Cancer Genes & Personalized Therapy

Hsing-Jien Kung
UC Davis Cancer Center

Human genome and cancer genes

Cancer as a disease of gene mutation

Cancer therapy: conventional and targeted, combination and personalized
23对染色体 = DNA (去氧核酸) = 基因 (Genes)
30,000基因 → 30,000蛋白质

人与人 99.9% 相同
猴 99.0% ”
鼠 90.0% ”
鸡 70.0% ”

结构相似，组成结构石一样，功能不一致
决定体形，结构，疾病倾向，性向．
Cancer Notes

**CANCER** is a disease of uncontrolled growth caused by DNA damages and altered gene expression.

**CANCER** is a genetic disease with heritable traits and mutated genes.

- ~30,000 genes encoded by human genome
- ~15,000 genes expressed in a given cell, cancer or normal
- Cancer and normal cells differ by the expression of >1,000 genes

In a given cancer cell, the significant reprogramming of gene expression is caused by the alteration of a few genes (say 10), which are the programmers or triggers.

They are called **ONCOGENES** and **TUMOR SUPPRESSOR GENES**.

In human genome, there are about 100 each, but individual cancers result from the alterations of different sets of 10 or fewer.
N: normal cells
T: tumor cells
Multi-step oncogenesis

Chromosome: 5q
Alteration: Loss
Gene: APC

DNA hypomethylation

12p
Activation
K-ras

18q
Loss
DCC

17p
Loss
p53

Normal epithelium → Hyperproliferative epithelium → Early adenoma → Intermediate adenoma → Late adenoma → Carcinoma → Metastasis

Other alterations
Oncogenic mutations of tyrosine kinases

## Tyrosine Kinase Inhibitors As Cancer Therapeutics

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>TK</th>
<th>type</th>
<th>Target Cancer</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herceptin</td>
<td>Her2/ErbB2</td>
<td>monoclonal antibody</td>
<td>Breast cancer</td>
<td>approved</td>
</tr>
<tr>
<td>Gleevec</td>
<td>Abl</td>
<td>small molecule</td>
<td>Myeloid leukemia</td>
<td>approved</td>
</tr>
<tr>
<td>IMC-C225</td>
<td>EGFR</td>
<td>monoclonal antibody</td>
<td>Colon Cancer</td>
<td>Phase III trial</td>
</tr>
<tr>
<td>Iressa</td>
<td>EGFR</td>
<td>small molecule</td>
<td>Lung Cancer</td>
<td>Phase III trial</td>
</tr>
<tr>
<td>Tarcerva</td>
<td>EFGR</td>
<td>small molecule</td>
<td>Head and Neck</td>
<td>Phase III trial</td>
</tr>
<tr>
<td>SU5416 semaxanib</td>
<td>VEGFR</td>
<td>small molecule</td>
<td>Colon cancer</td>
<td>Phase III trial</td>
</tr>
<tr>
<td>IMC-1C11</td>
<td>VEGFR</td>
<td>monoclonal antibody</td>
<td>Colon Cancer</td>
<td>Phase I trial</td>
</tr>
</tbody>
</table>

Krause & Van Etten (NEJM, 2005 353:172)

TK as targets for cancer therapy
Gene Expression Profiles

Microarray analysis

Red: high expression
Green: low expression
Conventional Therapy
Genotoxic Stress
(Poison to death)
Etoposide, Doxorubicin, cis-platin, Taxol
Damage DNA

Metabolic Stress
(starve to death)
Arginase, Asparaginase
Remove nutrition

Targeted Therapy
Tyrosine kinase inhibitors
Herceptin, Gleevec, Iressa
Growth inhibition

Combination Therapy

Personalized Therapy

---

Cancer Update from Johns Hopkins 2009

6. Chemotherapy involves poisoning the rapidly-growing cancer cells and also destroys rapidly-growing healthy cells in the bone marrow, gastrointestinal tract etc, and can cause organ damage, like liver, kidneys, heart, lungs etc.

7. Radiation while destroying cancer cells also burns, scars and damages healthy cells, tissues and organs.

8. Initial treatment with chemotherapy and radiation will often reduce tumor size. However prolonged use of chemotherapy and radiation do not result in more tumor destruction.

10. Chemotherapy and radiation can cause cancer cells to mutate and become resistant and difficult to destroy. Surgery can also cause cancer cells to spread to other sites.

11. An effective way to battle cancer is to starve the cancer cells by not feeding it with the foods it needs to multiply..

*CANCER CELLS FEED ON:

a. Sugar is a cancer-feeder. By cutting off sugar it cuts off one important food supply to the cancer cells. Sugar substitutes like NutraSweet, Equal, Spoonful, etc are made with Aspartame and it is harmful. A better natural substitute would be Manuka honey or molasses, but only in very small amounts. Table salt has a chemical added to make it white in color. Better alternative is Bragg's aminos or sea salt.
### Diagnosis

**Skin**

The old-fashioned way is best for detecting melanoma, the most serious skin cancer—by looking for and keeping track of irregular moles.

*62,480 new melanomas cases in the U.S. expected in 2008.*

<table>
<thead>
<tr>
<th>91%</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery can often remove early tumors, but if the melanoma has penetrated more deeply and widely into the body, doctors may choose to take out some lymph nodes and add radiation or chemotherapy. Efforts to create a vaccine to corral cancer cells are under way.</td>
<td></td>
</tr>
</tbody>
</table>

**Prostate**

A blood test for the prostate-specific antigen (PSA) is the most common screening test. A physical exam can also pick up changes in the gland's size or shape.

*184,450 new cases in the U.S. expected in 2008; 27% (if screened) to 95% (if localized) five-year survival rate.*

<table>
<thead>
<tr>
<th>99%</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doctors can cut out contained growths, while radioactive seeds implanted in the tumor can destroy tumors from within. Newer beam devices can focus radiation on the prostate from outside the body. Hormone therapies can also shrink growths and stall the cancer.</td>
<td></td>
</tr>
</tbody>
</table>

**Breast**

There is no screening test for brain cancer, and symptoms such as headache, blurred vision and seizure are often the first signs.

*21,610 new cases in the U.S. expected in 2008; 32% five-year survival rate.*

<table>
<thead>
<tr>
<th>27%</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery, radiation and chemotherapy are the standard anticancer measures. But because growths in the brain are difficult to reach with these methods, researchers are testing a number of potentially more effective ones, including hampering immune cells via immunization, targeting some of the tumors and cutting off the cancer's blood supply using targeted drug therapies.</td>
<td></td>
</tr>
</tbody>
</table>

**Brain**

No screening exists, so only 7% of cases are detected early. The rest are spotted when pain or other symptoms occur.

*37,680 new cases in the U.S. expected in 2008; 5% (if spread) to 20% (if localized) five-year survival rate.*

<table>
<thead>
<tr>
<th>32%</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery and chemotherapy are the standard anticancer measures. But because growths in the brain are difficult to reach with these methods, researchers are testing a number of potentially more effective ones, including hampering immune cells via immunization, targeting some of the tumors and cutting off the cancer's blood supply using targeted drug therapies.</td>
<td></td>
</tr>
</tbody>
</table>

**Pancreatic**

Doctors are investigating whether X-rays or spiral CT scans are better at finding lung cancers early.

*215,020 new cases in the U.S. expected in 2008; 15% (if spread) to 49% (if localized) five-year survival rate.*

<table>
<thead>
<tr>
<th>5%</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routine blood tests may reveal the hallmark of the disease—an abnormal number of white blood cells.</td>
<td></td>
</tr>
</tbody>
</table>

**Lung**

**Leukemia**

Doctors are investigating whether X-rays or spiral CT scans are better at finding lung cancers early.

*215,020 new cases in the U.S. expected in 2008; 15% (if spread) to 49% (if localized) five-year survival rate.*

<table>
<thead>
<tr>
<th>15%</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swollen lymph nodes may be the first sign of this most common variety of lymphoma, which can occur in 30 different forms.</td>
<td></td>
</tr>
</tbody>
</table>

**Lymphoma**

** Hodgkin's**

Chemotherapy is an old reliable, but highly specialized antibiotics that target proteins coating the cancer cell's surface are proving effective killers as well. While leukemias are destroyed from the inside out, lymphomas appear to be vulnerable to the traditional attack on the outer flanks—provided that the antibodies are designed to find the right lymphoma targets.

<table>
<thead>
<tr>
<th>45%</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>The most powerful new anticancer treatment to come along in decades, was introduced. Its first target—chronic myeloid leukemia, a difficult-to-treat blood cancer. By disabling a signaling pathway inside the cancer cell, Gleevec does what chemo and radiation can't: attack the tumor from the inside out. That proved effective for other leukemias as well; some childhood versions now have an 83% five-year survival rate.</td>
<td></td>
</tr>
</tbody>
</table>

**5 yr survival rate**

<table>
<thead>
<tr>
<th>85%</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alternating rounds of radiation and chemotherapy are the most effective treatment option. During the disease's early stages, radiation focused on the affected lymph nodes may prevent the lymphoma from spreading.</td>
<td></td>
</tr>
</tbody>
</table>

**Outlook**

About 80% of melanomas are detected early, before they have spread, and can be cured. Screening programs and self-exams are key.

**Outlook**

It's one of the more curable cancers, as long as it is detected early. Cases still remain high among African-American men.

**Outlook**

No other cancer comes with so many treatment options, which means more women than ever before can—and will continue to—survive.

**Outlook**

New treatment options have only recently started to emerge, but a better understanding of the molecular mechanisms behind it may be one of the toughest cancers to treat today, but that might change as a deeper understanding of what causes pancreatic cancer is

**Outlook**

Survival rates remain stubbornly low, but smarter treatments combined with better screening tests may soon raise those percentages. The next-generation targeted drugs will continue to assault leukemia cells' inner workings, making them more vulnerable to attack.

**Outlook**

New treatments provide hope that non-Hodgkin's cases can be controlled, but the incidence of the disease has climbed since the 1970s for once nearly always fatal, this lymphoma is now predominantly treatable, owing to recent detection and judiciously applied therapies.

---

*TIME Sept 15, 2008*