Etiology and pathogenesis of oral lichen planus: an overview

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Oral lichen planus is a noninfectious, chronic inflammatory condition that involves the oral mucosal stratified squamous epithelium and the underlying lamina propria and may be accompanied by skin lesions. This overview describes the current understanding of the immunopathologic mechanisms implicated in oral lichen planus. (Oral Surg Oral Med Oral Pathol Oral Radiol 2016;122:72-80)

Oral lichen planus (OLP) is recognized as a noninfectious, chronic inflammatory condition that involves the oral mucosal stratified squamous epithelium and the underlying lamina propria and may be accompanied by skin lesions. The causes that initiate and/or perpetuate OLP (with or without skin lesions) are, for the most part, unknown. The prevailing theories revolve around dysregulated T-cell-mediated disorder to exogenous triggers as opposed to a dysregulated response to autologous keratinocyte antigens (autoimmune), and definitive data necessary to resolve this dilemma, in particular, the initiating triggers and the target antigens, are currently missing. Common difficulties in the study of OLP are related to the overlap between the features of OLP and those of other oral mucosal conditions, the highly variable application of diagnostic criteria, and the potential coexistence of additional non-OLP inflammatory conditions in the same patients. Nevertheless, the growing database of information about this disorder suggests certain immune response patterns. The accumulating knowledge will eventually facilitate a more reliable separation of this condition from other disorders that are typically included on the differential diagnosis list.

In contrast to OLP, cutaneous LP is typically a self-limiting condition (except for the hypertrophic form) and usually resolves within 6 to 12 months,[1] suggesting that the underlying mechanisms in OLP and cutaneous LP may be distinct. It is not clear yet whether the mechanisms driving isolated OLP are different from those driving OLP with cutaneous lesions. The focus of this overview is on OLP.

A number of potential OLP triggers have been proposed, mainly (1) local and systemic inducers of cell-mediated hypersensitivity, (2) stress, (3) autoimmune response to epithelial antigens versus a dysregulated response to external antigens, and (4) viral infections.

Hypersensitivity reactions generally align with *lichenoid mucositis*, an umbrella term for OLP-like mucositis in response to restorative and other materials (e.g., amalgam), reactions to drugs, and so on. Hypersensitivity reactions usually resolve upon removal of the trigger, and do not maintain a chronic course, as is characteristic of OLP. Drugs may also be implicated in exacerbations of pre-existing OLP, which can create challenges in patient management.

Stress is thought to play a role in the pathogenesis of OLP because anxiety and depression are reportedly more common in patients with OLP in comparison with normal controls,[2] and OLP exacerbations correlate with episodes of anxiety.[3,4] However, a cause-and-effect relationship between stress and the onset of OLP has not been demonstrated. Moreover, studies show that acute and chronic psychological stress can induce pronounced changes in innate and adaptive immune responses. These immune response changes are predominantly mediated via neuroendocrine mediators from the hypothalamic−pituitary−adrenal axis and the sympathetic−adrenal axis (reviewed by Kemeny and Schedlowski[5]). The implication of these studies is that similar to other inflammatory conditions of various causes, stress is more likely to play a secondary, rather than a primary, role in OLP pathogenesis.

Autoimmune response to epithelial self-antigens remains a possibility. A single study of cutaneous LP reported evidence in support of autoimmunity by

Statement of Clinical Relevance

Oral lichen planus (OLP), a common inflammatory disorder of unknown cause, can result in significant morbidity. As studies investigate various aspects of this condition, updates on the accumulating knowledge are of value to clinicians who manage patients with this disorder. This overview is focused on the current understanding of OLP immunopathogenesis in an effort to facilitate better management of patients with OLP.

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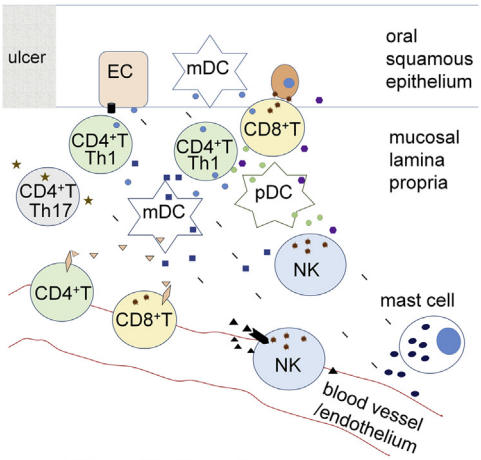

Fig. 1. Cells and molecules implicated in the pathogenesis of OLP. The following *hypothetical model of cell-mediated immunopathogenesis* combines data from OLP studies and known immune system functions. An unidentified trigger initiates cell/tissue damage and the immune response by activating the resident myeloid DC (Langerhans cells and/or stromal DC). Activated DC loaded with antigen undergo maturation, produce cytokines and chemokines, and migrate to regional lymph nodes to present the processed antigen to T cells. Some mature DC remain in the mucosal lamina propria and produce IL-12, IL-18 and TNF-alpha. The apparent lack of B cells and antibodies in OLP suggests the absence of soluble antigen. Mast cells in the damaged tissue release granules with inflammatory mediators. Various resident cells produce chemokines CCL5, CXCL9, CXCL10, which particularly attract Th1 and cytotoxic T cells. The vascular endothelial cells in the lamina propria also respond by producing chemerin, which attracts plasmacytoid DC and NK cells. Plasmacytoid DC interact with myeloid DC, T cells and NK cells and secrete IFN-alpha. T cells and NK cells are further activated by IL-12, IL18 and IFN-alpha to release IFN-gamma and TNF-alpha, which in turn activates DC. Some cytotoxic $CD8^+$ T cells kill basal/parabasal keratinocytes using perforin and granzyme, resulting in apoptotic ('colloid') bodies. TNF-alpha activates anti-microbial responses and may kill host cells. IFN-gamma stimulates the expression of MHC class II on keratinocytes, which may facilitate their antigen-dependent interaction with $CD4^+$ T cells. How this interaction affects the process is not clear. Equally unclear is what

expanding in vitro T cells isolated from the skin lesions of two patients, followed by testing the ability of these T cells to kill autologous keratinocytes (cytotoxicity).[6] Besides the lack of other convincing studies that support the autoimmune mechanism, it is difficult to reconcile autoimmunity with the typically self-limiting course of cutaneous LP. As stated above, although the immune response in OLP is dysregulated, none of the reported studies to date has provided definitive evidence for autoimmunity in OLP, that is, a response to self-antigens. Current knowledge about immune system cells and molecules participating in OLP pathogenesis is summarized below.

Contributions of *viral infections* are discussed under "OLP Associations with Microorganisms and Other Systemic Disorders."

OLP IMMUNOPATHOGENESIS

Investigations of immune system activities in OLP have focused largely on erosive and reticular forms, sometimes comparing the two. Published reports include evaluations of biopsy specimens, saliva, and blood. Studies that have examined changes in the composition of untreated OLP lesions over time are lacking; this is a limitation, given the chronic waxing and waning course of OLP. Following is a summary of published papers, complemented by a diagram and a table of important cells and soluble factors (Figure 1, Table I). A hypothetical model of interactions implicated in OLP pathogenesis is included in the legend to Figure 1.

Cells

T cells and NK cells. Established OLP lesions are typically found to contain T cells with alpha-beta T-cell receptors, including $CD4^+$ ("helper") and $CD8^+$ ("cytotoxic") T cells, both within the epithelium and lamina propria infiltrates. Both cell subsets can be involved in a type 1 immune response, where $CD4^+$ T cells produce Th1 factors, and $CD8^+$ cytotoxic T cells kill host cells and may contribute type 1 soluble factors. The vast majority of oral mucosal and peripheral blood studies show a dominant type 1 (Th1) cell-mediated immune response. This response likely includes cell-mediated cytotoxicity, as $CD8^+$ T cells were often found at the

stimulates parakeratosis that presents clinically as white plaques or striae. Erosive OLP, but not reticular OLP, is associated with Th17 $CD4^+$ T cells, a source of IL-17. Whether IL-17 is an initiator or a consequence of the destruction that results in mucosal ulceration, is not known. The lack of myeloid or lymphoid suppressor cells in OLP likely also contributes to the chronic and destructive inflammation. It is unclear what a gut barrier-associated cytokine IL-22 or TLR may be contributing to the OLP immunopathogenesis.