

# Oral epithelial cytokines

## Abstract

Oral mucosal epithelia as other types of mucosal epithelia are known traditionally as protective tissues. In the present mini-review, attempts were made to introduce oral epithelia as non-lymphoid, non-myeloid tissue with immune potentials. Today, opinions holds the believe that oral epithelial cells have TLR system and can recognize microbial invaders. Microbial invaders in turn, induce epithelia to produce pro-inflammatory TH1, TH2 cytokines and Chemokines. The induction processes described as species and strain specific. Natural epithelial cytokine production has been assured by a number of in-vitro models. Oral epithelial cytokine interplayed several immune functions like regulation of local immune responses, mediate autoimmune disease and induce tissue damage in case of increased secretion. They express multi-factorial influences on mucosal immune compartment, be an integral part of the local innate immune responses and might have a future implication in vaccine immunity.

**Keywords:** cytokine, epithelia, immune response, microbiome, toll-like receptor

Volume 2 Issue 2 - 2016

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**Received:** February 26, 2016 | **Published:** April 07, 2016

**Abbreviations:** OMC, oral mucosal compartment; OMM, oral mucous membrane; OEC, oral epithelial cytokines; EC, epithelial cells

## Introduction

**Overview:** The epithelial tissue lining the oral cavity is now being considered as an integral part of the oral innate immune system and displayed a multi-factorial influences on the oral mucosal immunity. Among these influences epithelial cell produced cytokines and chemokines.<sup>1</sup> The aim of the present mini-review is confined onto the oral epithelial cytokines.

**Oral Topography:** Stomium, oral cavity or mouth is situated at the port of entry of the gastro-intestinal tract, as a cavity. It is enclosed on the sides by lips and cheeks, above by the soft and hard plates and below by the floor of the mouth and the tongue. The lips are lined on the outside by skin and on the inside by mucous membrane. Small glands are situated beneath the mucous membrane and there are many bundles of muscles within the lips. The palate is divided into hard and soft. The hard palate at the front of the mouth and the soft at the back. The bones of the hard palate are covered by thick layer of firm soft tissue. The soft palate connects with the passageway from the mouth to the throat. It is continue with tissues en-circling the opening of the pharynx. The floor of the mouth lies in horse-shoe around the tongue. Near the front end are the openings of the sub-mandibular salivary glands.<sup>2-4</sup>

**Oral Mucosal Compartment (OMC):** The OMC is formed from mucosa associated lymphoid tissues beneath the mucosal membranes of the gum, Periodontium, salivary glands and tonsils<sup>5</sup> (Table 1).

**Oral Mucous Membrane (OMM):** The basic elements of the mucous membrane are formed from an epithelium<sup>6</sup>. OMM covers gingival surface, gingival part of the periodontium, tongue, salivary glands as well as tonsils. The epithelia of such mucous membrane can be keratinized, para-keratinized and non-keratinized with most evident type, the stratified Squamous epithelium<sup>7</sup> (Table 1). The immune functions of the mucous membrane are; mechanical barrier, lubrication, site for mucosal IgA and trapper of the microbial invaders<sup>7,8</sup> (Table 1).

**Table 1** The epithelia of the oral cavity

Structure	Type
Gum; Gingiva	Keratinized squamous
Gingival parts of Periodontium*	Keratinized squamous
Tongue	Stratified squamous, prekeratinized, keratinized
Salivary gland	Squamous glandular
Tonsils-Palatine	Crypts with deep invaginations of stratified squamous
Tonsils- lingual	Stratified squamous
Tonsils- pharyngeal	Pseudo stratified columnar

\*Periodontium composed of gingival, periodontal ligament, cementum and alveolar bone

**Table 2** The immune functions of epithelia

Innate immunity, mechanical barrier
TLRs immune recognition
Trapping
Innate immune responses
Constitutive and inductive cytokine production

## Epithelia

Epithelia is the plural of the singular epithelium. They are specialized layers that covered the external surface of the organs forming the body. An epithelium constitutes a sheet of cells lining close together with distinct biochemical, functional and structural domains that confer polarity, sidedness to the epithelia. Epithelia are avascular and receive nourishment through diffusion of the molecules via basal lamina. Their functions can be; trans-cellular transport, secretion of hormones mucous and proteins as well as, selective permeability.<sup>7</sup>

Epithelia have lateral epithelial surface and apical epithelial surface. The lateral surface contains specialized junctions that produce adhesions between cells and restrict movement of matters into and out of the lamina. Basal epithelial surfaces are formed from an extracellular supportive structure the basal lamina, Hemidesmosomes and basal plasma membrane in-foldings. While apical surfaces posses specialized structures like micro-vili, sterio-cilia and cilia.<sup>7,8</sup>

Two non-immune mediated diseases involving epithelia; the immotile cilia syndrome and the epithelial cell tumors, carcinoma and adeno-carcinoma. A third immune mediated autoimmune disease the Bullous pemphigoid also involves epithelia.<sup>7-9</sup>

In the immunologic sense, the epithelia played several functions of immune nature like; Mechanical barrier, trapping, innate immune recognition, innate immune response and cytokine production (Table 2).

## Cytokines

### Nomenclature

Before scientists be able to coin the term “cytokines” several names have been used to assign them as noted in Table 3.

**Table 3** The common nomenclature of cytokines

Lymphokines
Monokines
Chemokines
Virokines
Adipokines
Lymphocyte Activating factors LAF
Macrophage inhibition factor MAF
Leukocyte inhibitory factor LIF
Leukemia inhibitory factor LIF
Macrophage arming factor MAF
Erythropoietin
Tumor growth factor TGF
Tumor necrosis factor TNF
Macrophage colony stimulating MCSF
Granulocyte Macrophage colony stimulating factor GCMCSF
B-Lymphocyte growth factor BLGF

### Nature

Cytokines are secreted regulator proteins that have pleotropic regulatory effects on haemopoietic and non-haemopoietic cells. They are synthesized and secreted by every nucleated cell of the body.<sup>10</sup> Cytokines include; Interleukins, tumor necrotic factors, growth factors and interferons. The borders of the cytokine world are ill-defined and rather un-stable (Table 4). The basic functional features of cytokine action is the network signal language fashion.<sup>10,11</sup>

The oral cytokines and chemokines are either of systemic or local secreted origins. They have numerous immunologic and non-immunologic functions such as: Immune responses, immunoglobulin class switching, inflammatory responses, cell growth, cell differentiation and expansion.<sup>12</sup> Excessive cytokine production affects tissue damages.<sup>13,14</sup>

### Classification

Cytokine can be classified in accordance with various criteria like; structure, capacity to interact with different classes of receptors and functions.<sup>12</sup> In structural sense, cytokines have been classified according to their overall three dimensional structure and their receptor structure (Table 5 & 6). When cytokine structure and functions have been studied in details as a results six families are evident as; Interleukine family, hemo-poietin family, interferon family, tumor necrosis factor family, interleukine 17 family and chemokine family.<sup>10</sup>

### Oral Epithelial Cytokines (OEC)

The oral epithelial cells recognize microbial invaders through their TLRs. The invaders or their subunits can stimulate epithelial

cell to produce cytokines. The profiles of such cytokines can match that of natural immune cells, TH1, TH2 cytokines and chemokines. The mode of synthesis and release are through either constitutive or inductive pathways.<sup>14,15</sup>

OEC have been described as species and strain dependent manner. They may take part in; Regulation of local oral immune responses, augment epithelial cells to secrete more cytokines, mediate autoimmune responses and activate neutrophil. OEC can inhibit fungal growth, potentiate virulence of some fungi. Lipopolysacchrides, lipoteichoic acid and peptidoglycan potentiate oral epithelial cells to secrete cytokines, initiate and perpetuate oral mucosal inflammation and/or tissue damage in cases of excessive secretion.<sup>16-19</sup> Epithelial cells (EC) are important elements of the innate immune system. EC from periodontal pocket are integral part of the immune system in the oral cavity.<sup>18</sup>

INF g primed EC precondition them for stimulation by microbial component through up-regulation of their TLR system.<sup>19</sup> Cytokines and chemokines are involved in the interaction between gum epithelial cell and dendritic cells (DCs). The responses are bacterio-specific differential and coordinated regulation between gingival EC and DCs may be important in regulation of innate hemostasis and responses to pathogens in the oral cavity.<sup>1</sup> Polymorph nuclear cell induce protective type TH1 cytokines epithelial response in an in-vitro model of oral candidiasis.<sup>16</sup>

The infection of oral epithelial cells with *C. albicans* augments the antifungal activity of neutrophil.<sup>17</sup> Microbial but not the vaccine components initiate immune responses. Such responses will lead to the development of TNF alpha and mediate autoimmune inflammatory disease in the submandibular glands, in which the microbial subunits induce the release of TNF alpha that triggers the secretion of IL8 from ECs.<sup>20</sup>

In the cellular immune-biologic sense, there is a theme<sup>21</sup> of a tripartite local reaction that occurred between the oral epithelial cells with the oral resident microbiome and the OECs with the invading dental microbial pathogen. The local microbiome did an interplay with the oral immune compartment and has been reviewed.<sup>5,21,22</sup> So as that interplay, the OECs face and interact with commensal part of the local microbiome and established a state of harmony.<sup>23</sup> While, the OECs recognize and interact with the pathogenic microbe such interaction may lead to initiation of the innate inflammatory cytokine and antimicrobial peptide productions.<sup>24,25</sup> Parallel to these events, the pathogen may establish an intracellular persistence within the oral epithelial cells (As in case of *Porphyromonas gingivalis*). Thus, the net functional outcomes of OECs in such interplay are; Recognition, respond to, pro-inflammatory and inflammatory cytokine production and intracellular persistence of some dental pathogen like *P. gingivalis*. Such intracellular persistence might contribute in case of its course of chronicity to cellular hypersensitivity, and autoimmune reactions.<sup>26,27</sup> (Table 7).

## Immune simulation model

### Primary epithelial cell culture (ECC):

The epithelial layer from hard palate of the mouth biopsied by specialist. It is macerated, washed and treated with trypsin or collagenase for relatively short time to free the cells from the tissue remnants and mucus. Epithelial cells are, washed, centrifuged and suspended into tissue culture medium which support their growth. The cell suspension is dispensed in tubes and bottles where cells can adhere to the wall and grown into a monolayer. These monolayer cultures are found to be devoid of CD14 and did not enhance for

production of IL8 and GMCSF when stimulated by LPS and LTA. While when treated with INF $\gamma$  for three days, they will secrete IL8 and GMCSF in response to LPS and LTA.<sup>28,29</sup>

### An in vitro oral epithelial model

A tissue engineered model of oral cavity epithelium has been developed. Oral bacteria are used to induce the epithelium to produce pro-inflammatory cytokines and compared to that of sub-emerged epithelial monolayer. The epi-oral Epi-oral tissue model was characterized for keratin and beta defensin evaluations by RT-PCR after exposure to bacteria and TNF  $\alpha$  cytokines in the medium. The epi-oral responses were compared to the response of traditional

sub-emerged oral epithelial culture. Better cytokine responses were noted by the epi-oral model.<sup>30</sup>

### An in-vitro model for host-parasite interactions

Gingival epithelial primary culture was prepared as a monolayer. This monolayer was exposed to bio-film of plaque forming dental bacteria. The bio-film-monolayer culture system was incubated for certain time period. Bio-film invoked apoptosis in epithelial cells, triggering the release of pro-inflammatory cytokines and in parallel seen induced degradation of the cytokine by the action of the bio-film generating enzymes.<sup>31</sup>

**Table 4** Regulatory secreted proteins

Features	Cytokine	Hormones	Growth Factors
Chemical nature	Protein	Protein	Protein
Functions	Regulation	Regulation	Regulation
Source	All nucleated cells	Specialized cells and tissues	Specialized cells and tissues
Mode of secretion	Constitutive and inductive	Constitutive	Constitutive
Site of action	Short distance and short time	Distant site of action	Distant site of action
Nature of the action	Pleotropic	Restricted to certain cell type	Restricted to certain cell type

**Table 5** Functional classification of cytokines

Class	Examples <sup>12</sup>
Haemopoietic	IL5, GM-CSF, GCSF, SCF
Innate immunity, primary and secondary inflammatory cytokines	INF $\alpha$ , INF $\beta$ , IL1, IL8
Specific immunity	IL2, IL4, IL15
Anti-inflammatory/Immunosuppressive	IL1ra, IL10, TGF $\beta$

**Table 6** Clinical and biochemical variables of individuals with overweight-obesity

Cytokine	Sharing group <sup>12</sup>
INF $\gamma$ , IL18, IL12	Innate and adaptive immunity
MIF $\alpha$ -1	Growth factor, and inhibitory
IL6	Innate and growth factor
IL13	Adaptive and inhibitor

**Table 7** Oral Epithelial cytokines

Cytokine Features	Description
Inducer	Commensals, local mucosal infection
Cells	Epithelia
Pro-inflammatory	IL1- $\alpha$ , TNF- $\alpha$
TH1 type	IL2, INF $\gamma$
TH2 type	IL10, TNF- $\beta$
Chemokines	Monocyte chemoattractants, Protein-1, IL8

## Conclusion

Oral mucosal epithelium is being introduced into the world of immune function. They interplayed functional roles in both natural (innate) and adapted oral mucosal immune responses. Such responses are concerning, cytokines, chemokines and TLR system functions as well as they might have implications in vaccine local and/or systemic immune responses.

## Acknowledgments

None.

## Conflicts of interest

Author declares there are no conflicts of interest.

## Funding

None.

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