Genetic Basis of Cancer

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Bioc 461
2005
Overview

• Cancer in Modern America
• The Biology of Cancer
• The Causes of Cancer
• The Genetics of Cancer
• The Future of Cancer
Information on Cancer

- Information on different types of cancers
- Statistics
- How to diagnosis tumors
- Ongoing trials
What is killing us?

Cancer!

Cancer 19.2%
Chronic Lung Disease 2.3%
Heart Disease 37.8%
Cerebrovascular 10.3%
Pneumonia & Influ. 2.9%
Other Causes 22.0%
Accidents 5.4%

Cancer 22.8%
Chronic Lung Disease 5.1%
Heart Disease 28.5%
Cerebrovascular 6.7%
Pneumonia & Influ. 2.7%
Accidents 4.4%
Other Causes 29.8%

1975

2002

Cancer!
The cell cycle is a tightly regulated system with checkpoints at each step!
Biology of Cancer

Cancer Cells…

…contain several genetic mutations.
…disobey proper cell cycle control.
…reproduce excessively, forming tumors
…spread beyond their original site to other parts of the body
Six (Seven) Super Powers of Cancer

An effective cancer cell must be able to:

1. Grow when it’s not supposed to
2. Ignore orders to stop growing
3. Do this forever
4. Avoid self-destructing
5. Bring in nutrients
6. Mount an invasion

and to get this far it probably needs…

7. Genetic instability
Causes of Cancer: Risk Factors

- Radiation Exposure
- UV light
- Tobacco Smoke
- Food Contamination
- Tumor Viruses
- Family History (Genetic Background)
- Lifestyle
Most Universal Risk Factor…

Age!
Genetics of Cancer

Cancer is the result of genetic changes to the cell

Cancer requires an *accumulation* of mutations, creating a progression from a healthy cell to a malignant cell

- Normal Colon Cell
- Increased Cell Growth
  - APC gene loss
- Early Stage Adenoma
  - DNA loses methyl groups
- Intermediate Stage Adenoma
  - Ras gene mutation
- Late Stage Adenoma
  - DCC gene loss
- Carcinoma
  - P53 gene loss
- Metastatic Cancer
  - Other gene losses
Base Changes

GATTACA

↓

GAT\textbf{CACA}

Insertions

GATTACA

↓

GAT\textbf{ATGCTTACA}

Chromosome Translocations

\begin{align*}
\text{Chromosome Deletions}
\end{align*}
Many types of changes may promote the progression of cancer, including ones that affect the packaging of the DNA but not the nucleotide base sequence.

- **Chromosome Pair**
- **Metaphase**
  - (1000:1 packing ratio)
- **Nuclear scaffold proteins**
- **Solenoid**
  - (40:1 packing ratio)
- **Nucleosome**
  - (6-7:1 packing ratio)
### Inherited vs. Somatic mutations

<table>
<thead>
<tr>
<th>Inherited</th>
<th>Somatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present at birth, and in every cell</td>
<td>Acquired throughout life in individual cells</td>
</tr>
<tr>
<td>Passed from one generation to the next</td>
<td>Not passed on to the next generation</td>
</tr>
<tr>
<td>Increase the risk of cancer exponentially</td>
<td>Increased risk of cancer, but less so</td>
</tr>
<tr>
<td>Are found in many familial syndromes.</td>
<td>Not associated with familial syndromes</td>
</tr>
</tbody>
</table>
Some familial syndromes to know:

**Li-Fraumeni Syndrome:**

Members lack a universally important checkpoint guardian. High risk for *many* cancers. Most affected family members die before the age of 60.

**BRCA1:**

Members lack a protein that functions as a tumor suppressor. High risk for breast cancer.

**FAP (familial adenomatosis polyposis)**

Tumor Suppressor Genes

According to Wikipedia: “A tumor suppressor gene is a gene that reduces the probability that a cell in a multicellular organism will turn into a tumor cell.”

In other words:

Tumor Suppressor

No Cancer

Tumor Suppressor

Cancer
Tumor suppressor genes are often recessive, and require mutations in both copies before they lead to cancer.
P53: the most famous tumor suppressor gene of them all...

P53 is...
- found to be mutated or otherwise disrupted in the majority of all cancers
- nicknamed “The Guardian of the Genome”
- halts cell division in response to DNA damage
- destroys potentially malignant cells via apoptosis.
Mutations in p53 tend to disrupt or destabilize the DNA binding domain.
With functional p53
Cancer is prevented

Without functional p53
Malignant cells can proliferate
Oncogenes

“An oncogene is a modified gene that increases the malignancy of a tumor cell.”

Normal gene (proto-oncogene)  →  Normal Cell

Modified gene (oncogene)  →  Cancer

An oncogene represents a gain or increase of function mutation, rather than a deletion or inactivation.
Src, a proto-oncogene, signals growth in human cells

Protein tyrosine phosphatases
Reduced Csk activity
Displacement of intramolecular interactions
Mutational activation, e.g., mutation or deletion of tyrosine 527

Inactive

Active

Mutations which disrupt these interactions result in Src being inappropriately active.
A fusion of two genes can also result in an oncogene.
Role of genetic variability in cancer

- Normal epithelium
- Small adenomas
- Large Adenomas
  - (low risk of cancer)
  - (high risk of cancer)
- Cancer Metastasis
**ODC Genotype and Adenoma (benign tumor) Recurrence**

*Adjusted for age, gender, number of colonoscopies, and aspirin use*
The Future of Cancer Genetics

Genetic Screening
Pros: Can diagnose diseases earlier. Recommend more appropriate treatments and healthcare

Genetic Therapy?
Human cells can be genetically transformed, but a workable, safe method for treating a full organism has not been developed yet.