OBJECTIVES

1. List the major hallmarks of cancer

2. Relate specific genes/proteins to individual hallmarks

3. Explain how hallmarks of cancer lead to cancer development
Case Study

• 60 year old female

• Previously treated for breast cancer (5 years prior); no recurrence

• Presents with persistent cough, shortness of breath, fatigue

• X-ray reveals small mass in left lung

• A biopsy is performed

Source: www.123rf.com
A physician meets with this patient. What is the first question she asks about the patient’s lifestyle?
Estimated Attributable Portion of Lung Cancer Cases by Cause

- Active Smoking: 90%
- Radon: 9-15%
- Occupational Carcinogen Exposure: 10%
- Outdoor Air Pollution: 1-2%
Estimated Cancer Deaths by Site, 2015

- Prostate
- Breast
- Colorectal
- Other Cancers
- Lung Cancer

www.lung.org
A pathologist analyzes the biopsy sample. What does she look for?, *i.e.* What information is gained from the analysis of the biopsy?
TYPES OF LUNG CANCER

Two Main Types of Lung Cancer

- Small Cell
  - Small Cell Carcinoma (Oat Cell Cancer)
  - Combined Small Cell Carcinoma or Mixed Small Cell Non-Small Cell Carcinoma
- Non-Small Cell
  - Adenocarcinoma
  - Squamous Cell Carcinoma
  - Large Cell Carcinoma
Biopsy results indicate that patient has a metastatic tumor of breast cancer origin in lung. Tumor is a carcinoma.
QUESTION – What changes occurred to a breast epithelial cell that led to the formation of a metastatic tumor in the lung?

Biopsy results indicate that patient has a metastatic tumor of breast cancer origin in lung. Tumor is a carcinoma.
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

After a quarter century of rapid advances, cancer research has generated a rich and complex body of knowledge, revealing cancer to be a disease involving dynamic changes in the genome. The foundation has been set in the discovery of mutations that produce onco-genes with dominant gain of function and tumor suppressor genes with recessive loss of function; both classes of cancer genes have been identified through their alteration in human and animal cancer cells and by their elicitation of cancer phenotypes in experimental models (Bishop and Weinberg, 1996).

Some would argue that the search for the origin and treatment of this disease will continue over the next quarter century in much the same manner as it has in the recent past, by adding further layers of complexity to a scientific literature that is already complex almost beyond measure. But we anticipate otherwise; those researching the cancer problem will be practicing a dramatically different type of science than we have experienced over the past 25 years. Surely much of this change will be apparent at the technical level. But ultimately, the more fundamental change will be conceptual.

We foresee cancer research developing into a logical science, where the complexities of the disease, described in the laboratory and clinic, will become understandable in terms of a small number of underlying principles. Some of these principles are even now in the midst of being codified. We discuss one set of them in the present essay: rules that govern the transformation evolve progressively from normalcy via a series of premalignant states into invasive cancers (Foulds, 1954). These observations have been rendered more concrete by a large body of work indicating that the genomes of tumor cells are invariably altered at multiple sites, having suffered disruption through lesions as subtle as point mutations and as obvious as changes in chromosome complement (e.g., Kindei and Vogelstein, 1996). Transformation of cultured cells is itself a multistep process: rodent cells require at least two introduced genetic changes before they acquire tumorigenic competence, while their human counterparts are more difficult to transform (Hahn et al., 1999). Transgenic models of tumorigenesis have repeatedly supported the conclusion that tumorigenesis in mice involves multiple rate-limiting steps (Bergers et al., 1998; see Oncogene, 1999, R. DePinho and T. E. Jacks, volume 18[35], pp. 5248–5362). Taken together, observations of human cancers and animal models argue that tumor development proceeds via a process formally analogous to Darwinian evolution, in which a succession of genetic changes, each conferring one or another type of growth advantage, leads to the progressive conversion of normal human cells into cancer cells (Foulds, 1954; Nowell, 1976).

An Enumeration of the Traits
The barriers to development of cancer are embodied in a teleology; cancer cells have defects in regulatory circuits that govern normal cell proliferation and homeostasis. There are more than 100 distinct types of cancer, and subtypes of tumors can be found within specific organs. This complexity provokes a number of questions. How many distinct regulatory circuits within each type of target cell must be disrupted in order for such a cell to become cancerous? Does the same set of cellular regulatory circuits suffer disruption in the cells of the disparate neoplasms arising in the human body? Which of these circuits operate on a cell-autonomous basis, and which are coupled to the signals that cells...
GROWTH FACTOR (GF) -> RECEPTOR -> INTRACELLULAR SIGNALING PATHWAY -> CELL DIVISION
GROWTH FACTOR (GF) → RECEPTOR → Ras → INTRACELLULAR SIGNALING PATHWAY → CELL DIVISION

Self-sufficiency in growth signals
Hyperactive Mutant Ras in Cancers

Cell Division

Self-sufficiency in growth signals
Amplified EGF Receptors in Cancer

GROWTH FACTOR (GF)

INTRACELLULAR SIGNALING PATHWAY

CELL DIVISION

Self-sufficiency in growth signals
CLASSES OF LUNG ADENOCARCINOMA

TARCEVA – A DRUG WHICH TARGETS EGF RECEPTOR IN LUNG CANCER

Biomarker Testing

Biopsy tissue → Biomarker/Mutation Testing → Test Results → Targeted Therapy

www.lifewithlungcancer.org

EGFR signal
EGFR signals tell cancer cells to grow and multiply out of control.
Tarceva can slow or block these signals. This may cause cancer cells to die. It also affects healthy cells.

www.tarceva.com
EUKARYOTIC CELL CYCLE
Insensitivity to anti-growth signals

RECEPTOR

INTRACELLULAR SIGNALING PATHWAY

Rb

G₀
GROWTH FACTOR (GF)

RECEPTOR

INTRACELLULAR SIGNALING PATHWAY

Modified and Inactive Rb

Rb-P

CELL DIVISION

Insensitivity to anti-growth signals
Inactivation of Rb in mutants leads to insensitivity to anti-growth signals, which in turn affects cell division.
p53’s NORMAL ROLE IS TO INHIBIT CELL DIVISION IN RESPONSE TO CELLULAR STRESSES LIKE DNA DAMAGE
TUMOR CELLS LACKING p53 DO NOT ARREST CELL CYCLE

Source: Molecular Biology of the Cell, Alberts et al.
Hanahan and Weinberg (2000) 
*Cell*, 100: 57 – 70.
APOPTOSIS – PROGRAMMED CELL DEATH

Source: Molecular Biology of the Cell, Alberts et al.
INSULIN-LIKE GROWTH FACTOR (IGF-1)

- IGF-1R

  In Intracellular Signaling Pathway

  - Ras

  - Cell Survival
  - Cell Division

Evading apoptosis
INSULIN-LIKE GROWTH FACTOR (IGF-1)

IGF-1R

Ras

INTRACELLULAR SIGNALING PATHWAY

CELL SURVIVAL

CELL DIVISION

SOME CANCER CELLS UPREGULATE CELL SURVIVAL PATHWAYS TO EVADE APOPTOSIS

Evading apoptosis
Hanahan and Weinberg (2000)
*Cell*, **100**: 57 – 70.
TELOMERES ARE CHROMOSOME ENDS

TELOMERES ARE MADE BY TELOMERASE EARLY IN DEVELOPMENT; THEN TELOMERASE ACTIVITY IS NORMALLY TURNED OFF

TELOMERES SHORTEN WITH EACH CELL DIVISION, ULTIMATELY LEADING TO SENESCENCE
CANCER CELLS \textit{REACTIVATE} TELOMERASE

\begin{figure}
\centering
\includegraphics[width=\textwidth]{image}
\caption{Regulation of telomere length in normal and cancer cells by telomerase.}
\end{figure}

\textit{Limitless replicative potential}
Biopsy results indicate that patient has a metastatic tumor of breast cancer origin in lung. Tumor is a carcinoma.
Hanahan and Weinberg (2000)
*Cell*, **100**: 57 – 70.
The formation of new blood vessels from pre-existing blood vessels.

Sustained angiogenesis
VEGF = Vascular Endothelial Growth Factor
Targeted Therapies

Targets the VEGF and inhibits angiogenesis in NSCLC and colorectal cancer.

Sustained angiogenesis
Biopsy results indicate that patient has a metastatic tumor of breast cancer origin in lung. Tumor is a carcinoma.
Hanahan and Weinberg (2000)

*Cell*, **100**: 57 – 70.
PRIMARY BREAST CARCINOMA

Tissue invasion & metastasis

METASTATIC TUMOR IN LUNG
CELLS OF PRIMARY TUMOR REDUCE EXPRESSION OF INTERCELLULAR CONNECTIONS (E-CADHERINS) AND CONNECTIONS TO THE EXTRACELLULAR MATRIX (INTEGRINS) TO ALLOW METASTASIS.
CANCER DEVELOPMENT IS A MULTI-STEP PROCESS. INDIVIDUAL STEPS CAN OCCUR IN DIFFERENT ORDER.

### A

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

### B

![Diagram showing the steps of cancer development](image-url)
THE HALLMARKS OF CANCER

- Self-sufficiency in growth signals: Ras, EGF Receptor
- Insensitivity to anti-growth signals: Rb, p53
- Evading apoptosis: IGF
- Limitless replicative potential: Telomerase
- Sustained angiogenesis: VEGF
- Tissue invasion & metastasis: E-cadherin
You should be able to . . .

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2. Relate specific genes/proteins to individual hallmarks

3. Explain how hallmarks of cancer lead to cancer development