Microbial markers of oral carcinogenesis in Fanconi Anemia and cancer patients

Flavia Teles, DDS, MS, DMSc
The Forsyth Institute, Boston, MA
Harvard School of Dental Medicine
Introduction

- Infection as a risk of cancer
- Data begin as observational: people with cancer also harbor a given bacterial species
- Example: *Helicobacter pylori*
- Gastritis can lead to gastric cancer
- Infection with *H. pylori* correlates with incidence of gastritis: bacteria might be associated with initiation of gastric cancer
**Introduction**

- Other possible associations:

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Chlamydia trachomatis</em></td>
<td>Cervical</td>
</tr>
<tr>
<td><em>Chlamydophila (Chlamydia)</em></td>
<td>Lymphoma; lung</td>
</tr>
<tr>
<td><em>pneumoniae</em></td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus bovis</em></td>
<td>Colonic carcinoma</td>
</tr>
<tr>
<td><em>Salmonella typhi</em></td>
<td>Gallbladder</td>
</tr>
</tbody>
</table>

- ASSOCIATION DOES NOT MEAN CAUSATION...
Introduction

• The oral cavity harbors many types of bacteria

Health

Chronic periodontitis
Oral Bacteria and Head and Neck Cancer

- Elevated levels of common oral bacteria have been found in esophageal cancer lesions and their lymph nodes

- *Streptococci, Prevotella, Veillonella, Porphyromonas, Capnocytophaga*
Salivary Bacteria and Oral Cancer
Oral Squamous Cell Carcinoma (SCC)

OSCC - free | OSCC | OSCC - free matched | OSCC
---|---|---|---
N | 229 | 45 | 45 | 45
Mean age (± SEM) | 42.1 (± 1.04) | 57.6 (± 2.3) | 53.7 (± 2.1) | 54.5 (± 2.3)
Minimum age | 18 | 18 | 19 | 18
Maximum age | 81 | 92 | 81 | 85
Males | 107 (47%) | 32 (71%) | 32 | 32
Smokers | 46 (20%) | 18 (40%) | 18 | 18

- OSCC patients had elevated salivary levels of certain oral bacteria, specifically *Capnocytophaga gingivalis*, *Prevotella melaninogenica*, and *Streptococcus mitis*
- Potential non-invasive diagnostic tool

Mager et al 2005
How bacteria may cause cancer?

1) Activation of procarcinogenic chemicals

- Ethanol (alcohol) $\rightarrow$ Acetaldehyde
- Acetaldehyde can cause DNA damage
- *Streptococci* and *Neisseria* can convert ethanol into acetaldehyde
How bacteria may cause cancer?

2) Infection and Inflammation

- Local (chronic) inflammation can participate in the induction and expansion of malignant cells
- *H. pylori* & gastric cancer
- *P. acnes* & prostate cancer
- *C. pneumoniae* & lung cancer
- *S. bovis* & colonic carcinoma

→ Many oral bacteria can stimulate inflammatory response
Rationale

• Previous studies focused on up to 40 species of bacteria
• The oral cavity can harbor > 700 bacterial species
• They might also be associated with oral cancer
• Different bacteria are present in different oral locations
• Tongue (lateral) is #1 location of oral cancer
Human Oral Microbial Identification Microarray (HOMIM)

Healthy

Disease

http://mim.forsyth.org/homim.html

Paster & Dewhirst 2009
Human Oral Microbial Identification Microarray (HOMIM)

http://mim.forsyth.org/homim.html
Purpose

• To characterize the oral microbial profiles of FA patients, their non-FA sibling/parent (and non-FA oral SCC patients)

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Saliva</th>
<th>Tongue Lateral</th>
<th>OSCC lesion</th>
<th>Healthy contralateral to OSCC</th>
<th>Microarrays</th>
</tr>
</thead>
<tbody>
<tr>
<td>FA</td>
<td>42</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>84</td>
</tr>
<tr>
<td>Non-FA relative</td>
<td>42</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>84</td>
</tr>
<tr>
<td>OSCC</td>
<td>42</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>168</td>
</tr>
</tbody>
</table>

• **Personnel involved:** Bruce Paster, Dr. Phil Stashenko (Forsyth), Eva Guinan and Marshall Posner (DFCI), Meredith August (MGH), Carmen Bonfim (Federal University of Parana, Brazil), Eleni Gagari (University of Athens School of Medicine, Greece).
Sampling

• Approximately 30 min. visit

• Informed consent and medical questionnaire

• To the extent possible, participants will be asked to refrain from drinking, eating and brushing in the 2 hours prior to sampling

• Stimulated saliva samples will be collected (about 2 teaspoons) by spitting into a plastic tube after chewing on a paraffin stick

• Samples of the material covering the surfaces of the sides of the tongue (i.e., biofilm) will be collected using a sterile soft brush and swabbing the tongue
Sampling: Saliva
Sampling: Tongue

http://kimberlynunderwood.files.wordpress.com/2009/02/tongue2.jpg
Sampling: Tongue
Anticipated Results and Future Studies

• Types of bacteria present in FA patients will be different from those present in non-FA
• Selected bacterial species present only in FA patients will merit further study:
  1. Can they induce infection/inflammation?
  2. Can they make carcinogenic compounds?
  3. Are they similar to those present in non-FA OSCC patients?
• This study would be a first step in the development early diagnostic test for patients who are at greatest risk of developing head and neck SCC
Example: Multiple Salivary Biomarkers for Pancreatic Cancer Detection

- Search for compounds in saliva of 30 pancreatic cancer (PC), 30 chronic pancreatitis (CP) and 30 healthy matched-control (H) saliva samples.

- The levels of six microbial biomarkers, eleven mRNA biomarkers and eight metabolites were significantly different between PC, CP and H.

- Microbial biomarkers (Prevotella nigrescens, Neisseria elongata) contributed to provide a sensitive and specific means of distinguishing PC from H, as well as PC from CP.

- Combination of multiple (4) salivary biomarkers could detect pancreatic cancer with great clinical discrimination.

- First report demonstrating the value of salivary biomarkers for the detection of pancreatic cancer.

Zhang et al 2009
Questions?