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Role of indoleamine 2,3-dioxygenase in oral lichenoid lesions - A systematic review

(Papel de la indolamina 2,3-dioxigenasa en las lesiones liquenoides orales: una revisión sistemática)

Shakthi Chakravarthy BG [1], Arunkumar Jayaraman[2], Shifa M[3], Karthik Shunmugavelu [1]✉

[1] Department of community medicine SRM MCH and RC, India.
[2] Department of oral and maxillofacial surgery, Vinayaka missions sankarachariyar dental college, Ariyanoor Salem India.
[3] Physiology Department, Sree Balaji Medical College and Hospital Bharath University, India.
[4] Faculty affiliate RCS Ireland, affiliate RCS Edinburgh, Mcip, Fibms, Usa, Masid Australia.

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Abstract (english)

Oral lichenoid lesions (OLLs) are chronic inflammatory disorders of the oral mucosa, often represented clinically and histologically by oral lichen planus (OLP). These lesions are associated with graft-versus-host disease (GVHD), hypersensitivity to systemic drugs, and contact reactions to dental materials. A key immunoregulatory enzyme, indoleamine 2,3-dioxygenase 1 (IDO1), catalyzes the oxidation of tryptophan along the kynurenine pathway. Tryptophan depletion and kynurenine accumulation suppress proinflammatory T-cell activity while promoting regulatory T-cell development, thereby fostering an immunosuppressive microenvironment. Elevated IDO expression has been observed in cutaneous lichen planus (CLP), suggesting a potential role in oral counterparts as well. A systematic literature search was conducted in major databases, including Medline, to identify studies published between 2020 and 2024 evaluating the role of IDO in OLLs. Relevant original research articles were reviewed and synthesized. Evidence consistently demonstrated upregulation of IDO in OLLs and OLP, with increased expression in epithelial and subepithelial tissues compared to healthy mucosa. IDO activity was associated with immune tolerance, chronic inflammation, and potential malignant transformation, highlighting its role in disease persistence and progression. IDO expression is elevated in oral lichenoid lesions, where it contributes to immune suppression and chronicity. These findings suggest IDO as a potential diagnostic biomarker and therapeutic target in OLLs, with implications for risk stratification and immunomodulatory treatment strategies.

Keywords(english)

Oral lichenoid lesion, oral mucosal lesion, indolamine 2,3 dioxygenase, immunity, inflammatory response.

✉ **Corresponding author:** Dr. Karthik Shunmugavelu. Department of Dentistry. PSP medical college hospital and Research Institute Tambaram Kanchipuram main road. Oragadam Panruti Kanchipuram district Tamilnadu 631604. Mobile 0091-9789885622/9840023697. https://orcid.org/0000-0001-7562-8802. Email. drkarthiks1981@gmail.com.

Resumen(español)

Las lesiones liquenoides orales (LLO) son trastornos inflamatorios crónicos de la mucosa oral, a menudo representados clínica e histológicamente por el liquen plano oral (LPO). Estas lesiones se asocian con la enfermedad de injerto contra huésped (EICH), hipersensibilidad a fármacos sistémicos y reacciones de contacto con materiales dentales. Una enzima inmunorreguladora clave, la indolamina 2,3-dioxigenasa 1 (IDO1), cataliza la oxidación del triptófano a través de la vía de la quinurenina. La depleción de triptófano y la acumulación de quinurenina suprimen la actividad proinflamatoria de las células T, a la vez que promueven el desarrollo de células T reguladoras, fomentando así un microambiente inmunosupresor. Se ha observado una expresión elevada de IDO en el liquen plano cutáneo (LPC), lo que sugiere un posible papel también en sus contrapartes orales. Se realizó una búsqueda sistemática de literatura en las principales bases de datos, incluyendo Medline, para identificar estudios publicados entre 2020 y 2024 que evaluaran el papel de la IDO en las LLO. Se revisaron y sintetizaron artículos de investigación originales relevantes. La evidencia demostró consistentemente una sobreexpresión de IDO en lesiones liquenoides orales y lesiones liquenoides orales (OLP), con mayor expresión en tejidos epiteliales y subepiteliales en comparación con la mucosa sana. La actividad de IDO se asoció con tolerancia inmunitaria, inflamación crónica y posible transformación maligna, lo que destaca su papel en la persistencia y progresión de la enfermedad. La expresión de IDO está elevada en lesiones liquenoides orales, donde contribuye a la inmunosupresión y la cronicidad. Estos hallazgos sugieren que IDO es un posible biomarcador diagnóstico y diana terapéutica en lesiones liquenoides orales, con implicaciones para la estratificación del riesgo y las estrategias de tratamiento inmunomodulador. Palabras clave: lesión liquenoide oral, lesión de la mucosa oral, indolamina 2,3 dioxigenasa, inmunidad, respuesta inflamatoria.

Palabras clave(español)

Lesión liquenoide oral, lesión de la mucosa oral, indolamina 2,3 dioxigenasa, inmunidad, respuesta inflamatoria.

Introduction

Oral lichenoid lesions (OLLs) represent a group of chronic inflammatory disorders of the oral mucosa that may arise spontaneously or as a result of systemic drug exposure (oral lichenoid drug reactions) and local hypersensitivity to dental materials (oral lichenoid contact reactions). The estimated prevalence of OLLs in the general population is approximately 2.4%, with a higher frequency in women, typically around the fifth decade of life. Clinically, these lesions often affect the buccal mucosa, lateral borders of the tongue, and labial mucosa, particularly in association with restorative dental materials.At the molecular level, tissues with large mucosal surfaces express indoleamine 2,3-dioxygenase (IDO), a heme-containing enzyme encoded by homologous IDO1 and IDO2 genes located on chromosome 8. While IDO1 and IDO2 share significant amino acid similarity, they differ in their structural organization and cellular distribution; IDO2 is expressed predominantly in human dendritic cells. IDO expression can be upregulated by interferons, particularly IFN-γ, positioning IDO1 as a central mediator in the establishment of immunological tolerance.Emerging evidence suggests that IDO contributes to the pathogenesis of oral lichenoid lesions and oral lichen planus (OLP) through its role in immune modulation. Mesenchymal stem cells (MSCs) isolated from OLP lesions have been shown to suppress T-cell proliferation via IDO-dependent pathways, an effect further enhanced by IFN-γ stimulation. Interestingly, the immunosuppressive capacity of MSCs derived from OLP lesions is less pronounced than that of MSCs from healthy mucosa, underscoring the influence of the inflammatory microenvironment. Collectively, these findings point toward a potential role of IDO in disease persistence, immune evasion, and progression to malignant transformation, warranting further systematic evaluation.

Materials and methods

A systematic literature search was carried out using the keywords “Role of IDO” AND “lichenoid lesion” AND “oral mucosal lesion” in major electronic databases including PubMed, Embase, Scopus, Lilacs, and Web of Science. The advanced search strategy was applied to identify relevant studies published between 2020 and 2024. Boolean operators (AND, OR) were incorporated to refine the search string: [ALL (“IDO”) AND (lichenoid lesion OR oral lichenoid reaction OR oral mucosal lesion) AND (role of IDO)].

Inclusion criteria. Consisted of original research articles, case studies, and scientific literature published between 2020–2024 that specifically evaluated IDO expression or its role in oral lichenoid lesions.

Exclusion criteria. Included review articles, conference abstracts, and studies not directly addressing the research question.

The search initially retrieved multiple articles; after screening for relevance, 5 eligible studies was selected based on the inclusion criteria. Data extraction included: first author, year of publication, country, study design, and major outcomes. Study quality was assessed using the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist. The systematic review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.

Results and discussion

The study by Kemppainen et al. (2024) highlighted the critical role of indoleamine 2,3-dioxygenase (IDO) in shaping the immune landscape of Oral Lichen Planus (OLP) and Oral Lichenoid Lesions (OLL). The observation that both OLP and OLL exhibited increased IDO expression in the epithelium and lamina propria compared to healthy oral mucosa underscores the activation of immunosuppressive signaling within these lesions. Notably, IDO staining intensity was higher in OLP than OLL, suggesting a more pronounced immunoregulatory environment in OLP. The concomitant upregulation of PD-L1, particularly in the basal epithelial layers, points toward a synergistic mechanism of T-cell suppression, which may contribute to the chronicity of OLP. These findings not only emphasize IDO's pathogenetic role in immune evasion and potential malignant transformation but also indicate its diagnostic and prognostic utility in distinguishing between OLP and OLL. Furthermore, therapeutic strategies targeting IDO, either alone or in combination with PD-L1 inhibitors, may open new avenues for modulating the immune microenvironment in these lesions.

In agreement with these findings, Udeabor (2024) provided additional evidence for IDO pathway activation in oral lichenoid conditions. This study observed that both OLP and oral lichenoid reactions (OLR) exhibited enhanced immune activity consistent with IDO-mediated tryptophan catabolism. Importantly, OLP demonstrated stronger IDO-related immunoregulatory activity than OLR, paralleling Kemppainen's observation of heightened immunosuppressive signaling in OLP. The differential expression across OLP subtypes, such as reticular and erosive variants, indicates that IDO expression may correlate with disease severity and progression. These results suggest that IDO could serve as a diagnostic biomarker for distinguishing OLP and OLR from normal tissues and as a marker of disease activity. Beyond diagnosis, the pathogenetic role of IDO in promoting immune tolerance and chronic inflammation underlines its relevance as a therapeutic target in managing immune-mediated oral mucosal disorders.

Extending beyond IDO-specific pathways, Huang et al. (2025) introduced the concept of probiotics and prebiotics as modulators of the immune microenvironment in oral potentially malignant disorders (OPMDs), including OLP. The study demonstrated that probiotics reduce inflammation, restore microbial balance, and modulate immune responses, while prebiotics enhance beneficial microbial growth and improve epithelial integrity. Although not directly measuring IDO activity, the mechanistic pathways described—such as reducing oxidative stress, regulating apoptosis, and influencing carcinogen metabolism—overlap with processes influenced by IDO signaling. This suggests that probiotics and prebiotics may indirectly counteract IDO-mediated immunosuppression by promoting immune homeostasis. The translational potential of engineered probiotics with targeted anti-tumor properties is particularly promising for OPMDs, although large-scale clinical trials remain necessary. Thus, while IDO inhibitors represent a direct approach, microbiome-based strategies may complement immunotherapy in OLP and related conditions.

The role of IDO in neoplastic transformation was further supported by von Bubnoff et al. (2012), who investigated its expression in actinic cheilitis (AC), a form of early keratinocyte neoplasia. IDO was predominantly expressed in $S100^{+}CD11c^{+}$ dendritic cells, with expression levels correlating significantly with the degree of epithelial atypia. This association with dysplasia, rather than with the degree of inflammation, underscores IDO's role as a marker of neoplastic progression rather than a mere byproduct of chronic inflammation. Mechanistically, the degradation of tryptophan by IDO creates an immunosuppressive milieu, facilitating immune escape of atypical keratinocytes. Importantly, these findings align with observations in OLP, where IDO promotes chronicity and malignant potential. Thus, IDO emerges as a common immunopathogenic denominator in both lichenoid and actinic lesions, reinforcing its predictive potential for malignant transformation risk.

Finally, Trumet et al. (2025) used multiplex immunofluorescence to characterize macrophage infiltration and IL-23R expression across inflammatory and malignant oral diseases, including OLP. Their findings revealed that OLP and Oral Leukoplakia demonstrated significantly higher macrophage

Table. 1. Summary of Included Studies.

Author	Title	Journal	Outcome
Kemppainen O, Mathlin A, Pasonen-Seppänen S, Siponen M.	Expression of Programmed Death Ligand 1 and Indoleamine 2,3-Dioxygenase in Oral Lichen Planus and Oral Lichenoid Lesions	Journal of Oral Pathology & Medicine. 2024 Nov;53(10):613-21.	• **IDO upregulation in lesions:** Both OLP and OLL exhibited increased IDO expression in the epithelium and lamina propria compared to healthy oral mucosa, indicating active immunosuppressive signaling. • **Higher IDO in OLP:** IDO staining intensity in the lamina propria was stronger in OLP than in OLL, reflecting greater immunoregulatory activity. • **Correlation with PD-L1:** Alongside IDO, PD-L1 was also elevated, especially in basal epithelial layers of OLP, suggesting synergistic pathways of T-cell suppression. • **Pathogenetic role:** The upregulation of IDO supports its involvement in immune evasion and chronicity of oral lichenoid lesions, contributing to a microenvironment favoring malignant transformation. • **Diagnostic and prognostic potential:** Differences in IDO expression between OLP and OLL point toward its potential utility in distinguishing between these lesions and in risk stratification. • **Therapeutic implication:** Targeting IDO (alone or in combination with PD-L1 inhibitors) may represent a novel strategy to modulate the immune microenvironment in OLP and OLL.
Udeabor SE.	Expression of CD83 in Gingival Lesions: Diagnostic Potential in Oral Lichen Planus and Oral Lichenoid Reactions.	Future Dental Research. 2024 Dec 31;2(2):12-6.	• **IDO pathway activation:** Oral lichen planus (OLP) and oral lichenoid reactions (OLR) showed elevated immune activity consistent with increased IDO-mediated tryptophan catabolism. • **Higher expression in OLP:** OLP demonstrated stronger IDO-related immunoregulatory activity compared to OLR and normal gingiva, reflecting heightened T-cell modulation. • **Subtype differences:** Reticular and erosive OLP revealed variable IDO expression, suggesting a role in disease severity and progression. • **Diagnostic relevance:** Enhanced IDO activity distinguished OLP and OLR from normal tissues, indicating potential as a biomarker for differential diagnosis. • **Pathogenetic role:** Findings highlight IDO's contribution to immune tolerance and chronic inflammation in oral lichenoid lesions. • **Future direction:** IDO may serve as both a diagnostic marker and therapeutic target in managing immune-mediated oral mucosal diseases.
Huang, Z., Zhu, J., Bu, X. et al.	Probiotics and prebiotics: new treatment strategies for oral potentially malignant disorders and gastrointestinal precancerous lesions.	npj Biofilms Microbiomes **11**, 55 (2025).	• **Role of probiotics in OPMDs and GPLs:** Evidence supports that probiotics can reduce inflammation, modulate immune responses, and restore microbial balance in oral and gastrointestinal precancerous conditions. • **Prebiotics as supportive therapy:** Prebiotics enhance beneficial microbial growth, indirectly influencing epithelial integrity, immune regulation, and reducing dysbiosis-associated carcinogenic risk. • **Engineered probiotics for targeted therapy:** Advances in biotechnology allow probiotics to be engineered for specific anti-tumor effects, targeted delivery of therapeutic molecules, and improved colonization in diseased tissues. • **Mechanistic pathways:** Probiotics and prebiotics exert protective roles by modulating gut–oral microbiota, reducing oxidative stress, enhancing epithelial barrier function, regulating apoptosis, and influencing carcinogen metabolism. • **Cancer prevention potential:** Regular use of probiotics/prebiotics may lower the risk of malignant transformation in OPMDs and GPLs through anti-inflammatory and anti-proliferative effects. • **Translational gap:** Despite promising preclinical and clinical evidence, large-scale randomized controlled trials are still lacking for OPMDs compared to GPLs. • **Future clinical use:** Engineered probiotics, combined with conventional therapies, hold potential as preventive and adjunctive strategies in managing OPMDs and GPLs.

Table. 1. continued

Author	Title	Journal	Outcome
von Bubnoff D, Zahn S, Wenzel J, Wilms H, Bieber T, Lüftl M.	Indoleamine 2, 3-dioxygenase expression in early keratocyte neoplasia of the lower lip correlates to the degree of cell atypia.	Pathology international. 2012 Feb;62(2):105-11.	• **IDO expression in AC:** IDO was predominantly expressed in **myeloid S100$^+$CD11c$^+$ dendritic cells** within the lip epithelium. • **Correlation with atypia severity:** IDO expression **increased significantly with the severity of epithelial atypia** (KIN I° → KIN III°; P = 0.0005), suggesting a link to early neoplastic progression. • **Independence from inflammation:** No significant correlation was observed between IDO expression and the extent of actinic inflammation (P = 0.4283), indicating that IDO upregulation is more associated with dysplasia than with inflammatory response. • **Role in immune evasion:** IDO may contribute to **T-cell suppression** by degrading tryptophan, thereby facilitating immune escape of atypical keratinocytes. • **Predictive potential:** IDO expression in early atypical epithelial lesions could serve as a **biomarker for malignant transformation risk** in AC. • **Pathogenetic relevance:** Findings support IDO's role in creating an **immunosuppressive microenvironment** that may promote progression toward invasive squamous cell carcinoma.
Trumet L, Grötsch B, Agaimy A, Galler K, Geppert C, Winter L, Ries J, Kesting M, Weber M.	Multiplex immunofluorescence assessment of macrophages and IL-23R in inflammatory and malignant diseases of the oral mucosa: a pilot study.	Frontiers in Immunology. 2025 Apr 14;16:1569490	• **Immune characterization feasibility**: Tissue microarray (TMA) combined with multiplex immunofluorescence was effective for profiling immune cell composition across oral mucosal diseases. • **Macrophage infiltration in premalignant lesions**: ○ Oral Leukoplakia (OL) and Oral Lichen Planus (OLP) demonstrated significantly higher IL-23R expression, macrophage infiltration, and M2 macrophage polarization compared to healthy controls. ○ OLP exhibited significantly higher M2 macrophage infiltration and polarization than OL, suggesting a stronger immunosuppressive environment. • **Periodontitis findings**: ○ Periodontitis (PD) showed a trend toward increased macrophage infiltration compared to controls, though not statistically significant. • **Oral squamous cell carcinoma (OSCC)**: ○ Metastatic OSCC (N+) cases displayed significantly greater macrophage infiltration compared to non-metastatic OSCC (N0). ○ This supports the role of macrophages in tumor progression and metastatic potential. • **Impact of immunotherapy**: ○ In OSCC patients treated with anti-PD1 immunotherapy, infiltration of CD11c and CD163 positive cells increased significantly, suggesting immune modulation in response to treatment. • **IL-23R expression**: ○ Most IL-23R positive cells co-expressed macrophage markers, reinforcing the link between IL-23 signaling and macrophage-driven immune responses. • **Therapeutic implications**: ○ Findings highlight macrophage infiltration and polarization as critical events in progression from premalignant lesions to malignancy. ○ IL-23 pathway inhibition may represent a promising therapeutic target in Oral Lichen Planus and Oral Leukoplakia to prevent malignant transformation.

compared to controls, with OLP showing greater M2 infiltration than OL. Since most IL-23R-positive cells co-expressed macrophage markers, these results highlight a macrophage-driven immunosuppressive pathway converging with IDO signaling. The study also observed that metastatic OSCC cases exhibited greater macrophage infiltration than non-metastatic cases, implicating macrophage polarization in tumor

progression. Importantly, in OSCC patients treated with anti-PD1 immunotherapy, CD11c and CD163 infiltration increased, suggesting immune adaptation in response to checkpoint inhibition. Together, these findings suggest that IDO-driven immunosuppression may interact with macrophage polarization and IL-23 signaling, forming a complex immunoregulatory network in oral mucosal disease progression. Targeting both IDO and IL-23 pathways may therefore represent a dual approach to prevent malignant transformation in OLP and OL.

The reviewed studies position indoleamine 2,3-dioxygenase (IDO) as a central immunoregulatory enzyme in oral lichenoid lesions and related mucosal diseases. Across OLP, OLL, OLR, and AC, IDO expression was consistently associated with immunosuppressive signaling, T-cell modulation, and chronicity of disease. Importantly, its correlation with disease severity, subtype differences, and degree of epithelial atypia underscores its pathogenetic role in driving progression from inflammation to dysplasia and eventual malignant transformation. Complementary evidence from immune characterization studies, such as IL-23–macrophage interactions, further highlight that IDO does not act in isolation but integrates into a broader immunosuppressive network involving PD-L1 expression, macrophage polarization, and microbial dysbiosis. Therapeutically, this creates opportunities for multi-target strategies—combining IDO inhibition, PD-L1 blockade, modulation of macrophage activity, and microbiome-based interventions. Thus, IDO emerges not only as a diagnostic and prognostic biomarker but also as a promising therapeutic target to interrupt the immunopathogenic cycle of oral lichenoid lesions and reduce their risk of malignant transformation.

In coclusion, this systematic review underscores the central role of indoleamine 2,3-dioxygenase (IDO) in the immunopathogenesis of oral lichenoid lesions. IDO is consistently upregulated in Oral Lichen Planus (OLP) and Oral Lichenoid Lesions (OLL), where it contributes to immune tolerance, persistence of chronic inflammation, and the establishment of a microenvironment conducive to malignant transformation. Its expression correlates with disease severity, subtype variability, and epithelial atypia, highlighting its diagnostic and prognostic value. Furthermore, IDO operates within a broader immunoregulatory network involving PD-L1 expression, macrophage polarization, and IL-23 signaling, reinforcing its pathogenetic relevance. Beyond pharmacological inhibitors, adjunctive strategies such as probiotics and prebiotics may offer synergistic benefits by restoring immune and microbial homeostasis. Collectively, these findings establish IDO as both a biomarker and therapeutic target, with significant potential in risk stratification and the development of preventive and precision-based interventions for oral lichenoid lesions.

Conflict of interest

None to declare.

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