I. Understanding Cancer From Its Beginnings

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Cancer is a huge health challenge

• Over 6 million deaths per year *worldwide*

*In the USA alone:*
• 1 person dies from cancer each minute
• Over 3,800 people are diagnosed with cancer each day
• More than 20 million new cancer diagnoses since 1990
• 1/2 of all men and 1/3 of all women will get cancer
Some cancers can be prevented

- Smoking accounts for at least 30% of all cancer deaths and 87% of all lung cancer deaths

- Excessive sun exposure, including use of tanning booths, can cause melanoma

- A new vaccine against HPV promises to reduce cervical cancer
Early detection of cancer is key

- Screening is available for
  - Breast
  - Colorectal
  - Prostate
  - Cervical
  - Melanoma/skin cancer
How does cancer develop?
The human body is comprised of functional units called cells
Healthy tissue:
- Cells are well-organized;
- Cell growth is controlled
Normal tissue architecture is deranged in cancer
Cancer develops when cell number is not controlled
Hallmarks of cancer cells

- Self-sufficiency in growth signals
- Evading apoptosis
- In sensitivity to anti-growth signals
- Sustained angiogenesis
- Tissue invasion & metastasis
- Limitless replicative potential

Cell 100:57-70 (2000)
Our chromosomes encode a molecular blueprint for cell behavior.

Each human cell has a single nucleus with 23 pairs of chromosomes.
Chromosomes contain our genetic material (DNA) organized into units called genes.

Humans have about 30,000 genes.
The human genome project determined the locations and sequences of human genes
Alterations in genes are the early changes that lead to cancer.

**Gene (DNA)**
- Normal
- ★ Inherited damage (mutation)
- ★ Acquired damage

**Cell Growth**
- Normal
- Abnormal--Cancer
Genetic studies have identified many human cancer-causing genes

Colon Cancer: APC
Breast Cancer: BRCA1/2
Melanoma: p16
How genetic understanding helps patients: Colon Cancer

Normal Colon

"Gatekeeper" Mutations (e.g. APC)

"Initiated"

PROMOTION, PROGRESSION

Adenoma

• Screening

• Early Intervention

• Tailored Therapy

• Prevention

PROMOTION, PROGRESSION

Carcinoma

Additional Mutations

Metastasis

D. Jones
Molecular analysis of the activities of all 30,000 human genes in different cancers

- Different genes are turned on in different cancers.
- Variability occurs between tumors of the same type.
The changing view of disease and patient populations

We’re all the same.
Tumors are all the same

Genetic Understanding

Many differences
Genetic understanding leads to new strategies for cancer care

FROM: Seek and Destroy
TO: Target and Control

Predictive  Personalized  Preventive
Cellular circuits mutated in cancer

How do cancer cells acquire self-sufficiency with respect to growth signals?

1. Produce growth factors:
   - PDGF in glioblastomas
   - TGF-alpha in sarcomas
How do cancer cells acquire self-sufficiency with respect to growth signals?

2. Alter Growth Factor Receptor profile or activity:

- EGF-R/erbB upregulation in stomach and brain cancers
- HER2/neu overexpression in mammary carcinoma
How do cancer cells acquire self-sufficiency with respect to growth signals?

3. Alter downstream elements in the growth signaling pathway:

- Activation of Ras in bladder carcinoma
4. Influence cofactors:
   • Expression of integrins that favor cell proliferation
Integrins

- Receptors for extracellular matrix
- Identified by an antibody inhibition screen
- Genetic analysis in vertebrates and invertebrates
- Transmembrane signaling

(© Garland Science 1995)
Integrins are concentrated at specialized cell-substratum adhesion sites called Focal Adhesions.
Integrins:
A link between the extracellular matrix and the actin cytoskeleton
Proteins that are co-localized with Integrins facilitate adhesion and signaling.
Integrin-dependent adhesion is required for normal growth factor response

From: Renshaw, Ren and Schwartz, 1997
Integrins link to growth factor signaling pathways at multiple points:

1. Direct link to GF-Receptor
2. Regulation of Ras-GAP
3. Activation of Raf
4. Activation of MEK
5. Regulation of Erk nuclear localization
Anti-integrin antibody inhibits proliferation of ovarian tumor cells

Open Bar: Control Antibody
Filled Bar: Anti-Integrin Antibody

Integrin signaling affects diverse cell pathways and behaviors

Integrin inhibitors are in clinical trials for numerous cancer applications
Cancer is a genetic disease
  • Many genes can be mutated to give rise to cancer
  • Cell growth and death are influenced by many pathways, including those involved in cell adhesion
  • Understanding of cellular mechanisms leads to new therapies