Water Nuclease-Free. The amplification procedure consisted of pre-denaturation at 95°C for 30 s, denaturation at 95°C for 15 s, and annealing and extension at 60°C for 30 s, for totally 40 cycles. U6 gene was utilized as the reference gene, and the relative mRNA expression of target genes was analyzed by the 2-ΔΔΔCt method. The primer sequences are listed in Table 2.

Statistical analysis

Statistical analysis was completed by SPSS 25.0 software (IBM Inc., Armonk, NY, USA). Measurement data were described by mean ± standard deviation (x ± s) and compared between groups by the independent-samples t test. Count data were represented as percentage and compared between groups through the χ2 test. Pearson test was carried out to figure out the correlations of T cell glycolytic rate-limiting enzymes HK2, PEK1 and PKM2 with Th1/Th2 cytokines IFN-γ and IL-4. Receiver operating characteristic (ROC) curves were plotted to explore the diagnostic values of HK2, PEK1 and PKM2 as well as IFN-γ and IL-4 for OLP. $p<0.05$ was considered statistically significant.

Table 2. Primer sequences for qPCR

Gene	Primer sequence (5'→3')
HK2	F: CAACTTCCCTCCTCGCTTCCAGAC, R: CAAGGGTCTGTGCCTGTTCCA
PEK1	F: AGTTGCCCATGTTGTCTCGAAG, R: CATTGTGCCCCCTTTGAGCACG
PKM2	F: TGCCCTAACGCGTTGACGGT, R: AGTTGCGCGCTAAGCTAGTTATG
IFN-γ	F: ACCCTGATTGACTACCTTCTTGAC, R: TTGTTGACCCTGAAATTGGC
IL-4	F: GCCTATGAAGGGTACCACCCC, R: CAGGACTCGGAATATCCT
U6	F: GGCACTGGCACATCAAATC, R: TGCAGACCCTTGGCTCC

Abbreviations: F- forward, HK2- hexokinase-2, IFN-γ- interferon gamma, IL-4- interleukin-4, PEK1- phosphofructokinase-1, PKM2- pyruvate kinase-2, R- reverse.

RESULTS

Positive expressions of HK2, PEK1 and PKM2 in the oral mucosa

The positive expressions of HK2, PEK1 and PKM2 in the oral mucosa were significantly higher in the study group than those in the control group ($p<0.05$) (Table 3). Figure 1 shows the results of immunohistochemistry.

Relative mRNA expressions of HK2, PEK1, PKM2 and Th1/Th2 cytokines in the oral mucosa

The study group had significantly raised relative mRNA expressions of HK2, PEK1, PKM2 and IL-4 and declined relative mRNA expression of IFN-γ in the oral mucosa in comparison with those of the control group ($p<0.05$) (Table 4).

Table 3. Positive expressions of HK2, PEK1, and PKM2 in the oral mucosa

Group	n	HK2	PEK1	PKM2
Control	120	12 (10.0%)	10 (8.3%)	13 (10.8%)
Study	120	98 (81.6%)	102 (85.0%)	86 (71.6%)
χ2		124.129	141.696	91.623
p value		<0.001	<0.001	<0.001

Abbreviations: HK2- hexokinase-2, n- number of subjects, PEK1- phosphofructokinase-1, PKM2- pyruvate kinase-2.

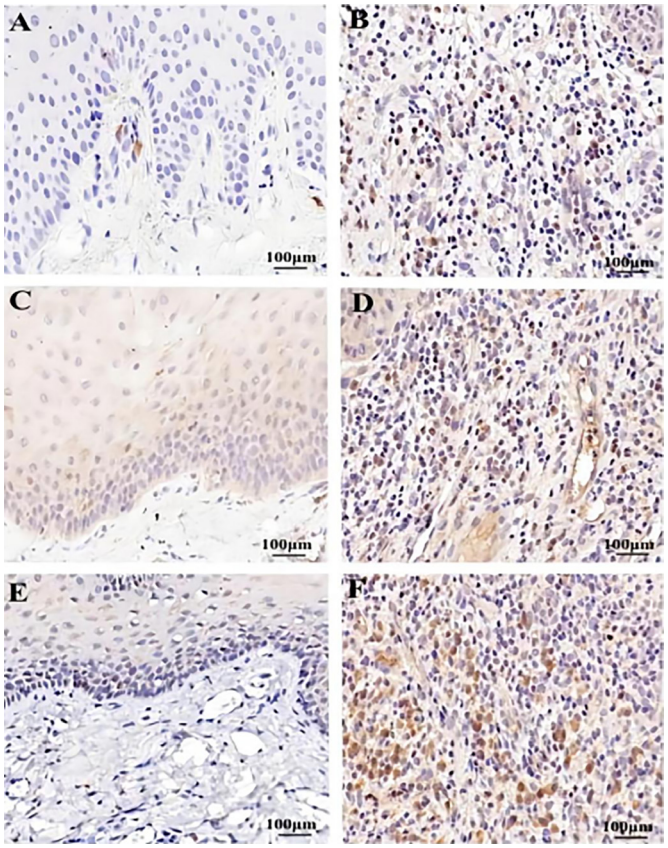

Figure 1. Positive expressions of HK2, PEK1, and PKM2 in the oral mucosa (immunohistochemistry, ×400). A, C, E: control group; B, D, F: study group.

Correlations of HK2, PEK1, and PKM2 plus Th1/Th2 cytokines with clinical characteristics of OLP

HK2, PEK1, and PKM2 plus Th1/Th2 cytokines had associations with disease type, degree of lymphocyte infiltration and degree of basal cell liquefaction degeneration in OLP patients. In other words, compared with non-erosive OLP patients with mild-moderate lymphocyte infiltration and mild-moderate basal cell liquefaction degeneration, erosive OLP patients with severe lymphocyte infiltration and severe basal cell liquefaction degeneration exhibited significantly increased relative mRNA expressions of HK2, PEK1, PKM2 and IL-4 and dropped relative mRNA expression of IFN-γ in the oral mucosa (p<0.05) (Table 5).

Correlations of HK2, PEK1, and PKM2 with Th1/Th2 imbalance

Pearson test revealed close correlations of HK2, PEK1 and PKM2 with Th1/Th2 imbalance. The enzymes were negatively correlated with Th1 cytokine IFN-γ and positively correlated with Th2 cytokine IL-4 (p<0.05) (Figure 2).

Diagnostic values of HK2, PEK1, and PKM2 as well as Th1/Th2 cytokines for OLP

The ROC curves were plotted with the development of OLP as the state variable and the relative mRNA expressions of HK2, PEK1, and PKM2 plus Th1/Th2 cytokines as the test variables. PEK1 had the highest diagnostic efficiency in terms of single indicator diagnosis, that is, the area under curve (AUC) [95% confidence interval (CI)] of PEK1 was 0.890 (0.835-0.946), with the sensitivity of 87.67% and specificity of 82.12%. In comparison with single indicator diagnosis, the combination of indicators displayed significantly improved diagnosis efficiency, that is, AUC (95% CI) of such a combination was 0.901 (0.843-0.957), with the sensitivity of 89.98% and specificity of 85.64% (p<0.001) (Table 6 and Figure 3).

Table 4. Relative mRNA expression levels in the oral mucosa (x ± s)

	n	HK2	PEK1	PKM2	IFN-γ	IL-4
Control group	120	1.02±0.11	1.12±0.21	1.19±0.18	1.00±0.10	1.03±0.12
Study group	120	1.87±0.21	1.90±0.27	2.20±0.24	0.45±0.05	1.44±0.17
t		39.280	24.980	36.880	53.890	21.580
p value		<0.001	<0.001	<0.001	<0.001	<0.001

Abbreviations: HK2- hexokinase-2, IFN-γ- interferon gamma, IL-4- interleukin-4, n- number of subjects, PEK1- phosphofructokinase-1, PKM2- pyruvate kinase-2.

Table 5. Relative mRNA expression levels in patients with different clinical characteristics (x ± s)

Clinical characteristics		n	HK2	PEK1	PKM2	IFN-γ	IL-4
Disease type	Non-erosive OLP	55	1.45±0.21	1.65±0.19	1.97±0.21	0.54±0.06	1.26±0.17
	Erosive OLP	65	2.03±0.23*	2.24±0.23*	2.43±0.30*	0.32±0.04*	1.73±0.14*
Degree of lymphocyte infiltration	Mild	30	1.23±0.18	1.43±0.21	1.78±0.17	0.67±0.06	1.24±0.15
	Moderate	56	1.90±0.23	2.00±0.25	2.21±0.21	0.43±0.05	1.46±0.20
	Severe	34	2.65±0.28*	2.45±0.38*	2.59±0.23*	0.30±0.03*	1.80±0.12*
Degree of basal cell liquefaction degeneration	Mild	42	1.34±0.16	1.38±0.20	1.80±0.16	0.65±0.07	1.21±0.18
	Moderate	49	1.89±0.19	1.98±0.25	2.14±0.24	0.41±0.04	1.52±0.23
	Severe	29	2.76±0.23*	2.47±0.31*	2.40±0.29*	0.29±0.03*	1.79±0.18*

Abbreviations: HK2- hexokinase-2, IFN-γ- interferon gamma, IL-4- interleukin-4, n- number of subjects, OLP- oral lichen planus, PEK1- phosphofructokinase-1, PKM2- pyruvate kinase-2. *p<0.001.

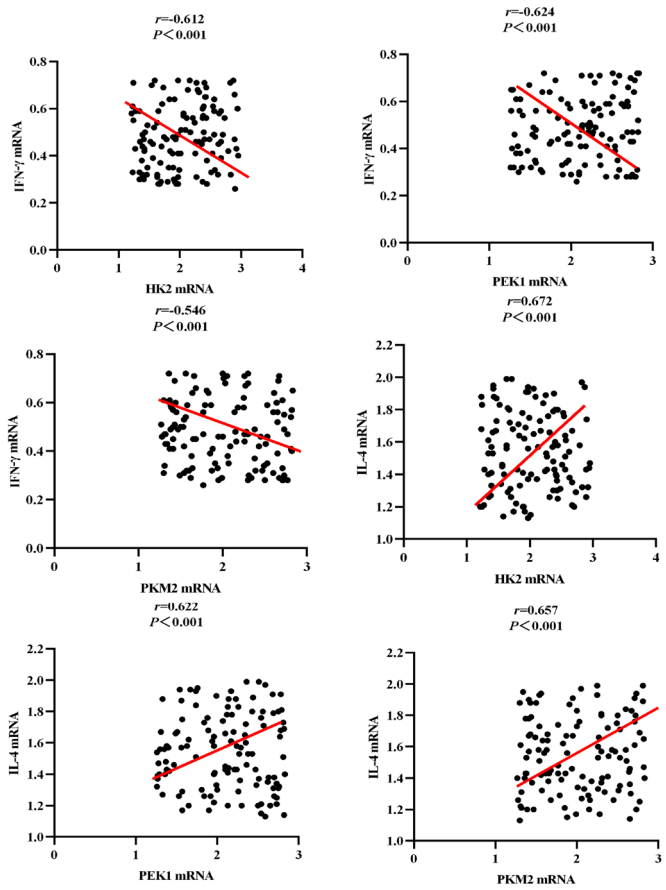

Figure 2. Correlation diagrams of T cell glycolytic rate-limiting enzymes expressions with Th1/Th2 balance via Th1 cytokine IFN-γ and Th2 cytokine IL-4.

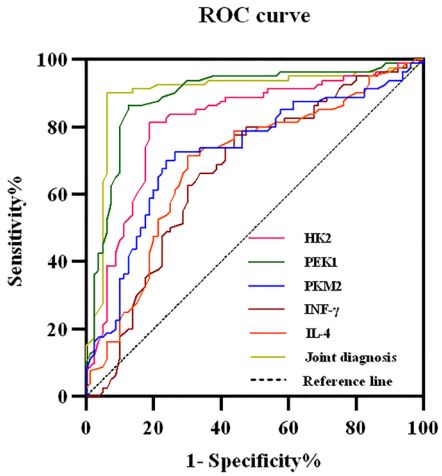

Figure 3. ROC curves of HK2, PEK1, PKM2, and Th1/Th2 cytokines in diagnosis of oral lichen planus.

DISCUSSION

Cell-mediated autoimmune abnormalities may act as a key pathological mechanism of OLP [14]. In the case of T-cell-mediated immune abnormalities, Th1/Th2 imbalance occurs, characterized by immune network disorders. As a vital factor secreted by Th1 cells, IFN-γ is expressed in about 1% of basal cells in the oral mucosa of OLP patients, and is distributed in both epithelial cells and superficial mononuclear cells in the lamina propria [15,16]. IL-4, an important factor derived from Th2 cells, not only facilitates the proliferation and differentiation of B cells, but also stimulates Th2 cells to secrete more IL-4, thereby forming an antibody-mediated immune response [17,18]. Moreover, the IL-4 level in the peripheral blood of OLP patients is not different from that of normal people, but the excessive secretion of IL-4 suppresses Th1 cells and the formation of IFN-γ, thereby resulting in Th1/Th2 imbalance and a restrictive balance state of local immunity [19]. Liu et al. reported that the polymorphism of Th1/Th2-related cytokines was associated with OLP, and that Th1 cytokine IFN-γ (874A/T) polymorphism displayed a significant correlation with OLP, whereas Th2 cytokine IL-4 (590C/T) polymorphism exhibited no significant correlation with OLP [20]. Mehrbani et al. found that IL-4 mediated immune abnormalities and inflammatory responses in various ways, thus inducing OLP [21]. In the present study, compared with the normal oral mucosa, the relative mRNA expression of IFN-γ declined, whereas the relative mRNA expression of IL-4 rose in the oral mucosa of OLP patients, suggesting that Th1 cells drifted to Th2 cells in the case of Th1/Th2 imbalance due to immune network disorders.

OLP induced by T cell-mediated immune abnormalities is related to glycolytic metabolism, especially three glycolytic metabolism-associated rate-limiting enzymes, namely HK2, PEK1, and PKM2 [22]. As the first rate-limiting enzyme in glycolysis, HK2 principally catalyzes the conversion of glucose into glucose-6-phosphonic acid and induces glucose to enter the glycolysis cycle, which is an indispensable substance for the early activation of T cells and is modulated by various signaling pathways such as the PI3K/Akt/HIF-1α axis [23,24]. Hypoxia response elements in the promoter region of HK2 are activated to bind with HIF-1α in the case of tissue hypoxia or

Table 6. Diagnostic values of HK2, PEK1, PKM2, and Th1/Th2 cytokines for oral lichen planus

Indicator	AUC (95% CI)	Sensitivity (%)	Specificity (%)	Cut-off value	*p*-value
HK2	0.832 (0.742-0.882)	84.53	80.19	1.24	<0.001
PEK1	0.890 (0.835-0.946)	87.67	82.12	1.18	<0.001
PKM2	0.810 (0.713-0.876)	82.23	79.98	1.67	<0.001
IFN-γ	0.768 (0.710-0.836)	78.90	74.35	0.73	<0.001
IL-4	0.798 (0.724-0.845)	80.11	76.87	1.14	<0.001
Combination	0.901(0.843-0.957)	89.98	85.64	-	<0.001

Abbreviations: AUC- area under the receiver operating characteristic curve, HK2- hexokinase-2, IFN-γ- interferon gamma, IL-4- interleukin-4, PEK1- phosphofructokinase-1, PKM2- pyruvate kinase-2.

cell hypoxia, increasing HK2 expression and accelerating glycolysis [25-27]. PEK1, the second rate-limiting enzyme in glycolysis, mainly converts fructose-6-phosphate into fructose-1,6-diphosphate through ATP. An increase in PEK1 expression can accelerate cell proliferation and migration and suppress cell apoptosis [28,29]. The glycolytic flux can be lowered by blocking the function of PEK1. PKM2 is the last rate-limiting enzyme in glycolysis. Its expression and transcription activity are modulated by the PI3K/mTOR signaling pathway and HIF-1α, respectively, and its catalytic activity is high. It is well-documented that PKM2 functions in two ways [30-32]. First, PKM2 facilitates the formation of pyruvic acid, accelerating ATP production and glycolysis. Second, PKM2 enhances the transcription activity of HIF-1α in cells, promoting the expression of other glycolytic enzymes. The elevation in PKM2 expression exerts a negative effect, accelerating apoptosis. In the present study, HK2, PEK1 and PKM2 had significantly high expressions in the oral mucosa of OLP patients, especially in lymphocyte infiltration zone in the lamina propria. Besides, the expressions of HK2, PEK1 and PKM2 increased in erosive OLP patients, and rose with increasing degree of lymphocyte infiltration and basal cell liquefaction degeneration. Thus, the progression of OLP is accompanied by abnormal glycolysis of T cells, namely, increased expressions of HK2, PEK1 and PKM2. Possibly, the increase in HK2, PEK1 and PKM2 levels speeds up glycolysis, breaks the original glycolytic stability, and adversely affects the differentiation of T cells into Th1 and Th2 cells, resulting in local immune abnormalities, inducing inflammatory responses, and eventually giving rise to OLP.

Moreover, we herein found significant negative correlations and positive correlations between HK2, PEK1 and PKM2 and Th1 cytokine IFN-γ and between HK2, PEK1 and PKM2 and Th2 cytokine IL-4, respectively. Hence, highly expressed HK2, PEK1 and PKM2 may promote the proliferation together with the differentiation of T cells into Th1 and Th2 cells, inducing Th1/Th2 imbalance and thus taking part in lymphocyte infiltration and basal cell liquefaction degeneration to result in OLP. Furthermore, the ROC curve analysis revealed that the combination of HK2, PEK1, and PKM2 with Th1/Th2 cytokines performed better in diagnosing OLP.

The biomarkers in this study can potentially be integrated into diagnostic protocols to help the early identification of OLP, offering a more precise and non-invasive method for distinguishing it from other oral inflammatory conditions. Moreover, targeting these metabolic pathways and immune imbalances may open new therapeutic avenues. However, this study is limited. The variability in glycolytic enzyme expression and immune profiles across patients requires the development of individualized diagnostic criteria. Additionally, further research is needed to determine whether targeting these pathways can provide sustained therapeutic benefits without obvious side effects. Similar to many biomarker-based approaches, the cost and accessibility of such testing may also limit widespread clinical application.

CONCLUSIONS

In conclusion, OLP patients have elevated expressions of T-cell glycolytic rate-limiting enzymes HK2, PEK1 and PKM2 in the oral mucosa, together with obvious Th1/Th2 imbalance, which is associated with the basic pathological variations in such patients. T-cell glycolytic rate-limiting enzymes may take part in the development and progression of OLP by mediating Th1/Th2 imbalance through the immune mechanism.

ABBREVIATIONS

AUC- area under the ROC curve

HK2- hexokinase-2

IFN-γ- interferon gamma

IL-4- interleukin-4

OLP- oral lichen planus

PEK1- phosphofructokinase-1

PKM2- pyruvate kinase-2

AUTHORS' CONTRIBUTION

GS – writing

LL – data analysis

LX– data collection

MY – study design, data analysis

YZ – data collection

CONFLICT OF INTEREST

None to declare.

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