Six “Hallmarks” of Cancer

Hanahan and Weinberg (2000)
Three key concepts

1) Signal transduction

2a) Oncogenes/proto-oncogenes

2b) Tumor suppressor genes
Signal transduction

1. Signal received by the cell
2. Amplification of signal
3. Transduction of signal throughout the cell
4. Biological output

Gene transcription → Cell growth → Cell division
Examples of a signal transduction pathways:
Alterations in cancer genes drive tumorigenesis

**Oncogenes** are altered versions of normal cellular genes (“proto-oncogenes”) that when mutated or deregulated lead to hallmarks of cancer
  - Increased activity promotes cancer
  - Typically activated by mutation, amplification, or chromosomal translocations

- Promote proliferation
- Activate cell cycling
- Anti-apoptotic
- DNA damage

**Tumor Suppressor Genes**
- Check proliferation
- Block cell cycling
- Pro-apoptotic
- DNA repair

**ACCELERATOR**
**BRAKES**

**Tumor suppressors** maintain cellular homeostasis to counteract cancer development
  - Decreased activity promotes cancer
  - Typically inactivated in cancer by mutation, truncation, deletion, or silencing.
  - Proteins from cancer viruses often disable tumor suppressors.

**MOST CELLULAR PATHWAYS INCLUDE BOTH ONCOGENES AND TUMOR SUPPRESSORS**
## Common oncogenes & tumor suppressors

<table>
<thead>
<tr>
<th>Oncogenes</th>
<th>Tumor Suppressors</th>
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<tbody>
<tr>
<td>Ras (GTPase)</td>
<td>p53 (transcription factor)</td>
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<tr>
<td>Myc (transcription factor)</td>
<td>pRb (cell cycle protein)</td>
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<tr>
<td>Receptor Tyrosine Kinases (RTKs)</td>
<td>PTEN (lipid phosphatase)</td>
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Cancer viruses encode proteins that inactivate tumor suppressors

Human Papilloma Virus
99% of cervical cancers
40% of oral cancers

Destruction of Rb drives cellular growth...
Which should be countered by a p53 dependent checkpoint

GENETIC INSTABILITY & ADDITIONAL MUTATIONS

Nature Reviews of Cancer, 2007
“Research into HPV eventually uncovered how Henrietta’s cancer started: HPV inserted its DNA into the long arm of her eleventh chromosome and essentially turned off her p53 tumor suppressor gene. What scientists still haven’t figured out is why this produced such monstrously virulent cells both in and out of Henrietta’s body, especially since cervical cancer cells are some of the hardest of all cells to culture.”

-Chapter 27, pg. 213
-Disk 7, chapter 27a 2:08-2:43
Hallmark 1: Insensitivity to growth inhibitors
How do these signals block proliferation?

1) Force cells into quiescence ($G_0$)

2) Enter post-mitotic states (terminal differentiation)
The logic of the mammalian cell cycle

A balance of tumor suppressor proteins and proto-oncogenes govern cell cycle transitions.

Loss of cell cycle checkpoints leads to uncontrolled cycling.
Hallmark 2: Self-sufficiency in growth signals
How do cells achieve this?

- Autocrine stimulation
  - Produce their own growth factor ligands
- Stimulate normal surrounding cells which in turn release growth factors
- Upregulation of growth factor receptors
- Ligand-independent receptor signaling
- Activation of downstream signaling cascades
The Hallmarks of Cancer

- Self-sufficiency in growth signals
- Insensitivity to anti-growth signals
- Evading apoptosis
- Sustained angiogenesis
- Tissue invasion & metastasis
- Limitless replicative potential
What determines the size of a tumor cell population?

Population = Rate of Replication – Rate of Death
The beginnings of apoptosis

• John Kerr in the 1960s noticed that cells underwent “shrinkage necrosis”

• In combination with Andrew Wyllie and A.R. Currie they postulated that this is a natural coordinated event

Apoptosis is a natural process that is essential for development
Evading apoptosis promotes cancer formation

- Genes involved in apoptosis started being implicated in cancer in late 80s/early 90s

- High levels of *bcl-2* protect human B and T lymphoblasts under stress

- Hyperproliferation of B cells and increased tumor formation with increased *bcl-2* and *myc* expression
Apoptosis is a response to physiological stresses

- Elevated oncogenic signaling
- DNA damage associated with hyperproliferation
Apoptosis machinery can be divided into two classes

Sensors
- BH3
- Bcl-2
- Bax
- Cryt C
- Apaf-1

Effectors
- Caspase-9
- tBid
- Caspase-8
- Caspases 3, 6, 7

Stress pathway:
- Cytokine deprivation
- Intracellular damage
- Oncogenes

Death receptor pathway:
- FasL, TNFα, TRAIL

Apoptosis
The ‘stress pathway’ ultimately requires the mitochondria.
Multiple cellular pathways regulate apoptosis
p53 regulates apoptosis in response to DNA damage

Gillham et al. World Journal of Surgical Oncology 2007
The Hallmarks of Cancer

- Self-sufficiency in growth signals
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Uncoupling of cell’s growth from its environment is not enough...

• Three big capabilities that lead to cancer:
  1. Growth signal autonomy
  2. Insensitivity to antigrowth signals
  3. Resistance to apoptosis

• Cells contain a cell-autonomous program that limits replicative potential
Hayflick’s Limit (1965)

“unlimited cellular division or escape from senescent like changes can only be achieved by [somatic] cells which have assumed properties of cancer cells.”

Bypassing Hayflick’s limit

Scientists knew from studying HeLa that cancer cells could divide indefinitely, and they’d speculated for years about whether cancer was caused by an error in the mechanism that made cells die when they reached their Hayflick Limit. They also knew that there was a string of DNA at the end of each chromosome called a telomere, which shortened a tiny bit each time a cell divided, like time ticking off a clock. As normal cells go through life, their telomeres shorten with each division until they’re almost gone. Then they stop dividing and begin to die. This process correlates with the age of a person: the older we are, the shorter our telomeres, and the fewer times our cells have left to divide before they die.

Immortal Life of Henrietta Lacks
The end replication problem

- With each replicative generation the telomeres undergo a 50-100 bp loss
- Eventually, end-end fusion events occur, leading to crisis

Telomerase and cancer

By the early nineties, a scientist at Yale had used HeLa to discover that human cancer cells contain an enzyme called telomerase that rebuilds their telomeres. The presence of telomerase meant cells could keep regenerating their telomeres indefinitely. This explained the mechanics of HeLa’s immortality: telomerase constantly rewound the ticking clock at the end of Henrietta’s chromosomes so they never grew old and never died. It was this immortality, and the strength with which Henrietta’s cells grew, that made it possible for HeLa to take over so many other cultures—they simply outlived and outgrew any other cells they encountered.

Immortal Life of Henrietta Lacks
Shortened telomeres causes cells to arrest cell division

• Short telomeres induce a DNA damage response that activates p53 and p16/pRB pathways
• Cancer bypasses these pathways to continue cellular proliferation

Campisi, 2005
Circumventing senescence pathways leads to crisis and karotypic dissarray

- Crisis results in massive cell death

- Early/late passaged cells supplemented with telomerase do not show crisis

- $P16^{\text{INK4A}}$ mutant mice that lack telomerase have reduced tumor incidence
Cells become senescent to avoid tumor formation

Cancer cells avoid senescence!

HALLMARK OF CANCER:
ANGIOGENESIS
The human body requires:

1. **NUTRIENTS**  
   (food and water)

2. Oxygen
Blood vessels provide tissues and organs with vital nutrients and oxygen.
When do new blood vessels form?

- Embryonic development
- To help in wound repair
- To repair tissue damage (muscles after exercise)
- To bypass blocked vessels.
VEGF signals blood vessel formation

Bates and Pritchard Jones, 2003
Signaling Pathways Activated by VEGF

- VEGF binds to VEGF-R2
- SHP-1, SHP-2, Shc, Grb2, Sos
- PLC-γ, PI_3K
- PIP_2, IP_3, DAG, Ca^2+
- PKC
- NO, NOS
- Angiogenesis
- Cell Proliferation
- Vasopermeability
- Cell Survival
- Gene Expression
- Cell Proliferation

Endothelial Cell
VEGF signaling during sprouting

Initiation of vessel formation

Activation  Selection  Sprouting  Elongation

Key:
- Tip cell
- Stalk cell
- Activated cell
- VEGF
- VEGFR2
- Soluble VEGFR1
- notch receptor
- DLL4 ligand
- jagged1 ligand
Tumors also require nutrient and oxygen supplies as they grow larger

- Tumors can grow up to 1-2 mm without a blood supply
- To grow larger, they require nutrients and oxygen

http://bio-alive.com/categories/angiogenesis/angiogenesis2.htm
Tumor angiogenesis:
Tumors trick the body into building new blood vessels

Small localized tumor

Tumor that can grow and spread

Angiogenesis

Blood vessel

Signaling molecule
ANGIOGENESIS is essential for tumor growth AND metastasis.
What is metastasis?

- Spread of disease from one organ to another
- Cancer begins to grow in one area of the body and moves to another area
- Often associated with advanced cancers
- Metastatic cancers are often termed “aggressive”
Some Terminology

• Benign = not metastatic
• Malignant = invasive, possibly metastatic

• Adenoma, melanoma, lipoma = benign tumor
• Carcinoma, sarcoma = malignant tumor
Invasion and Metastasis

cells grow as a benign tumor in epithelium
break through basal lamina
invasive capillary
connective tissue
capillary
travel through bloodstream
(less than 1 in 1000 cells will survive to form metastases)
adhere to blood vessel wall in liver
escape from blood vessel (extravasation)
proliferate to form metastasis in liver
Epithelial-Mesenchymal Transition: EMT
EMT Signaling

Occurs normally during development
Common Sites of Metastasis

- Depends on type of cancer
- Depends on what circulatory system the tumor invades
Why is metastatic cancer considered “aggressive?”

- No longer confined = harder to treat
- More potential for fatal tumor growth
Why does cancer kill you?

Tumors take up space
- Brain tumors create pressure within the skull
- Tumors in internal organs can put pressure on neighboring organs
- GI tumors cause blockage
Why does cancer kill you?

Tumor cells take nutrients away from normal cells

- Normal Cell Energy Production
- Cancer Cell Energy Production
Why does cancer kill you?

• Large tumors can impair essential organ function
  – Oxygen absorption in lungs
  – Nutrient absorption in digestive tract
  – Chemical balance in liver
  – Red vs. white cell count in blood