Methylome Profiling of Esophageal Squamous Cell Carcinoma

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Identification of a DNA methylome signature of esophageal squamous cell carcinoma and potential epigenetic biomarkers

Sheila C.S. Lima, Hector Hernandez-Vargas, Tatiana Simão, Geoffroy Durand, Cleber Dario Pinto Kruel, Florence Le Calvez-Kelm, Luis Felipe Ribeiro Pinto and Zdenko Herceg

Identification of a DNA Methylome Profile of Esophageal Squamous Cell Carcinoma and Potential Plasma Epigenetic Biomarkers for Early Diagnosis

Xufeng Li, Fuyou Zhou, Chunyu Jiang, Yinguo Wang, Yanqiang Lu, Fei Yang, Nengchao Wang, Haijun Yang, Yanfang Zheng, Jiren Zhang

Genome-wide profiling of DNA methylation and gene expression in esophageal squamous cell carcinoma

Chen Chen, Hao Peng, Xiaojie Huang, Ming Zhao, Zhi Li, Ni Yin, Xiang Wang, Fenglei Yu, Bangliang Yin, Yunchang Yuan, Qianjin Lu

The detective, prognostic, and predictive value of DNA methylation in human esophageal squamous cell carcinoma

Kai Ma, Baoping Cao and Mingzhou Guo
The squamous epithelium

Squamous cell carcinoma

? 

Squamous cell carcinoma

Epidheliun

Lamina propria

Muscularis mucosae
Field cancerization

Lima et al., 2014.
Comparisons performed

- **T** – Tumor
- **N** – Non-tumor adjacent tissue
- **H** – Healthy esophageal mucosa

ESCC patients

Vonluteers without cancer
Field cancerization in the Esophagus

Epigenetic alterations

Lima et al., 2011.

Lee et al., 2011.
Objectives of genome wide methylation studies

Identify potential epigenetic drivers in ESCC

Complement genetic data on altered signalling pathways

Identify potential early diagnosis biomarkers

Identify novel potential druggable targets

Analyse potential etiological specific associated methylation signatures
## Profile of the individuals included in the study

<table>
<thead>
<tr>
<th></th>
<th>Healthy Individuals</th>
<th>ESCC patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy mucosa</td>
<td>7</td>
<td>17</td>
</tr>
<tr>
<td>Non-tumor adjacent tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor</td>
<td></td>
<td>24</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>4 (57%)</td>
<td>21 (87%)</td>
</tr>
<tr>
<td>Male</td>
<td>3 (43%)</td>
<td>3 (13%)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>54.5</td>
<td>56</td>
</tr>
<tr>
<td>Minimum</td>
<td>38</td>
<td>39</td>
</tr>
<tr>
<td>Maximum</td>
<td>63</td>
<td>77</td>
</tr>
</tbody>
</table>
Number of differentially methylated probes in each comparison

Healthy esophagus → Non-tumor adjacent tissue → ESCC

460 DMPs

Adjusted p-value < 0.01

82,465 DMPs

Adjusted p-value < 0.001
Number of differentially methylated probes in each comparison

Healthy esophagus  
460 DMPs

Non-tumor adjacent tissue  
82,465 DMPs

Adjusted p-value < 0.01

Adjusted p-value < 0.001
Healthy vs Non-tumor Adjacent Tissue
TFF1 alterations in non-tumor adjacent mucosa and ESCC
TFFs: protectors of the mucosa

Putative pathways involved in esophageal carcinogenesis

- **TFF1** promoter hypermethylation
- **BCL3** gene body hypermethylation
- Loss of mucosa protection
- Resistance to apoptosis
Putative pathways involved in esophageal carcinogenesis

- **IL6** promoter hypermethylation
- **DSG1** promoter hypermethylation
- **FBXL7** gene body hypomethylation

**Inflammatory stimuli to proliferation and survival**
**Loss of cell adhesion/differentiation**
**Resistance to apoptosis/Induction of cell proliferation**
Questions and difficulties

Are there epigenetic drivers in ESCC?

What is the intra-tumor methylation heterogeneity in ESCC?

Are most of methylation alterations produced by etiological factor transitory or permanent?

Can we perform an unique and large Genome Wide Methylation Study with different ESCC patients exposed to different etiological factors? (Unique protocols, funding, etc...)

Can we identify etiological specific associated methyltion profile in ESCC?

Can we use methylation data to develop non-invasive early diagnosis biomarker and adjuvant epigenetic therapy?
Thank you

Obrigado