

Overexpression of IL-23/IL-17 Axis in the Pathogenesis of Oral Lichen Planus Lesions: A Literature Review

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Abstract

Lichen planus is a chronic inflammatory disease affecting the oral mucosa. It is a relatively common idiopathic inflammatory disease of skin and mucous membranes, that often affects the oral mucosa. The clinical manifestations of oral lichen planus (OLP) can be symptomless, presenting with characteristic interlacing white lines and sometimes with papules, annular forms or plaques.

The interleukin- (IL-) 23/IL-17 axis is a newly discovered proinflammatory signaling pathway and has been implicated in the pathogenesis of many chronic inflammatory and immune disorders. Here we investigated whether the IL-23/IL-17 axis was present and functional in the lesions of oral lichen planus (OLP). Using immunohistochemistry and quantitative PCR, we found that the sub-units of IL-23 and IL-17 were overexpressed in OLP lesions than in normal oral mucosa tissues. In addition, the expressions of IL-23 and IL-17 are positively correlated in reticular OLP tissues. Results from in vitro studies revealed that exogenous IL-23 could increase the percentage of Th17 cells and IL-17 production in the CD4+T cells from reticular OLP patients. Taken together, our results revealed an overexpression pattern and selectively regulatory roles of IL-23/IL-17 axis in the OLP lesions, suggesting that it may be a pivotal regulatory pathway in the complex immune network of OLP lesions.

Keywords: Overexpression; Regulatory Roles; IL23/IL17 Axis; Oral Lichen Planus

Introduction

Lichen planus is a idiopathic inflammatory disease of skin and mucous membranes, that usually affects the oral mucosa. Oral lichen planus (OLP) can be symptomless, presented as an interlacing white lines and even sometimes with papules, annular forms or plaques. In most of these cases, the histology of oral lichen planus reveals an epithelial basal cell degeneration with a lymphocytic infiltrate in the superficial connective tissue, associated to a keratinisation surface, and the prickle cell thickness appears to be normal for the involved site. Atrophic OLP is another clinical pattern of oral lichen planus. It is the most aggressive and painful form, with different degrees of erythema and ulceration, often surrounded by fine white striae. The histology of the atrophic oral lichen planus reveals a basal cell degeneration associated to a lymphocytic infiltrate in the superficial connective tissue, unless the area is disrupted by ulceration. When the epithelium is intact, the prickle cell layer will be thin.

The interleukin- (IL-) 23/IL-17 axis is a newly discovered proinflammatory marker which has been implicated in the pathogenesis of many chronic inflammatory and immune disorders. Here we investigated the possibility whether the IL-23/IL-17 axis was present and

positive in the lesions of oral lichen planus (OLP). The aim of this paper was to reveal an overexpression pattern and selectively regulatory roles of IL-23/IL-17 axis in the OLP lesions, suggesting that it may be a pivotal regulatory pathway explaining the pathogenesis of OLP lesions [1,2].

Materials and Methods

Our Literature review was basically based on studies in which OLP cases were clinically diagnosed, pathologically confirmed, and subdivided as reticular or erosive forms based on the modified WHO diagnostic criteria of OLP. The literature review included the English articles in which they distinguished only two OLP subgroups. Subjects with other oral or systematic diseases or taking corticosteroids or immunosuppressive drugs within 3 months prior to the specimen collection were excluded from the literature review.

Results and Discussion

To identify whether IL-23/IL-17 is involved in the local pathogenesis of OLP, many studies firstly detected the expression and distribution of IL-23p19, a unique subunit of IL-23, and IL-17 in OLP lesions and normal oral mucosa (NOM) tissues [1,2]. A study using IHC detection observed diffuse and strong expressions of IL-23p19 in both erosive and reticular OLP lesions. The positive staining of IL-23p19 has predominantly been concentrated not only on the epithelium of OLP lesions but also on the extracellular matrix of the lamina propria. In contrast, only a few keratinocytes in the epidermis layer of the normal oral mucosa (NOM) tissues showed the presence of a weak stain of IL-23p19. Moreover, they found abundant IL-17 positive stainings on the cytoplasm of the infiltrated lymphocytes in the lesions of both erosive and reticular OLP, but only a few sporadic IL-17+ cells in the normal oral mucosa. The statistical study data showed that both the erosive and reticular OLP lesions had significantly increased immunostaining scores of IL-23p19, as well as the numbers of IL-17+ cells, compared to the normal oral mucosa. In addition, erosive OLP lesions contained a significantly increased number of IL-17+ cells compared to the reticular OLP lesions [3,4].

IL-23 is the upstream driving cytokine in the IL-23/IL-17 axis. The importance of the latter in inflammation and autoimmunity has been widely demonstrated by many studies. To determine whether IL-23 is involved in the development of OLP, a recent study first detected its expression in the OLP lesions compared with the NOM tissues. IL-22 is the stimulator cytokine of T22 cells, and IL-23 is required to produce IL-22 [5,6]. OLP is characterized by a T-cell mediated immune response against epithelial cells, causing epithelial cell damage and subepithelial infiltration of T lymphocytes. To our knowledge, there has been studies on serum IL-23 in OLP patients such as the study carried out by Wang, *et al.* [7]. The latter study reported an increased expression level of serum IL-23 by using ELISA in patients with OLP concomitant chronic periodontitis compared with healthy controls [7]. Hardly any reports that are available so far on IL-22 and IL-23 may be implicated in the local immune response observed in the tissue samples of patients with OLP. Another recent study presented new information that IL-22 expression level in the OLP lesions was increased compared to normal controls; IL-23 expression level in the OLP lesions was increased compared to normal controls; the significant correlation between IL-22 and IL-23 expression in OLP lesions infiltration was found. These results suggested that the two major immune molecules may play roles in the pathogenesis of OLP, enhancing our understanding of the inflammatory response in OLP.

Based on the results of the current study, we briefly hypothesize that IL-22 can be expressed by T22 cells in an IL-23-dependent fashion. Secreted by a newly found CD4+ T-helper subset called T22 subset, IL-22 was found to mediate infiltration of T lymphocytes and epithelial cell damage by binding to the IL-22 receptor in epithelial cells. Moreover, IL-22 mediates early host defense against bacterial pathogens [8].

IL-17 is the key component in the IL-23/IL-17 axis. This interleukin (IL17) primarily functions as a downstream effector of the axis. Overexpression of IL-17 have been observed in many autoimmune and inflammatory diseases, and its pivotal roles in the pathogenesis of OLP have been profoundly identified [9,10]. Although IL-17 can be secreted by a variety of innate and adaptive immune cells, T cells

are still its major sources, especially the new subset of CD4+Th cells, named Th17 [9]. Considering the involvement of a T-cell-mediated immune response in the pathogenesis of OLP, it is evident that IL-17 and Th17 cells may be present and play a crucial regulatory role in the local environment of the disease. Indeed, we observed in many studies a large number of IL-17+ cells located in the subepithelial lymphocytic infiltrate in the OLP lesions. Besides, our literature data showed an increased numbers of IL-17+ cells and higher mRNA expressions of IL-17 in the OLP lesions compared to the NOM tissues. In addition, compared to the reticular OLP lesions, erosive OLP lesions contained more IL-17+ cells. These findings are consistent with the recent published studies such as the one carried out by Piccinni, et al. who also found an elevated mRNA expression of IL-17 with other Th17 type molecules in the OLP lesions compared to the healthy mucosa [4]. Moreover, the presence of Th17 was also identified in another recent study conducted by Xie., et al. [5,6,7,10]. The overexpression of IL-17 in OLP lesions is attributed partly to the infiltration of lymphocytes in the local environment. However, the large number of IL-17 cytokine in the local lesions of OLP cannot be overlooked. For its potent proinflammatory properties, it may induce profound biological effects and play an important role in the formation and progress of the disease [11].

Conclusion

IL-23/IL-17 axis has been recently considered as a relevant therapeutic target in chronic inflammatory and autoimmune diseases, and specifically for oral lichen planus. For this, several biological agents blocking IL-23 or IL-17 have been currently developed. Therefore, further understanding of the role of IL-23/IL-17 axis in the pathogenesis of OLP may contribute to the development of novel therapeutic strategies for the prevention and management of OLP in the future.

Conflict of Interest

No Conflict of Interest.

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