Discuss the implications of alternative molecular biologic tumorigenesis pathways on cancer surveillance.

- Discuss colorectal cancers as an example of tumors that evolve via different pathways with genomic and epigenetic changes in DNA methylation.
- Discuss the clinical implications of the different pathways of origin.
- Reassess the types of data that cancer registries should collect in the future.

### Theories of carcinogenesis

#### Somatic Mutation Theory (SMT)
- **Cancer**: A single cell that accumulates DNA mutations and proliferates out of control.
- **Gene**: Gene in the default state of cells.
- **Principles**:
  - Mutations necessary and sufﬁcient for cancer to occur.
  - Cancer can arise from any cell in the body.
  - Changes in the tissue environment predispose to cell transformation.
- **Genetic instability**: A byproduct of carcinogenesis.

#### Tissue Organization Field Theory (TOFT)
-**Conventional**: Development gone awry.
- **Developmental field**: Problem of tissue organization and intercellular signaling.
- **Progenitor cell**: Developmental field of all normal cells of the body.
- **Principles**:
  - Mutations are not needed.
  - Cancer can arise normally from the location of an exposure.
  - Changes in the tissue environment predispose to cell transformation.
- **Genetic instability**: A byproduct of carcinogenesis.

### Colorectal cancer: Example of a tumor with 'epi-genetic' changes in a causal pathway

- Colorectal cancer (CRC) is the second leading cause of cancer-related deaths in the United States, with an overall lifetime risk of about 1 in 20 (5%).
- Recent studies have identified several molecular subtypes of colorectal cancer that differ based on their biologic pathway of origin.
- DNA alterations involving both genetic (e.g., mutations) and epigenetic (e.g., methylated loci) are involved in differentiating the subtypes of colorectal cancer.
- The prevalence and type of these DNA alterations vary by smoking status.

### NH State Cancer Registry Data

<table>
<thead>
<tr>
<th>Gene Name</th>
<th>Methylation level (mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RNF39</td>
<td>0.2</td>
</tr>
<tr>
<td>CUGBP2</td>
<td>0.4</td>
</tr>
<tr>
<td>MECoM</td>
<td>0.6</td>
</tr>
<tr>
<td>IR886</td>
<td>0.8</td>
</tr>
<tr>
<td>RASSF1</td>
<td>1.0</td>
</tr>
<tr>
<td>PLEKHA6</td>
<td>0.8</td>
</tr>
<tr>
<td>FRMD4A</td>
<td>1.0</td>
</tr>
<tr>
<td>NCRNA00181</td>
<td>0.0</td>
</tr>
<tr>
<td>ADAMTS16</td>
<td>0.2</td>
</tr>
<tr>
<td>BIN2</td>
<td>0.4</td>
</tr>
<tr>
<td>C16orf54</td>
<td>0.2</td>
</tr>
<tr>
<td>ZSCAN18</td>
<td>0.4</td>
</tr>
</tbody>
</table>

### Several pathways to colorectal cancer

- The NH State cancer registry data above show that smokers are more likely to have KRAS "normal" tumors.
- This suggests that the cancer in these smokers did NOT arise via the "Conventional Pathway" (blue) or the "Alternative Pathway" (yellow), as both have KRAS mutations as an early event.
- In fact, smokers are more likely to have cancers arising via the "Somatic Serrated Pathway" (red) as a molecular mechanism.

### Types of DNA alterations

- The carcinogenesis pathways shown involve DNA alterations that include specific:
  - mutations (changes to the DNA sequence)
  - epigenetic changes (e.g. attachment of methyl groups to the DNA)

### Clinical utility

- **Cancer prevention**: We can identify molecular "fingerprints" of exposure to tumor to reconstruct causal exposure. E.g. Smoking causes tumors to arise via the sessile serrated pathway.

### Methylation level by smoking status:

<table>
<thead>
<tr>
<th>Gene Name</th>
<th>Never (n=200)</th>
<th>Current (n=100)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRAS</td>
<td>0.00</td>
<td>0.20</td>
<td>0.035</td>
</tr>
</tbody>
</table>

### Clinical study

- **Study group**: Colorectal cancer NH State Cancer Registry patients diagnosed with colorectal cancer 2011–2014 via ICD-O, the registry-initiated collection of smoking history and KRAS mutation status.
- **Cox polyps**: Pathology slides from patients diagnosed with hyperplastic polyps (HP), and/or sessile serrated polyps (SSA/Ps) between 2006 and 2009 (n=460) were reviewed to select phases for the study from the New Hampshire Colonoscopy Registry (NCHR).
- **Total of 42 sessile serrated polyps (SSA/P) in this analysis**.

### Methods

- **Array-based DNA methylation**:
  - Single-base-wide DNA methylation of 460,790 CpG loci was assessed using the Illumina Infinium HumanMethylation450 BeadChip (Illumina, San Diego, CA).

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