Genotype-Phenotype Characterization of Loss of Genomic Imprinting of IGF2-Positive Colorectal Cancer

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Genomic Imprinting

- Epigenetic form of gene silencing
- Does not involve modifications on DNA
- Is heritable during cell division
- Results in monoallelic expression

Feinberg, Cancer Research 1999;59:1743-46
Genomic Imprinting

Mendelian

Imprinting

Transcript

DNA

RNA

P

M

P

M

P

M

X
Loss of Genomic Imprinting (LOI)

- Failure of cell to maintain normal monoallelic expression
- Abnormal activation of tumor promoting genes such as IGF2 gene
- Abnormal inactivation of tumor suppressor genes
Loss of Genomic Imprinting (LOI)

Imprinting

LOI

P
DNA
P

M

RNA

Transcript

X

P

RNA

Transcript

M
Insulin-like Growth Factor 2 Gene

- Located in chromosome 11p15
- Paternally expressed, maternally silenced
- LOI of \( IGF-2 \) found in embryonic tumors and tumors of ovarian, lung, breast, and colon
- LOI of \( IGF-2 \) is considered an independent risk factor for colorectal cancer (CRC)

Aims

- To determine if LOI of IGF2 was associated with specific clinicopathological characteristics (is there a LOI-positive CRC phenotype?)

- To examine *response* to preoperative chemoradiation therapy in rectal cancer patients according to LOI of IGF2 status (does LOI-positive RC has an enhanced response?)
Methods
Subject Recruitment

- Consecutive patients from three centers: JHU, CCF, UPR who underwent colorectal surgery for management of CRC
- Risk factors, exposure, medical history and family history of cancer questionnaires
- Peripheral blood sample (40 ml) for lymphocyte extraction
Statistical Analysis

- Differences in clinical characteristics between groups were examined with Chi square and Fisher Exact test.
- Univariate and bivariate analysis were constructed for the association of independent covariates with LOI of IGF2.
- Statistical analysis was performed on STATA 9.0 (Stata, TX)
PCR and Apa I digestion on gDNA

RT-PCR and Apa I digestion on RNA

1:0 1:2 1:0 1:2 1:4 1:0 1:6 1:3

LOI LOI LOI

Informative

Informative
Results
## Study Population

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>N(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number patients</td>
<td>199</td>
</tr>
<tr>
<td>Informative Apal</td>
<td>67 (34.0)</td>
</tr>
<tr>
<td>Mean Age (± SD)</td>
<td>60.8 (±14.3)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>110 (55.2)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>157 (79)</td>
</tr>
<tr>
<td>Black</td>
<td>42 (21)</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
</tr>
<tr>
<td>Hispanics</td>
<td>39 (19.5)</td>
</tr>
</tbody>
</table>
Earlier Age at Diagnosis for LOI-Positive CRC Patients

Kaplan-Meier Survival Function for CRC

P < 0.001
LOI-positive CRC were Right-Sided Tumors

Right Colon

Left Colon

P = 0.03

- LOI
- Normal
## Colon vs. Rectal Cancer

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>LOI Positive</th>
<th>LOI Negative</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon Cancer (n=48)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age Diagnosis (± SD)</td>
<td>56.1 ± 11.4</td>
<td>64.9 ± 11.6</td>
<td>0.04</td>
</tr>
<tr>
<td>Dukes (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A/B: C/D</td>
<td>72:18</td>
<td>90:10</td>
<td>0.31</td>
</tr>
<tr>
<td>Differentiation (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low: Mod/Well</td>
<td>32:68</td>
<td>8:92</td>
<td>0.02</td>
</tr>
<tr>
<td>Rectal Cancer (n=39)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age Diagnosis (± SD)</td>
<td>55.6 ± 13.8</td>
<td>58.0 ±13.7</td>
<td>0.56</td>
</tr>
<tr>
<td>Dukes (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A/B: C/D</td>
<td>91:9</td>
<td>92:8</td>
<td>0.86</td>
</tr>
<tr>
<td>Differentiation (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low: Mod/Well</td>
<td>20:80</td>
<td>13:87</td>
<td>0.61</td>
</tr>
</tbody>
</table>
Response to Chemoradiation Therapy in Rectal Cancer

92 RC Patients

39 Informative (Apal) RC

29 Imprinted

10 LOI of IGF2
Change in Rectal Tumor Size After Chemoradiation

- LOI
  - Median % tumor size reduction: 95.0
  - 95%CI: 64.9-119.2
  - p=0.023

- Imprinted
  - Median % tumor size reduction: 42.5
  - 95%CI: 15.2-71.1

Legend:
- Median % tumor size reduction
- 95% confidence interval (CI)
- p-value
Summary

- LOI-positive CRC individuals have an earlier age at diagnosis, have tumors which are less differentiated and preferentially right-sided.

- LOI-positive RC patients have an improved tumor response to adjuvant chemoradiation compared to LOI-negative RC patients.

- These findings suggest a distinct carcinogenic pathway for LOI-positive patients, which may have implications in screening, risk assessment, and management.
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