Overview of Immunology: Mucosal Immunology- the guardian of oral health

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Statement of Disclosure: I have no actual or potential conflict of interest in relation to this presentation
Outline

• Role of the immune system in health and disease
• Overview of mucosal immunity
• Defenses of the oral cavity
The Oral Cavity is the Gateway to the Body

- Gingiva
- Buccal Mucosa
- Tonsils
- Sublingual Immune Response
Protecting the Oral Cavity

1. Physical Defenses
   a) Oral mucosal integrity
   b) Epithelial shedding
   c) Tissue organization
   d) Microbiome

2. Innate Defenses
   a) Saliva
   b) Host defense peptides
   c) IgA

3. Cellular Immune Defenses
   a) Neutrophils
   b) Macrophages
   c) Natural killer cells
   d) T cells (Th17)
   e) B cells
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Physical defenses of the oral cavity prevent pathogen entry

<table>
<thead>
<tr>
<th>Tissue region</th>
<th>Median epithelial turnover time (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small intestine</td>
<td>4</td>
</tr>
<tr>
<td>Buccal mucosa</td>
<td>14</td>
</tr>
<tr>
<td>Floor of mouth</td>
<td>20</td>
</tr>
<tr>
<td>Hard palate</td>
<td>24</td>
</tr>
<tr>
<td>Skin</td>
<td>27</td>
</tr>
</tbody>
</table>

- Oral mucosa (keratinized and non-keratinized) provides:
  - Thermal protection
  - Sensory information
  - Physical barrier to bacteria, viruses, yeast and toxins

- Oral epithelial cells are constantly shed

*Squier and Kremer (2001)*
Structure of the Oral Mucosa

Modified from Pocket Dentistry, Ch. 12 and 2016 BioRad Laboratories Mini-review Series. The Mucosal Immune Response in Health and Disease
Mucosal Immune System

- Largest immune organ in the body
- Humans have a mucosal surface area of over 300m²
- Gut, nasal and oral cavities, female genital tract

- Mucosal inductive sites:
  - Mucosa-associated lymphoid tissue (MALT)
    - Gut.. GALT
    - Nasopharyngeal... NALT
    - Bronchus... BALT
Mucosal Immune System Overview

**INDUCTIVE SITES**
- GALT (Peyer’s Patches)
- Oral Mucosa
- NALT
- BALT

**EFFECOR SITES**
- Lamina propria (GI tract, upper respiratory tract, genitourinary tract)
- Glandular Tissues (Mammary, Salivary)

- Treg
- Th1
- Th2
- Th17
- DC
- Plasma cells
- dIgA

MLN

Blood Stream

2016 BioRad Laboratories Mini-review Series. The Mucosal Immune Response in Health and Disease
Structure of the Gut Mucosal Immune System

Antigen presenting cells interact with naïve T and B cells in the lymph node.
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The oral cavity is equipped with innate immune defenses
## Protecting the Oral Cavity

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Protein in Whole Saliva comes from multiple sources

Serum via gingival crevicular fluid

Oral Microbiome

Mucosal epithelial cells

Parotid gland
Submandibular gland
Sublingual gland
# Key Host Defense Peptides in the Oral Cavity

<table>
<thead>
<tr>
<th>Antimicrobial peptide</th>
<th>Produced by</th>
<th>Activity</th>
</tr>
</thead>
</table>
| Secretory IgA                  | • Plasma cells involved in mucosal-associated lymphoid tissue  
|                                | • B and T lymphocytes                           | • Major antibody in saliva  
|                                |                                                   | • Inhibits microbial adherence  
|                                |                                                   | • Agglutinates bacteria  
|                                |                                                   | • Neutralizes virus  |
| Cathelicidins                  | • Neutrophils  
|                                | • Monocytes  
|                                | • T cells                                        | • Antifungal, antiviral, antiparasitic  
|                                |                                                   | • Broad-spectrum activity against Gram-positive, Gram-negative bacteria and HIV  |
| Defensins                      | • Azurophilic granules of neutrophils  
|                                | • Epithelial cells                               | • Antimicrobial against Gram-positive and Gram-negative bacteria, HIV, mycobacteria, and fungi  
|                                |                                                   | • Induce TLR signaling and recruitment/activation of dendritic cells  |
| Histatins                      | • Component of saliva synthesized by parotid and submandibular salivary duct cells  
|                                |                                                   | • Potent activity against fungi (including *Candida albicans*)  
|                                |                                                   | • Regulate oral hemostasis  
|                                |                                                   | • Bond metal ions in saliva  |
| Lactoferrin                    | • Exocrine glands  
|                                | • Neutrophils in infected/inflamed sites         | • Binds iron  
|                                |                                                   | • Bacteriostatic  
|                                |                                                   | • Bacteriocidal, anti-HIV  
|                                |                                                   | • Decreases biofilm formation  
|                                |                                                   | • Decreases reactive oxygen formation  |
| Lysozyme                       | • Present in saliva  
|                                | • Cytoplasmic granules of macrophages and polymorphonuclear neutrophils | • Antibacterial  
|                                |                                                   | • Antiviral, anti-HIV  
|                                |                                                   | • Binds to and aggregates Gram-positive bacteria  |
| Secretory leukocyte protease inhibitor | • Component of saliva  
|                                | • Produced by neutrophils, macrophages, submandibular glands | • Antiviral, anti-HIV  
|                                |                                                   | • Inhibits proteases  
|                                |                                                   | • Inhibition of neutrophil elastase  
|                                |                                                   | • Bactericidal, antifungal  |

Heron and Elahi. *Front Immunol.* 2017 Mar 7;8:241
• Secreted IgA on the mucosal surface can bind and neutralize pathogens and toxins

• IgA is able to bind and neutralize antigens internalized in endosomes

• IgA can export pathogens and toxins from the lamina propria while being secreted
T-Dependent IgA Class Switching in the Gut
T-Independent IgA Class Switching in the Gut

[Diagram showing the process of T-Independent IgA class switching in the gut, involving Bacterium/PAMP recognition by TLR, Dendritic cell activation with APRIL and TGF-β, and IgM+ B cell differentiation into IgA-producing cells in the lamina propria.]
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Cells of the Oral Mucosal Immune System

- Dendritic Cells
  - Langerhans Cells
- Macrophages
- Innate Lymphoid Cells
- Neutrophils
- NK Cells
- B Cells
- T cells
  - CD4⁺
    - Tregs (secrete IL10)
    - Th17 cells
  - CD8⁺
  - Gamma Delta T cells
Types of Adaptive Immunity

### Humoral Immunity
- **Microbe**: Extracellular microbes
- **Responding Lymphocytes**: B lymphocyte
- **Effector Mechanism**: Secreted antibody
- **Transferred by**: Serum (antibodies)
- **Functions**: Block infections and eliminate extracellular microbes

### Cell-Mediated Immunity
- **Microbe**: Phagocytosed microbes in macrophage
- **Responding Lymphocytes**: Helper T lymphocyte
- **Effector Mechanism**: Cells (T lymphocytes)
- **Transferred by**: Cells (T lymphocytes)
- **Functions**: Activate macrophages to kill phagocytosed microbes

- **Microbe**: Intracellular microbes (e.g., viruses)
- **Responding Lymphocytes**: Cytotoxic T lymphocyte
- **Effector Mechanism**: Cells (T lymphocytes)
- **Transferred by**: Cells (T lymphocytes)
- **Functions**: Kill infected cells and eliminate reservoirs of infection
IL-17 cells are critical for oral immunity
Antifungal Mucosal Defenses
Plenary Session 1: Oral Medicine and Immunology as Friends