Recurring themes in this course:

Multi-step progression

Genomic Instability

Selective Advantage

Regulatory circuits, pathways and ‘nodes’

Throughout this course, ask yourself …
… How does a ‘new concept fit into these categories?

Cell, Vol. 100, 57–70, January 7, 2000, Copyright ©2000 by Cell Press

The Hallmarks of Cancer

Douglas Hanahan* **and Robert A. Weinberg†**
*Department of Biochemistry and Biophysics and
Hormone Research Institute
University of California at San Francisco
San Francisco, California 94143
†Whitehead Institute for Biomedical Research and
Department of Biology
Massachusetts Institute of Technology
Cambridge, Massachusetts 02142

Today's objective is to outline the …

'Rules that govern the transformation of normal cells into malignant cancer….'

'Concept based on the discovery of a small number of molecular, biochemical, and cellular traits - acquired capabilities - shared by most and perhaps all types of human cancer.'

'Tumorigenesis in humans is a multistep process and that these steps reflect genetic alterations that drive the progressive transformation of normal human cells into highly malignant derivatives.'

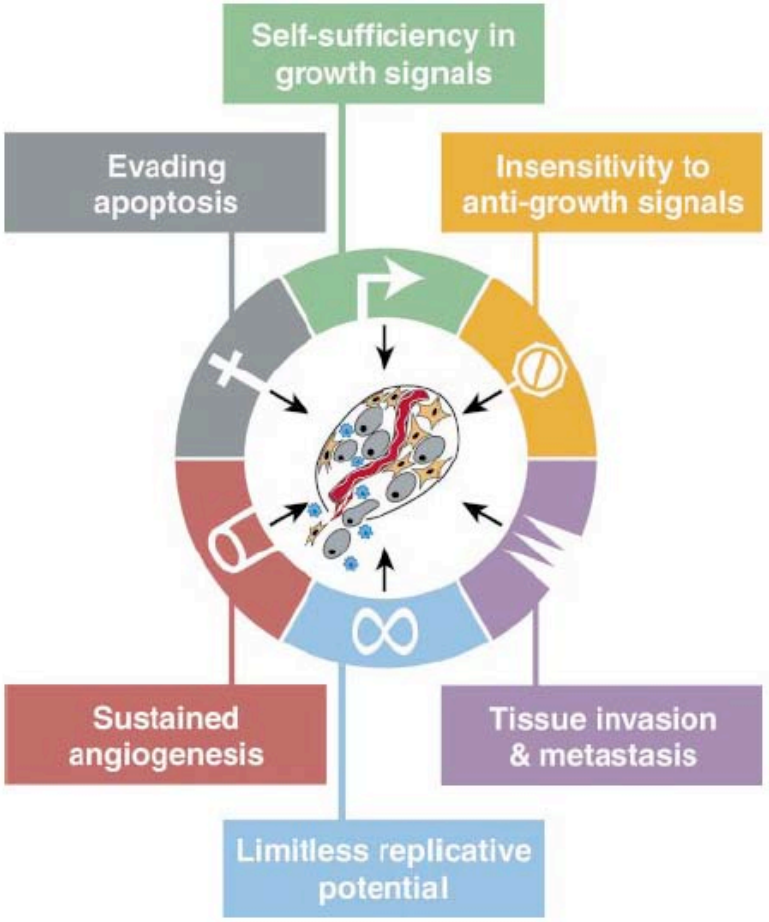


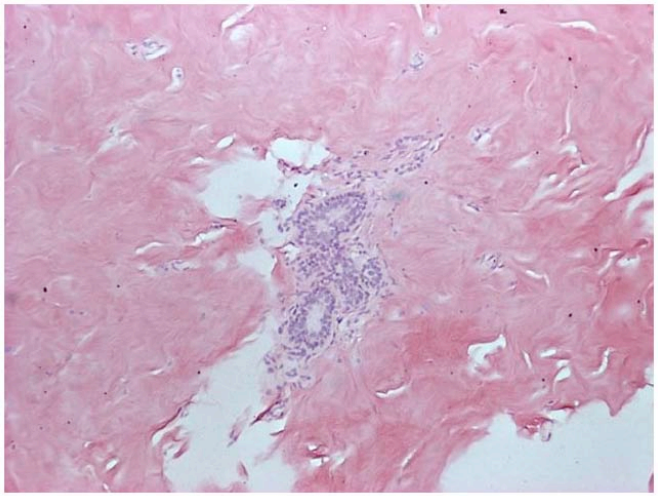
Figure 1. Acquired Capabilities of Cancer

We suggest that most if not all cancers have acquired the same set of functional capabilities during their development, albeit through various mechanistic strategies.

Six essential alterations that dictate malignant growth:

1. Self sufficiency in growth signals
2. Insensitivity to ‘anti-growth’ signals
3. Evasion of apoptosis
4. Limitless replicative potential
5. Sustained angiogenesis
6. Tissue invasion and metastasis

1. Self sufficiency in growth signals



Cells require positive growth signals to progress from a quiescent to active state …

- diffusible growth factors
- extracellular matrix
- cell adhesion molecules

Many 'oncogenes' mimic these natural signaling pathways …

- cancer cells don't need to rely on these signals from the host tissue environment.

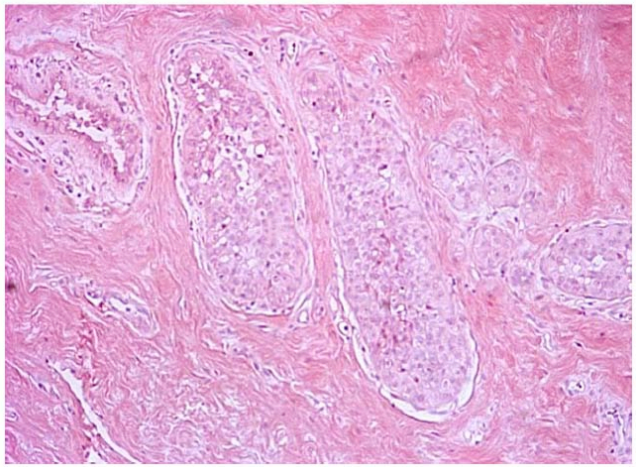
3 strategies for acquired growth signal autonomy:

- alteration of extracellular growth signals
- alteration of transducers of these signals
- alteration of intracellular circuits to translate these signals into action

- Cancer cells manufacture their own growth factors (PDGF, TGFa)
- Overexpression of cell surface receptors (EGF-R or HER2/neu)
- Truncated versions of receptors
- Switches in extracellular matrix receptors (to pro-growth types; integrins)

- Changes in circuitry (the Ras-Raf-Map kinase pathways; 25% of cancers: ras 'alterations'))
  - crosstalk roles within other pathways

1. Becoming insensitive to antigrowth signals



Normally, negative growth signals exist that can drive cell from an active to quiescent state

Cells may reemerge from this quiescent G_o state at some future time when the appropriate positive signals are present.

Also, cells may be induced to be permanently relinquish their proliferative potential …differentiation….

Focus on cell cycle: monitor environment and decide to proceed through G1 phase.

Rb / E2F pathway is critical in regulating initiation of DNA replication

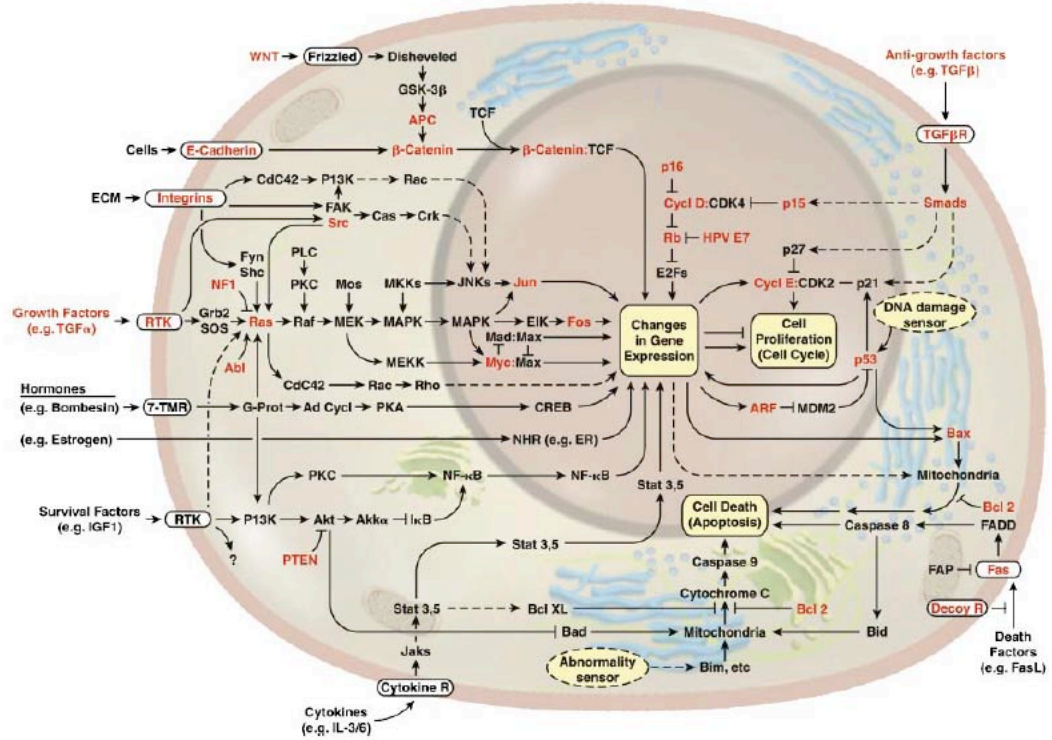
Retinoblastoma (Rb) protein family (pRb and p107, p130)

- E2F transcription factors regulates genes involved in G_1 to S progression

- Unphosphorylated-Rb blocks proliferation (sequesters E2Fs)

- Disruption of pRb pathway liberates E2Fs and allows cell proliferation

The pathway is disrupted in virtually all cancers.



The Integrated Circuit of the Cell

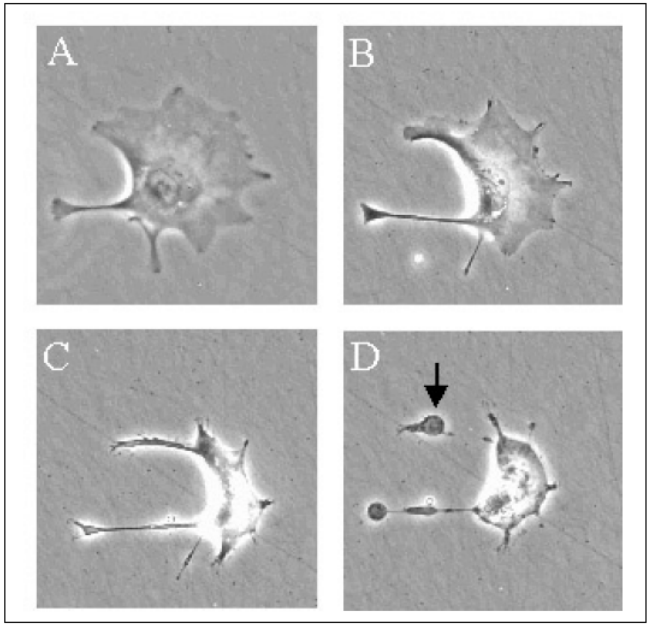
- Growth signaling circuit centered around Ras and coupled to a spectrum of extracellular cues

- Component circuits transmit antigrowth and differentiation signals or mediate commands to live or die by apoptosis.

- Genetic reprogramming of this integrated circuit in cancer cells;
(some of the genes known to be functionally altered are highlighted in red)

- Critical proteins in this process act as ‘control nodes’.

1. Evading Apoptosis: programmed cell death



30-120 minute process

- Membranes disrupted
- Cytoplasmic and Nuclear - matrices broken down
- Cytosol extruded
- Chromosomes degraded
- Nucleus fragmented

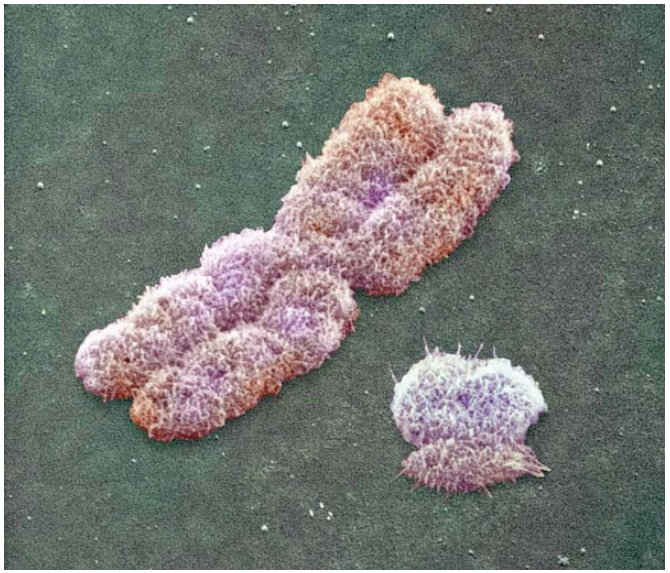
The ability of tumours to expand is determined by:
….the rate of proliferation and …. the rate of attrition

Resistance to apoptosis is a frequent if not universal characteristic of all cancers.

1. Apoptosis triggered by internal signals: (intrinsic pathway)
2. Apoptosis triggered by external signals: (extrinsic pathway)
3. Apoptosis triggered by reactive oxygen species.

Sensors - internal / cell surface; activate death pathway in response to damage
Effectors - caspase family members; involve mitochondria
p53 is a key component in apoptosis

1. Limitless Replicative Potential (cancer cell can divide indefinitely)



- Most cancer cells have kept the ability to synthesize high levels of telomerase throughout the cell cycle: (prevent further shortening of their telomeres).

Apparent intrinsic program exists in cells that limits their potential to replicate.

Finite replicative potential: 60-70 doublings
- senescent phenotype (no longer able to divide but metabolically active
- disabled p53 and Rb: cells continue to divide

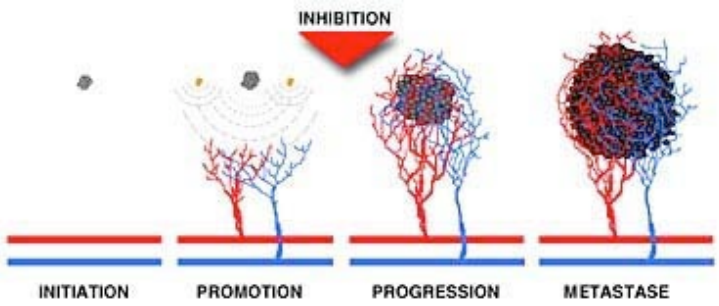
Telomeres: cell's counting device

- the physical ends of eukaryotic chromosomes.
- protection, replication, and stabilization of the chromosome ends.
- kb long stretches of tandemly repeated DNA sequences: (TTAGGG)n.

Unprotected c'some ends:

- end to end chromosome fusions, karyotype disarray, genomic instability
- Telomerase protein: necessary for telomere maintenance:
- Normal somatic cells: low telomerase levels.
- Most cancer cells: High levels of telomerase expression / short telomeres
- New Cancer therapies: Telomerase inhibitors; Anti-telomerase immunotherapy

5. Sustained Angiogenesis: Vasculature is essential for cell function and survival



Angiogenesis performs a critical role in cancer development.

- Normally, angiogenesis is a fine balance between factors that induce (and inhibit) the formation of blood vessel.

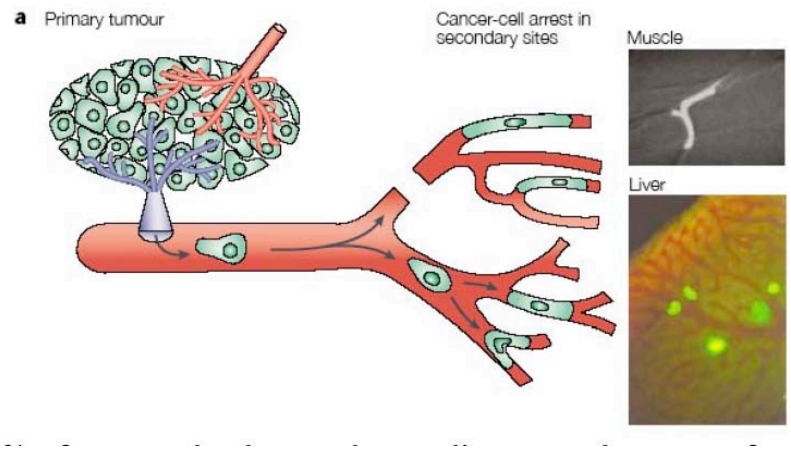
- When this balance is destroyed, it results in pathological angiogenesis that causes increased blood-vessel formation (as in cancer).

- 20+ endogenous positive regulators of angiogenesis are upregulated in cancer.
(growth factors:VEGF, TGF-b, FGF, EGF; matrix metalloproteinases, cytokines, integrins).

- Endogenous negative regulators are downregulated in cancer:
(thrombospondin-1, b-interferon)

- Angiogenesis offers a powerful target for new targeted Cancer therapies.

6. Tissue Invasion and Metastasis



90% of cancer deaths are due to distant settlements of tumour cells (metastases)

- growth at 1° site
- vascularization of 1° tumour
- invasion of surrounding tissue
- entry into circulation
- aggregation and arrest in capillary bed at 2° site
- invasion into 2° site tissue
- growth at 2° site

Each of these stages: a hurdle for the metastasizing cell.

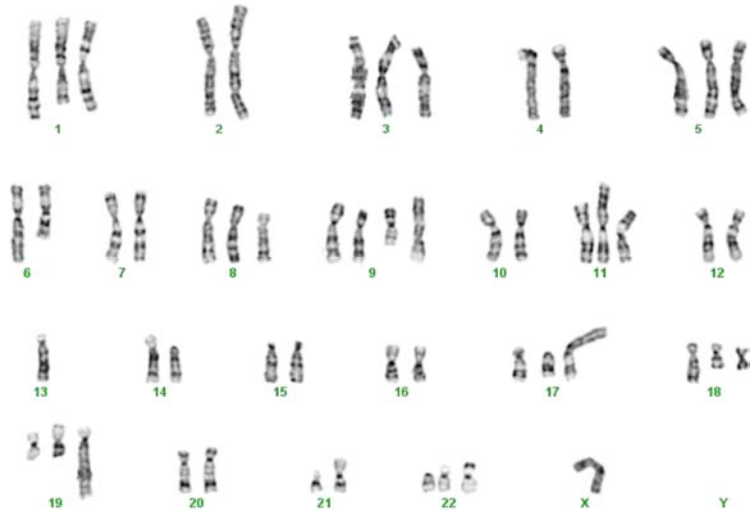
Targeted genes: encode cell adhesion molecules

Extracellular Proteases: upregulated / Protease inhibitors: downregulated

These changes facilitate invasion of 1° cancer cells into 2° sites.

A complex process: genes may be expressed by cells at the 2° site but not by the original tumour cells.

Tumourigenesis is enabled by … Genomic Instability



J. Xu et al. / Cancer Genetics and Cytogenetics 181 (2008) 1e7

These 6 capabilities are acquired through genomic changes in cells.

Genomic integrity maintained by:

- Checkpoints: karyotype monitoring
- DNA Repair defenses
- Ensure that mutations are rare events

How does increased mutability occur?

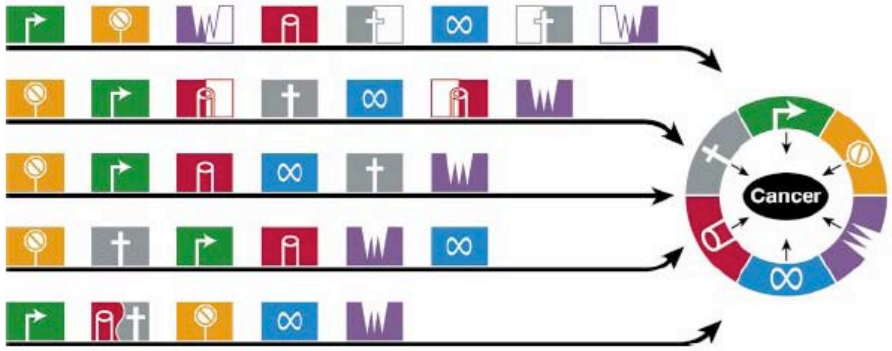
- Malfunction of critical caretakers; p53
- Loss of cell cycle arrest to allow DNA repair to occur
- Loss of apoptosis in the event of excessive damage
- Loss of specific components of these systems ('tumour suppressor function')

Loss of function allows genome instability … mutant cells acquire a selective advantage

A

Component	Acquired Capability	Example of Mechanism
	Self-sufficiency in growth signals	Activate H-Ras oncogene
	Insensitivity to anti-growth signals	Lose retinoblastoma suppressor
	Evading apoptosis	Produce IGF survival factors
	Limitless replicative potential	Turn on telomerase
	Sustained angiogenesis	Produce VEGF inducer
	Tissue invasion & metastasis	Inactivate E-cadherin

B



- parallel pathways of tumourigenesis …..
- order of acquisition varies dependent on cancer type