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Receptors in Oral Epithelial Innate Immunity

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As the first line of defense between the outside environment and the host, epithelial tissues utilize an elaborate signaling network in the presence of colonizing bacteria. A number of signal transduction pathways and Pattern Recognition Receptors (PRRs) are involved in the bacterial-host communication and the production of innate immune responses by the host. Oral epithelia, in particular, are constantly exposed to hundreds of different species of bacteria, yet maintain healthy homeostasis. Numerous studies have reported on a complex biological system in the oral epithelia and what roles different epithelial PRRs play on the induction of appropriate innate immune responses.

Members of Toll-like receptor (TLR) family, one of the well-studied receptors, are expressed on many cell types, including macrophage, monocytes, dendritic cells and epithelial cells. They are transmembrane receptors which play a significant role in recognizing the microbe-associated molecular patterns [1]. Among the 13 TLRs identified in mammals, TLRs 1-10 are expressed in humans. The role of each TLR in innate immunity against bacteria and how TLRs active inflammatory cytokines and antimicrobial peptides have been well documented [2,3]. In addition, Asp299Gly and Thr399Ile mis-sense mutations in extracellular domain of TLR4 have been associated with decreased late diabetic complication and aggressive periodontitis [4,5].

Protease-Activated Receptors (PARs) are G-protein-coupled receptors (GPCR) which can be activated via proteolytic cleavage by serine proteinases [6,7]. Among various memebrs of PAR familes, PAR2 is involved in inflammatory processes in several tissues [8-10], and the mRNA expression of PAR2 is increased in chronic periodontitis patients with high prevalence to *Porphyromonas gingivalis* infection [11].

Nucleotide-binding Oligomerization Domain Receptors (NODs) are cytosolic pattern-recognition molecules expressed mainly in cell types which are exposed to bacterial PGN, including epithelial cells, macrophages and dendritic cells [12-14]. Multiple studies demonstrated the role NODs play in host immune responses against microbial infection, including NOD1 protein involved in host response to *Helicobacter pylori* in the gastric mucosa [15,16], an association of mutations in NOD2 gene with susceptibility to Crohn's disease and skin rash [17,18], and localization of NOD9 in the outer membrane of mitochondria leading to interferon production in response to viral infection [19,20].

A newest receptor reported to play a role in epithelial innate immunity is the bitter taste receptor T2R38 [21]. It was initially identified to regulate mucosal innate immune responses in the upper airway epithelia and lungs [22]. The T2R38 receptor was also shown to respond to Pseudomonas quorum-sensing molecules by regulating mucociliary clearance and antibacterial effects [23]. In gingival epithelia, T2R38 plays a role in the regulation of IL-1α and IL-8 secretion as well as in antimicrobial peptide induction [24]. A recent study also suggests that a high level of antimicrobial peptide effective against cariogenic bacteria is induced by particular SNP carriers who have demonstrated protection against caries [24].

In the oral cavity, where hundreds of microorganisms interact with host tissue, it is essential that the host produces appropriate innate immune responses for different bacteria present. As it is reasonably expected, oral epithelial cells have been shown to balance receptor expression for specific bacterial recognition and subsequent innate immune responses and cytokine production [25,26]. These studies reveal how appropriate host epithelial innate immune responses to different bacteria are induced by balancing multiple receptors. As various bacterial virulence factors activate different receptors of innate immunity, interaction of different receptors may be crucial in determining host defense responses.

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