PMS2 elevation is associated with prostate cancer

Karin D. Scarpinato, Ph.D.
Assistant Professor
Cancer Biology
Wake Forest University School of Medicine
MISMATCH REPAIR

from: Modrich, 2006
• **Loss of mismatch repair proteins** (MSH2, MLH1) is often associated with the predisposition or development of cancer, particularly a hereditary form of colon cancer, HNPCC

• We show that the **elevation of a mismatch repair protein** is significantly associated with a type of cancer that is not part of the HNPCC spectrum: PROSTATE CANCER
Prostate Cancer & Mismatch Repair

- Only 25-30% of tumors become aggressive, regardless of previous treatment

- Most commonly used prostate cancer cell lines contain defects in at least one MMR protein

- MMR defects have been observed in prostate cancer

Elevated levels of the mismatch repair protein PMS2 are associated with prostate cancer. *Prostate*, 67, 214-225.
PMS2 elevation in prostate cancer

PMS2 is significantly elevated in prostate cancer, independent of MLH1

Prostate Cancer Stages

from: Prostate Cancer, 2nd edition
Elevated levels of the mismatch repair protein PMS2 are associated with prostate cancer. *Prostate*, 67, 214-225.
**Statistical analysis of PMS2 elevation in prostate cancer**

<table>
<thead>
<tr>
<th>Protein</th>
<th>Comparison between</th>
<th>p-value</th>
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<tbody>
<tr>
<td>MSH2</td>
<td>Normal – Cancer</td>
<td>0.107</td>
</tr>
<tr>
<td></td>
<td>grade 3 – 4</td>
<td>0.74</td>
</tr>
<tr>
<td></td>
<td>grade 3 – 5</td>
<td>0.57</td>
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<tr>
<td></td>
<td>grade 4 – 5</td>
<td>0.38</td>
</tr>
<tr>
<td>MLH1</td>
<td>Normal – Cancer</td>
<td>0.501</td>
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<tr>
<td>PMS2</td>
<td>Normal – Cancer</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td></td>
<td>grade 3 – 4 *</td>
<td>0.017</td>
</tr>
<tr>
<td></td>
<td>grade 3 – 5 *</td>
<td>0.019</td>
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<tr>
<td></td>
<td>grade 4 – 5 *</td>
<td>0.86</td>
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</tbody>
</table>

PMS2 is significantly elevated in all Gleason grades of prostate cancer

Prostate Cancer Stages

from: Prostate Cancer, 2nd edition
Prostate Cancer & Mismatch Repair

PMS2 elevation is observed in premalignant lesions of the prostate: PIN

Microsatellite Instability

- Isolation of neoplastic prostate tissue by laser capture microscopy
- Determine microsatellite instability according to NCI guidelines (ABI)

<table>
<thead>
<tr>
<th>Microsatellite instability in mono- and dinucleotide runs of tissue with elevated PMS levels</th>
<th>Elevation of</th>
<th>BAT25</th>
<th>BAT26</th>
<th>D2S123</th>
<th>D17S250</th>
<th>D5S346</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>mono</td>
<td>mono</td>
<td>di</td>
<td>di</td>
<td>di</td>
</tr>
<tr>
<td>MSI-H</td>
<td>PMS2</td>
<td>-</td>
<td>-</td>
<td>ND</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>MSI-H</td>
<td>PMS2</td>
<td>ND</td>
<td>-</td>
<td>+</td>
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<tr>
<td>MSI-H</td>
<td>PMS2</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>MSI-H</td>
<td>PMS2</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>no MSI</td>
<td>PMS+MLH1</td>
<td>-</td>
<td>-</td>
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</tr>
<tr>
<td>no MSI</td>
<td>none</td>
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</tbody>
</table>

PMS2 elevation is associated with microsatellite instability

Summary

1. PMS2 is significantly elevated in prostate cancer.

2. PMS2 elevation is already observed in premalignant prostate lesions, suggesting that it is an early event in tumorigenesis.

3. PMS2 elevation is independent of MLH1 expression.

4. PMS2 elevation causes microsatellite instability.

5. Microsatellite instability is ameliorated when MLH1 is co-overexpressed.

6. PMS2 elevation can be observed in biopsy samples, and in an independent cohort of patient samples.

7. PMS2 elevation increases resistance to cytotoxic agents.

8. PMS2 elevation provides a growth advantage under oxidative stress.
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