Molecular Characterization of Gastric Cancer in Alaska Native People

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Objectives

• Identify the differences in gastric cancer among Alaska Native people in comparison to U.S. Non-Hispanic Whites

• To understand the commonly mutated genes in the gastric cancers among the Alaska Native people

• To understand the role of infection and inflammation in the initiation and progression of gastric cancer among Alaska Native people
Gastric Cancer among Alaska Native People: A Cancer Disparity

Alaska Native Population
- 5th most common cancer
- 3rd leading cause of cancer death
- 5-year survival rate: 10%
- Median age: 59

United States Population
- 15th most common cancer
- 15th leading cause of cancer death
- 5-year survival rate: 30%
- Median age: 69

* Rates among Alaska Native people are statistically different from US White rates; p < 0.05. Rate ratio for nasopharynx = 17.25* not shown, but included in oral cavity/pharynx group.

Kelly J et al. Cancer in Alaska Native People: 45 year report, 2015, ANTHC
Risk Factors for Gastric Cancer

- Helicobacter pylori
- Epstein-Barr Virus
- Age
- Male
- Gastritis
- Pernicious anemia
- Family History/Genetics
- Smoking
- Alcohol
- Environment
- Gastroesophageal Reflux Disease
- Poor Nutrition/Diet
  - Smoked-nitrates
  - Salted
  - Preserved foods

John Hopkins Medicine Gastroenterology & Hepatology: https://www.halstedsurgery.org/
Alaska Native GC Incidence in Regions of Alaska

- Far North: 28.8%
- Interior: 8.3%
- Southcentral: 30.3%
- Southwest: 30.3%
- Southeast: 2.3%
Alaska Native Gastric Cancer Patients Differ in Clinical and Pathological Features

Poster Presentation: Tuesday
Molecular Characterization of Cancer

Early Detection, Prognostic Biomarkers, and Therapeutic Targets
Genetic Mutations among Alaska Native Gastric Cancer Patients

- Mayo Clinic
  - 50 gene targeted sequencing panel
  - 83 patients analyzed
- 69% of AN gastric cancer patients have a Single Nucleotide Polymorphisms
  - Younger at time of diagnosis (<55)
  - Chronic inflammation (gastritis)

<table>
<thead>
<tr>
<th>Alterations</th>
<th># Patients</th>
<th>Percent</th>
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<tbody>
<tr>
<td>Mutation</td>
<td>57</td>
<td>68.7%</td>
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<tr>
<td>Tp53</td>
<td>30</td>
<td>36.1%</td>
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<tr>
<td>PIK3CA</td>
<td>13</td>
<td>15.7%</td>
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<tr>
<td>STK11</td>
<td>6</td>
<td>7.2%</td>
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<tr>
<td>PTEN</td>
<td>5</td>
<td>6.0%</td>
</tr>
<tr>
<td>KRAS</td>
<td>5</td>
<td>6.0%</td>
</tr>
<tr>
<td>Total Patients</td>
<td>83</td>
<td></td>
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</tbody>
</table>
Tumor Microenvironment
Chronic Infection and Inflammation

Adapted from Balkwill et al., *J Cell Science* 2012; 125: 5591-5596
Chronic Infection: Role of *H. pylori* and EBV in Gastric Cancer

- **Helicobacter pylori (H. pylori)**
  - 75% of Alaska Native people have been exposed to *H. pylori*
  - *H. pylori* IgG positively associated with gastric cancer
  - 40% AN gastric cancer patients with active infection at time of diagnosis

- **Epstein-Barr Virus (EBV)**
  - 21% Alaska Native gastric cancer patients in our study had EBV-associated gastric cancer
    - History of *H. pylori*, tobacco use, chronic inflammation

Chronic Inflammation: High Risk Factor

- Immunologic Factors
  - PD-L1 - 12 patients positive (13.4%)
  - Immune cell presence
    - CD8+ T cells - CD8
    - Macrophages - CD68
    - NK Cells - CD57
    - MDSC - CD33
  - COX-2
COX2 Expression among Alaska Native Gastric Cancer Patients

- Expression associated with *H. pylori* infection
- Promotes cancer by influencing cell growth and invasion
- Aspirin use reduces risk of non-cardia gastric cancer


Xiang HG, et al., *Oncology Reports.* 2014; 13: 1140

High Expression of Mucin 1 Early Detection Biomarker?

- Glycoprotein-oncogenic signaling molecule
- Upregulated in *H. pylori* infected gastric cancer patients
- Associated with poor prognosis in cancer patients

Conclusions

- The Alaska Native people have increased incidence and mortality rates of gastric cancer compared to the U.S. white population.
- Alaska Native patients are diagnosed with gastric cancer that differs in clinical and pathological features when compared to the US population.
- Infection and inflammation are potential driving factors in the pathogenesis of gastric cancer among the AN people.
- Further investigation into the interactions between *H. pylori*, EBV, inflammation, and gastric cancer pathogenesis is needed.
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Questions?