Outline

- Cancer prevalence
  - Why haven’t we made more progress?
- 6 Hallmarks of cancer
  - Cell proliferation and death in an adult
  - Tumor suppressors vs. oncogenes
  - Gene Expression 101/cancer results from mutations
- Study to understand biology of colon tumor suppressor APC
- Future studies/goals
### US Mortality, 2009

<table>
<thead>
<tr>
<th>Rank</th>
<th>Cause of Death</th>
<th>No. of deaths</th>
<th>% of all deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Heart Diseases</td>
<td>598,607</td>
<td>24.5</td>
</tr>
<tr>
<td>2</td>
<td>Cancer</td>
<td>568,668</td>
<td>23.3</td>
</tr>
<tr>
<td>3</td>
<td>Chronic lower respiratory diseases</td>
<td>137,082</td>
<td>5.6</td>
</tr>
<tr>
<td>4</td>
<td>Cerebrovascular diseases</td>
<td>128,603</td>
<td>5.3</td>
</tr>
<tr>
<td>5</td>
<td>Accidents (unintentional injuries)</td>
<td>117,176</td>
<td>4.8</td>
</tr>
<tr>
<td>6</td>
<td>Alzheimer disease</td>
<td>78,889</td>
<td>3.2</td>
</tr>
<tr>
<td>7</td>
<td>Diabetes mellitus</td>
<td>68,504</td>
<td>2.8</td>
</tr>
<tr>
<td>8</td>
<td>Influenza &amp; pneumonia</td>
<td>53,582</td>
<td>2.2</td>
</tr>
<tr>
<td>9</td>
<td>Nephritis*</td>
<td>48,714</td>
<td>2.0</td>
</tr>
<tr>
<td>10</td>
<td>Intentional self-harm (suicide)</td>
<td>36,547</td>
<td>1.5</td>
</tr>
</tbody>
</table>

*Includes nephrotic syndrome and nephrosis.


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### Cancer Statistics, 2006

Graph showing the rate of death per 100,000 population for younger than 85 years and 85 and older, with a decline in heart disease and cancer rates over the years.
Cancer

- Not one, but 100s of diseases

Biological attributes “hallmarks” shared by most cancers

1. generate own mitogenic (proliferation) signals
Cancer

- Starts as a normal cell that has gone awry
- Early step is malfunction of the control systems that regulate cell proliferation

Cell Proliferation in the Adult

- Human body (~150 lbs) consists of about $1 \times 10^{14}$ cells (100 trillion).

- Certain cells in the mucosal lining of the intestine are replaced 4,400 times during our life. Together, this equals ~25 miles.

- Epidermal cells are replaced about 1,000 times and connective tissues are replaced about 400 times.

- Bone marrow weighs on average 3.2 lbs. Its turnover time is two weeks. During our lifetime, we produce 3 tons of bone marrow.
What controls the balance of cell growth and death?

- Proteins!
  - Oncogenes = proteins that promote growth
  - Tumor suppressors = proteins that inhibit growth or promote cell death

Cancer

- Starts as a normal cell that has gone awry
- Cancer results from mutations in tumor suppressor genes and oncogenes (5-6)
- After one cell gets mutation, the next ones occur in descendants of original mutant cells—takes decades
Basic Gene Expression

Genes contain instructions for making proteins. Proteins act alone or in complexes to perform many cellular functions.

Mutations in Cancers

Oncogenes = proteins that promote growth

Tumor suppressors = proteins that inhibit growth or promote cell death
Biological attributes “hallmarks” shared by most cancers

1. generate own mitogenic signals
2. resist exogenous growth-inhibitory signals
3. evade apoptosis (programmed cell death)
Apoptosis
A cell fate that plays a key role in embryonic development (e.g. cells between digits, loss of tadpole tail), but also in the maintenance of adult tissues…

“From 50 to 70 billion cells die each day due to apoptosis in the average human adult. In a year, this amounts to the proliferation and subsequent destruction of a mass of cells equal to an individual's body weight”

(see "Cell Proliferation, Differentiation, and Apoptosis" by Michael Andreeff "et al." in "Cancer Medicine", 5th Edition)

Biological attributes “hallmarks” shared by most cancers

1. generate own mitogenic signals
2. resist exogenous growth-inhibitory signals
3. evade apoptosis (programmed cell death)
4. proliferate without limits (undergo immortalization)
Biological attributes “hallmarks” shared by most cancers

1. generate own mitogenic signals
2. resist exogenous growth-inhibitory signals
3. evade apoptosis (programmed cell death)
4. proliferate without limits (undergo immortalization)
5. to acquire vasculature (angiogenesis)
Biological attributes “hallmarks” shared by most cancers

1. generate own mitogenic signals
2. resist exogenous growth-inhibitory signals
3. evade apoptosis (programmed cell death)
4. proliferate without limits (undergo immortalization)
5. to acquire vasculature (angiogenesis)
6. to invade and metastasize (in more advanced cancers)

Mortality from Cancer

- Most often from metastases, which may be local, regional, or distant
- By definition then, if one can identify cancers early and remove them, prevent them, or treat them effectively mortality associated with cancer can be reduced
Neufeld lab studies the basic cellular functions of tumor suppressor APC with the intent that these activities can be exploited for colon polyp/cancer prevention, screening, or therapeutic purposes.

Adenomatous Polyposis Coli (APC)

- Name of both a gene and its protein product
- Inherited mutation in APC gene results in 100s-1000s of polyps in colon by age 20-30
- Polyps are benign, but if not removed, each has 5% chance of becoming cancer in 10 yrs→ likely develop colon cancer by age 40 if colon not removed.
- Gene identified/mapped in early 1990s (3 labs: White, Vogelstein, Nakamura) using large families with history of colon cancer
- >80% of all colon cancers (both inherited and sporadic) have mutations in the APC gene.
**APC mutations in colon cancer**

- Tumor suppressor
- Mutated early in 80% of all Colorectal Cancers


**Colon anatomy**

APC is located in both cytoplasm and nucleus of cultured normal epithelial cells

What does nuclear APC do?

- In cytoplasm APC helps to put brakes on a cell that isn’t exposed to a “Wnt” proliferation signal
- Nuclear APC also participates in this process
Generate mouse model to assess roles of nuclear Apc in whole organism

- Proliferation
- Differentiation
- Wnt signaling
- Incidence of intestinal tumors
- Other changes?

Mutate NLS\textsubscript{Apc} in mouse

Mice without nuclear Apc show increased proliferation of intestinal epithelial cells

\begin{itemize}
\item \textbf{Apc\textsuperscript{+/+}}
\item \textbf{Apc\textsuperscript{mNLS/+}}
\item \textbf{Apc\textsuperscript{mNLS/mNLS}}
\end{itemize}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{proliferation.png}
\caption{Proportion of EdU-positive cells in jejenum under different conditions.}
\end{figure}

\textit{p < 0.0001}
Mouse model to assess roles of nuclear Apc in whole organism

- Proliferation
- Differentiation
- Wnt signaling
- Incidence of intestinal tumors
- Other changes?

Mutate NLS\textsubscript{Apc} in mouse

\textbf{Apc\textsuperscript{mNLS/mNLS} mice show decreased differentiation into intestinal goblet cells}

- Secrete mucus
- Mucin produced by Goblet cells stained using Alcian Blue

\textbf{Jejunum, p < 0.05}

![Box plot showing comparison between Apc\textsuperscript{mNLS/mNLS} and Apc\textsuperscript{+/+}](image)
Mouse model to assess roles of nuclear Apc in whole organism

- Proliferation
- Differentiation
- Wnt signaling (abnormal)
- Incidence of intestinal tumors
- Other changes?

A Role for nuclear APC in inhibition of inflammation

- Inflammation is a response of the body to harmful stimuli → remove it and start healing
- Inflammation is a major risk factor for colon cancer
- 20% of IBD patients develop colon cancer (colitis-associated cancer)
- Poor prognosis
- Anti-inflammatory drugs including Aspirin and Celebrex reduce the risk of colon cancer
Some mediators of inflammation are more abundant in mice lacking nuclear APC

Cox-2 inhibits apoptosis, induces angiogenesis, increases proliferation

Chemical induction of colitis induces more colon tumors in mice lacking nuclear APC

* p<0.05

Zeineldin & Neufeld, manuscript in preparation
Mouse model reveals roles for **nuclear** Apc in whole organism

- Loss of nuclear Apc

  - Proliferation
  - Differentiation
  - Wnt signaling
  - Incidence of intestinal tumors
    - Colon tumors (AOM/DSS)
    - Other changes?
      - Inflammation

### Therapeutic potential of increasing cellular APC levels

- KN1 increases the level of APC in cultured cells and mice

- Might this chemical inhibit colon tumor formation in a mouse model of ulcerative colitis?
Conclusions and future directions

- Nuclear APC has role in signaling a cell to stop proliferating
- Nuclear APC might inhibit inflammation
- Drugs that increase APC levels appear to inhibit colon tumor formation in a mouse model of ulcerative colitis
- Mechanism?

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HOW ARE WE DOING?: CANCER SURVIVORS

- More than 10 million survivors living in the US
- Over the past 25 years, the 5-year relative survival rate for all cancers combined improved from 56% to 64% in women
- The 5-year survival rate for breast cancer is approaching 90%
- Between 1975 and 1995, the 5-year survival rate for childhood cancers improved from 56% to 75%
Unique translocation in Chronic Myelogenous Leukemia (CML)

Druker, B. J. Blood 2008;112:4808-4817

Success of Gleevec

<table>
<thead>
<tr>
<th></th>
<th>New Cases</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997</td>
<td>4300</td>
<td>2400</td>
</tr>
<tr>
<td>2008</td>
<td>4830</td>
<td>450</td>
</tr>
</tbody>
</table>

- The annual mortality rate has been reduced from 15-20% to 2%
- Estimated median survival rate is expected to exceed 20 years based on current data
Morbidity and Mortality from Cancer

- Metastases may replace and or destroy vital organs
- Rupture into major vessels, structures
- Starvation (cachexia)
- Infection, particularly with abscess, fistula and immunocompromise
- Compression of vital organs
- Organ failure