The Hallmarks of Cancer

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What Is Cancer?

- What is cancer?
- What causes cancer?
- What is the link between genes and cancer?
- How is cancer diagnosed?
- Can cancer be prevented?
Cancer surgery, circa 1689
Established 1937
1971.: Nixon declares “War on Cancer”

2001: Andrew von Eschenbach “eliminate suffering and death” by 2015

2004.: “Why We're Losing The War On Cancer”
Fortune Magazine ..

Age-adjusted Death rates
Cancer is the Result of a Multistep Process
What are the underlying events of carcinogenesis and how do they come about?

Question:
The Hallmarks of Cancer

Douglas Hanahan* and Robert A. Weinberg †

Cell, Vol. 100, 57–70, January 7, 2000
Hallmarks of Cancer: The Next Generation

Douglas Hanahan* and Robert A. Weinberg

In Vitro Studies
cell monolayer

Petri dish

infect with RSV particle

transformation of a cell

focus
• **Oncogenes** – mutated forms of normal cellular genes generally involved in promoting cell proliferation. These mutations result in dominant gain of function.

• **Tumor Suppressor genes** – genes whose normal function in regulating proliferation is to stop it. Mutation results in recessive loss of function.
The diagram illustrates the concept of monoclonal and polyclonal tumors.

Monoclonal tumors:
- Start with normal tissue.
- Undergo normal behavior.
- Undergo transformation, resulting in cancerous behavior.
- Lead to tumors.

Polyclonal tumors:
- Start with normal tissue.
- Undergo transformation, resulting in multiple cell lineages with different behaviors.
- Lead to a mixture of normal and cancerous tissue.

The transformation process is highlighted in red, emphasizing the transition from normal tissue to cancerous behavior.
Carcinogenesis is the accumulation of multiple genetic alterations that drive a normal cell to malignancy.

Hypothesis: Mutation in one gene associated with each step in progression.
Reductionist View of a Tumor
Realistic View of a Tumor
Normal Mitogenic Growth Stimulation

Transmembrane Receptor

Signal Transduction Proteins

Growth Factor

Cytoplasm

Nucleus
Strategies of Tumor Cell Self-Sufficiency

Loss of Normal Growth Control

Normal cell division

Normal cell division

Cell damage — no repair

Cell Suicide or Apoptosis

Cancer cell division

First mutation  Second mutation  Third mutation  Fourth or later mutation

Uncontrolled growth
Insensitivity to Anti-Growth Signals

Anti-Growth Signal such as TGFβ

TGFβR

Smads

pRB

Cell Proliferation

Mad Max

Myc Max
Regulation of Apoptosis

Sensor Molecules

- Fas ligand

Antiapoptosis signal

- p53

Proapoptosis signal

- Bcl2
- Bax
- Fas

Effector Molecules

- ?

Mitochondrion

Cell Death
Telomeres
Your Biological Clock is Ticking

(TTAGG)nTTAGGTTAGGTTAGGTTAGGTTAGG
(TTAGG)nTTAGGTTAGGTTAGGTTAGGTTAGG
(TTAGG)nTTAGGTTAGGTTAGGTTAGGTTAGG
(TTAGG)nTTAGGTTAGGTTAGGTTAGG
(TTAGG)nTTAGGTTAGGTTAGG
Angiogenesis

Region of insufficient blood supply

Angiogenic Factors

Antiangiogenic Factors

Region of insufficient blood supply
Immune Evasion

Some data supports:

Selective killing of highly immunogenic tumors, leaving weakly immunogenic ones

Tumors disable parts of the immune system by secreting or recruiting cells that secrete immunosuppressive factors (ex. TGF $B$)

Tumor cells down-regulate expression of MHC genes
Tumor-Promoting Inflammation

Tumor- infiltrating immune cells provide factors which:

- Stimulate growth
- Inhibit cell death
- Promote angiogenesis
- Degrade extracellular matrices
- Induce epithelial-mesenchymal transition
- Damage DNA (reactive oxygen species)
Deregulating Cellular Energetics

Figure 2.22 The Biology of Cancer (© Garland Science 2014)
PET SCAN
Cancer - evolution at a vastly accelerated rate favoring the growing tumor mass over the organism.

Genomic Instability introduces genomic alterations and Natural Selection chooses “the fittest” tumor to survive.
Genomic Instability: Cause or consequence

Normal cell

Cancer Cell