Oral mucosal immunity

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Oral keratinocytes and dendritic cells of the oral mucosa, through molecular pattern recognition receptors, distinguish between commensal and pathogenic microorganisms and mediate the generation of protective immunoinflammatory responses to potentially invading pathogens or mediate immune tolerance toward commensal microorganisms. Oral immune tolerance is the result either of lack of activation of T cells in response to immunogenic presentation of antigens or of suppression of activity of effector T cells by regulatory T cells.

Secretory immunoglobulin A (sIgA) antibodies at oral mucosal sites contribute to oral immunity by limiting colonization of microorganisms and their invasion of the epithelium. Ig isotype class switching to IgA is either dependent on or independent of T helper cells and is facilitated by cytokines secreted by dendritic cells and monocytes. (Oral Surg Oral Med Oral Pathol Oral Radiol 2013;116:576-583)

The oral epithelium and its associated lamina propria provide a physical barrier that protects the underlying tissues from invasion by microorganisms and blocks the penetration of some environmental threats. This protective mucosa is endowed with cells of the innate arm of the immune system: macrophages, dendritic cells, natural killer cells, and polymorphonuclear leukocytes and their associated immunoinflammatory soluble mediators, including cytokines, chemokines, antibacterial peptides, and components of the complement system. Salivary secretory immunoglobulin A (sIgA), oral keratinocyte-derived biologic mediators, and gingival crevicular fluid components lend an additional dimension to oral mucosal immunity[1-3] (Figure 1).

Oral mucosal immunity neutralizes harmful foreign antigens, limits colonization by pathogenic microorganisms, mediates the generation of protective immunoinflammatory responses against invading pathogens, and mediates tolerance of commensal microorganisms and of soluble nonself-antigens derived from a variety of exogenous proteins.[4,5] Dysregulation of oral mucosal immunity may result in the development of oral immunopathogenic reactions, or infections, and possibly plays an auxiliary role in the development of oral cancer.

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The purpose of this article is to discuss the mechanisms of oral mucosal immunity with special emphasis on the roles of pathogen-associated molecular pattern receptors of dendritic cells and of keratinocytes.

PATTERN RECOGNITION RECEPTORS

Oral keratinocytes and cells of the innate immune system in the lamina propria of the oral mucosa, through germline-encoded pattern recognition receptors, detect distinct pathogen-associated molecular patterns that have been conserved by evolution in specific classes of microorganisms.[6,7] The pattern recognition receptors can reliably and accurately distinguish between different molecular structures of microorganisms, such as mannans in the walls of yeast cells, lipoarabinomannan in the walls of mycobacteria, lipopolysaccharide of gram-negative bacteria, and peptidoglycan of gram-positive bacteria. They can also distinguish between these molecular structures and self-antigens, thus avoiding the generation of immunoinflammatory responses against self-antigens.[6,8,9]

There are several families of pattern recognition receptors, including the Toll-like receptor family (TLR-1 to TLR-10), the C-type lectin receptor family

Statement of Clinical Relevance

This review article discusses some aspects of oral immunity that bring about immune tolerance to oral commensal microorganisms but immunoinflammatory responses against oral pathologic microorganisms. Understanding the mechanisms associated with the development of clinical infections is important to be able to prevent them.

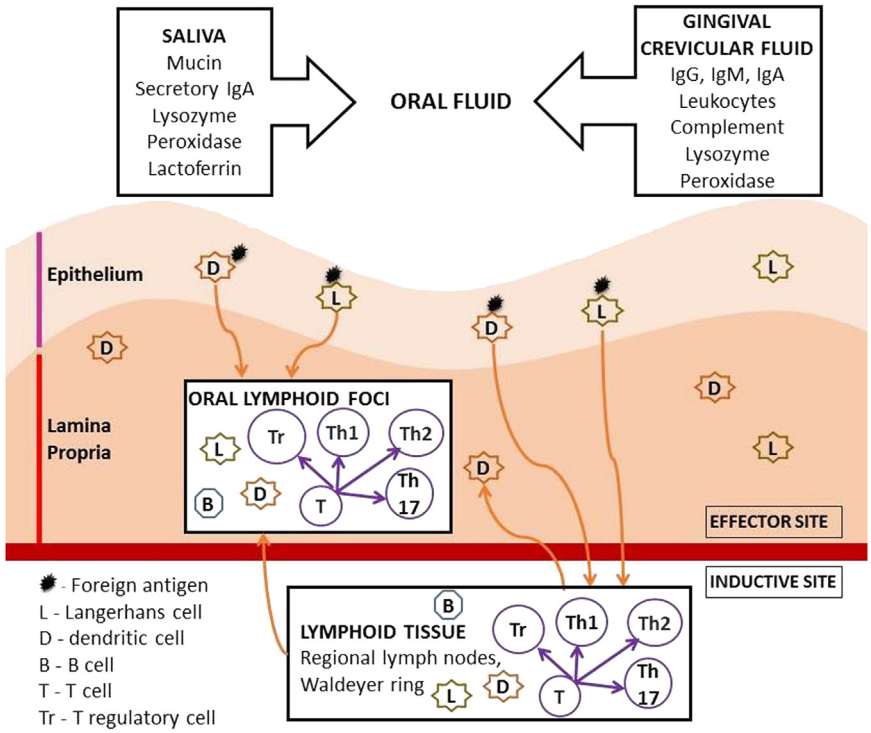

Fig. 1. Factors associated with oral immunity. The saliva contains secretory immunoglobulin A (sIgA), mucins, and enzymes that protect the oral mucosa from bacterial colonization. The gingival crevicular fluid that reaches the oral cavity contains leukocytes, IgG, IgM, IgA, and a range of other agents that contribute to oral immunity. Langerhans cells and other myeloid dendritic cells, after capturing foreign antigens, migrate to immune inductive sites (regional lymph nodes, Waldeyer ring) where they prime immune effector cells. In turn, these immune effector cells migrate to the lamina propria (mucosal lymphoid foci) where they mediate either active immune responses or immune tolerance.

(Dectin-1, Dectin-2, dendritic cell−specific intercellular adhesion molecule 3−grabbing nonintegrin), the mannose receptor family, and nucleotide-binding oligomerization domain (NOD)−like receptor (NLR) family (NOD1, NOD2, NLRP3). These receptors recognize a variety of bacterial, viral, fungal, and protozoal molecular patterns and upon activation; they mediate the secretion of cytokines and chemokines and the upregulation of cell surface molecules, thus inducing immunoinflammatory responses (Th1, Th2, Th17) or inducing peripheral immune tolerance.[8,10-13] Although all of the families of pattern recognition receptors play a part in generating effective immune responses, members of the TLR family are particularly important in combating infective agents.[14]

The pattern recognition receptors not only initiate and determine the type of the specific adaptive immune responses that are induced but also dictate the magnitude and the duration of the responses, and whether or not long-term memory T lymphocytes will be activated.[8] The type, specificity, and sensitivity of the adaptive immune responses mediated by pattern recognition receptors are determined by the nature of the infective agents, whether bacterial, viral, fungal, or protozoal; by whether the infective agent is an intracellular or an extracellular pathogen; and by the interactions between the intracellular signaling pathways of specific combinations of activated pattern recognition receptors.[8,15-17]

The type, specificity, and sensitivity of the adaptive immune responses are also determined by the characteristics of the cytokine milieu in the local microenvironment, by the type of cells that express each family of pattern recognition receptors, by the anatomic site in which these particular cells reside, and by the combination of interactions occurring between these multiple factors.[8,15-17] Danger signals generated by various potentially tissue-damaging factors, including hypoxia, trauma, and non-iodizing radiation, also influence the rapidity and the magnitude of the generated immune response.[16,18,19]

It has been reported that under physiologic noninflammatory conditions, specific TLR signaling pathways in epithelial cells induced by commensal microorganisms play an important role in epithelial homeostasis and in repair after epithelial injury. This may be because the signaling pathways of TLRs also have the capacity to