TUMOR CELL HETEROGENEITY AND EVOLUTION
Tumor cell heterogeneity and evolution

Tumor cell heterogeneity: cellular differences within a single neoplasm

Tumor heterogeneity: Causes and consequences

- Monoclonality of tumors
- Heterogeneity of tumors
- Experimental and theoretical evidence for clonal diversity in tumor progression
- Chromosome instability and cancer cell aneuploidy
Knowing the nature of cancer from our 200 years battle with cancer

- **En bloc resection** (19th and early 20th centuries): a minority of patients could be cured by surgical removal of their tumors alone. too much for small tumors and too little for large tumors that had already metastasized.

- **Radiation therapy** (began in 1950): Only about a third of all cancers could be cured by the use of surgery and radiation, alone or together.

- Proof of cure by **chemotherapy** on childhood leukemia and advanced Hodgkin’s disease in adults (mid-1960). By 1991, the rate of death from breast cancer began to fall, a trend that has continued from availability of multiple effective chemotherapeutic agents and hormone treatments, improved diagnostic tools for early diagnosis, and intelligently designed clinical trials.


- **Immunotherapy**: therapeutic antibody to inhibit growth factor receptors on the surface of cancer cells, rituximab for the treatment of B-cell lymphomas in 1997, bevacizumab for blocking blood vessel supplies of cancer growth. **Immunomodulatory agents** (Interleukin-2) caused regression of invasive metastatic disease (1985)

Monoclonality of tumors

- Starch gel electrophoresis assay on G6PD showed that all of the cancer cells in a tumor arising in a G6PD heterozygous patient express either one or the other form of this enzyme (Fialkow, *N. Engl. J. Med.* 291:26–35, 1974.)

- Analysis of immunoglobulin showed replacement of heterogeneous immunoglobulin populations by a single antibody species (termed an M-spike) in multiple myeloma, indicating arising from a single clonal population of antibody-secreting tumor cells. (“The Biology of Cancer”, Robert Weinberg)
Heterogeneity of tumors

- Intra-tumor phenotypic heterogeneity (Cellular morphology, gene expression (including the expression of cell surface markers and growth factor and hormonal receptors), cellular metabolism, motility, and angiogenic, proliferative, immunogenic, and metastatic potential)

- Genetic heterogeneity (the number of genes and chromosomes and the structure and epigenetic (methylation)

Non-heritable sources of diversity in tumor cell populations

- **Cancer stem cells**
  These cells are able to self-renew and to give rise to phenotypically diverse nontumorigenic daughter cells with limited division properties that can differentiate and that compose the bulk of the tumor.

References:


Non-heritable sources of diversity in tumor cell populations

- Phenotypic plasticity

**Epithelial-mesenchymal transition (EMT)**

References:


**Endothelial transdifferentiation**

References:


Heritable heterogeneity

- Intra-tumor clonal diversity: prognostic factor of tumor progression
- Chromosome instability: the sources of clonal heterogeneity
- The biological impact of clonal heterogeneity to cancer therapy
Genetic clonal diversity predicts progression to esophageal adenocarcinoma

A, diploid, LOH in TP53 and D9S1121
B, aneuploid (3.7N), LOH in TP53 and D9S1121
C, tetraploid, LOH in TP53 and D9S1121
D, diploid, LOH in TP53, D9S925, D9S1121 and D9S1118
E, diploid, LOH in TP53
F, diploid with no LOH).
G, diploid, LOH at D9S2169 and D9S1121
H, diploid, LOH at D9S2169, D9S935 and D9S1118
I, diploid, LOH at D9S2169, D9S935, D9S925 and D9S1118;
J, diploid with no LOH).
K, diploid, LOH at D9S935, D9S925 and D9S1118
L, diploid, LOH in TP53
M, diploid, LOH in all markers on chromosome 9p
K and L differ by two LOH events in four informative loci, resulting in a divergence of 0.27.
Accumulation of viable, clonal genetic variants is a greater risk factor for progressing to cancer than a recent homogenizing clonal expansion.

Aneuploidy: hallmark of Cancer

Mitelman Database of Chromosome Aberrations and Gene Fusions in Cancer

http://cgap.nci.nih.gov/Chromosomes/Mitelman

Carcinogens initiate carcinogenesis by causing aneuploidy, i.e., losses or gains of chromosomes.


Transgenic oncogenes induce oncogene-independent cancers with individual karyotypes and phenotypes


Analyzed the karyotypes and phenotypes of mammary carcinomas of mice with transgenic SV40 tumor virus- and hepatitis B virus-derived oncogenes.

1. a given transgene induced diverse carcinomas with individual karyotypes and phenotypes
2. these karyotypes coevolved with newly acquired phenotypes such as drug resistance
3. 8 of 12 carcinomas were transgene negative.

Activated oncogenes destabilize karyotypes and are dispensable in cancers, function indirectly, like carcinogens.

Carcinogenesis is a form of speciation and that individual karyotypes maintain cancers as they maintain species.
“aneuploidy” is “cancer's fatal flaw”? 

- Non-random distribution of chromosomal gains and losses seen in clinical tumors.
- Equilibrium of tumor heterogeneity.
Facts about cytogenetic chaos in carcinomas

1) Carcinomas are defined by a non-random distribution of chromosomal gains and losses;
2) The distribution of these imbalances is tumor specific;
3) Tumor specific chromosomal gains and losses occur before the transition to invasive disease;
4) These imbalances are not present in normal cells;
5) Such imbalances often comprise entire chromosome arms or chromosomes;
6) Aberrations emerging early in disease progression are usually maintained at advanced stages of the disease, in metastases, and in tumor-derived cell lines;
7) Specific aneuploidies are the basis for the clonal evolution and expansion of precancerous lesions;
8) The majority of structural aberrations result in genomic copy number changes, i.e., balanced translocations, the hallmark of hematological malignancies, are rare

non-random distribution of chromosomal gains and losses

Fig. 1. Distribution of chromosomal gains and losses in cervical and colorectal carcinomas. The distribution of genomic imbalances is tumor specific. The results are normalized to n = 10. Note that essentially all cervical carcinomas carry a gain of chromosome arm 3q, and colorectal carcinomas are defined by a recurrent gain of chromosomes 7, 8q, 13, and 20q, and losses of chromosomes 8p, 17p, and 18.
Fig. 2. Composite of CGH profiles from 22 GBM cases. Each line depicts the chromosomal region lost (red) and gained (green) in a single case.
Stochastic state transitions give rise to phenotypic equilibrium in populations of cancer cells

Benefit of tumor from heterogeneity

- **Synergize tumor growth**

Benefit of tumor from heterogeneity

- **Genetic clonal diversity predicts progression to esophageal adenocarcinoma**

  Cancers can be viewed from an ecological perspective that focuses on interactions of organisms with their environment and among each other. When applying an ecological perspective to human cancers, subclonal populations of tumor cells that differ in heritable traits are considered distinct “species,” whereas infiltrating normal cells, extracellular matrix, vessels, etc., are considered the environment.

- **Chromosomal instability, a source of clonal heterogeneity, confers intrinsic multidrug resistance**


Hsp90 stress potentiates rapid cellular adaptation through induction of aneuploidy

Pre-treatment: vehicle

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No colony observed

Pre-treatment: radicicol 20 μg ml⁻¹

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The effect of clonal heterogeneity on the ability to explore the fitness landscape


Clonal heterogeneity increases the probability of tumor progression

Cancer therapy might lead to dramatic alterations of the adaptive landscape
CIN: source of drug resistance of cancer cells


Maintenance tumor heterogeneity with an equilibrium optimal for tumor growth

- Complex interplay of various types of cells.
- Mutations in landscaper genes, alterations promoting angiogenesis and mutations enabling the cell to fight off the immune system
TUMOR CELL HETEROGENEITY AND EVOLUTION
Six hallmarks of cancer

- Self-sufficiency of cells in signals controlling growth.
- Loss of sensitivity to antigrowth signals.
- Evasion of apoptosis via mutation or loss of gatekeeper genes.
- Development of limitless replicative potential, usually via the expression of telomerase.
- Sustained angiogenesis, whereby the blood supply to a tumor is augmented.
- Tissue invasion and metastasis, which causes 90% of cancer deaths.

Functional category of cancer genes

- **Caretaker**: genes that help maintain genetic integrity; their mutation can lead to microsatellite or chromosomal instability.

- **Gatekeeper**: genes that regulate growth and differentiation, which include oncogenes and tumor suppressor genes.

- **Landscaper**: genes that, when mutated, lead to an abnormal extracellular and intercellular environment that contributes to carcinogenesis.
Cancer evolution theories/models
### Table 1. Cases of retinoblastoma

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The data presented here and in the literature are consistent with the hypothesis that at least one cancer, retinoblastoma, can be caused by two mutations, each of which occurs at a rate of the order of $2 \times 10^{-7}$ per year. One of these mutations may be inherited as a result of a previous germinal mutation that occurs at about the same rate. Those patients that inherit one mutation develop tumors earlier than do those who develop the nonhereditary form of the disease; in a majority of cases those who inherit a mutation develop more than one tumor. On the other hand, the probability that an individual not inheriting a mutation would develop more than one tumor is vanishingly small, so that nonhereditary cases are invariably unifocal.
The Clonal Evolution of Tumor Cell Populations

Breast cancer hierarchy model

Dick (2003) PNAS 100:3547–3549
Alternative cancer models

CANCER CLONE DIVERSITY AND PROPAGATION

- Chromosomal instability

Sustains cancer
Self-renews
Target for therapy

MODELS

- Stem cell
  (fixed; developmentally hierarchical)
  or
- Stochastic
  (random, variable)
  or
- Dominant sub-clone
  (dynamic, sub-clone genetic advantage and selection)

Greaves, Seminars in Cancer Biology 20 (2010) 65–70
Concepts in tumor evolution

- **Cellular genetic heterogeneity:** Genetic instability will lead to clonal diversity only if the genetic variants are viable and can expand into detectable clones.

- **Clonal genetic heterogeneity:** e.g. Increased Shannon diversity but lack of increased divergence in TP53 LOH epithelium suggests that TP53 LOH increases generation of viable genetic variants that may derive from a recent common ancestor, hence TP53 LOH epithelium is clonal. Clonal diversity predicts progression to cancer, although whether cellular diversity predicts progression remains an open question.
Schematic view of monoclonal and multiclonal models of tumor progression

A

Fraction of population

Time

B

Fraction of population

Time
Evolution in a hypothetical case of Barrett’s esophagus

Mathematical models of tumor suppressor describe the process of cancer initiation and progression

- Small lesions without genetic instability can take a very long time to inactivate the next TSG, whereas the same lesions with genetic instability pose a much greater risk for cancer progression.
- Knudson’s two-hit hypothesis is compatible with the idea that one mutation occurs in the first allele of the TSG and one mutation occurs in a CIN gene. The mutation inactivating the second TSG allele is not rate-limiting in a CIN cell.

Chromosome aberrations in human solid tumors are hallmarks of gene deregulation and genome instability

Figure 1 Schematic illustration of mechanisms by which chromosomal aberrations arise plus a summary of the ability of commonly applied technologies to detect the aberrations. (a) Aberrations that lead to aneuploidy. (b) Aberrations that leave the chromosome apparently intact.
Evolution of chromosomal aberrations in tumors


T47D
Mismatch repair–proficient

HCT116
Mismatch repair–defective
Stability-within-instability of cancers

1. Cultures of primary human mammary and muscle cells
2. Transformation with 6 Retrovirus activated genes and with SV40 (Human telomerase, cyclin, cyclin kinase, p53, myc, and ras)
3. Cloning transformed cells in 0.4% agar gels
4. Identification of metaphase chromosomes by m-FISH

Table 14
Chromosomal variations at any one time, and karyotypic stability over time, of all clones examined, based on their predominant stemlines

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<td>Clone-specific total</td>
<td>Vary within ±18% of average</td>
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<td>Clone-specific copy</td>
<td>For each specific chromosome: variation</td>
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Abbreviations: Focus 10, a focus of SV40-infected human dermal fibroblasts; Ma6, 6 virus-transformed human mammary cell; M-SV-62, SV40-transformed human mesothelial cells; Mu6, 6 virus-transformed human muscle cell; SV40, simian virus 40.
The Karyotypic cancer theory

Carcinogenesis by speciation from karyotypic variations

Potential mechanisms to generate aneuploid cells

Classes of CIN

- Class 1 — trigger CIN if one allele of the gene is lost (haploinsufficiency): MAD2, STAG2
- Class 2 — trigger CIN if one allele is mutated in a dominant (negative) fashion: BUB1
- Class 3 — require mutations in both alleles to trigger CIN (recessive at the cellular level): BRCA1
MAD, BUB, BUBR1, CENP-E,

STAG2

TP53, STK15, RB1, BRCA1, Pericentrin, TACC, CEP135, C-NAP1, MCAK
STAG2, a X-lined gene encoding a subunit of cohesin—a protein complex that regulates sister chromatid separation during cell division—is frequently altered in diverse human cancers.

STAG2-deficient H4 cells

(A) Schematic of the STAG2 locus in 42MGBA cells

1. STAG2 locus
2. LHTB
3. LEFT
4. right homology
5. -1 kb
6. IRES-NeoR
7. TGA (STOP)
8. Homologous recombination
9. Cre/LoxP recombination

(B) Western blot analysis

- STAG2
- α-tubulin

42MGBA clones

(C) Images of cell morphology

- Cohered
- Parallel
- Separated

(D) Graphs showing percentage of mitotic cells

- HCT116 clones
- H4 cells
- 42MGBA clones

- Parallel chromatids
- Separated chromatids
STAG2 inactivation resulted in altered chromosome counts (i.e., aneuploidy)
Global deregulation of gene expression by chromosome gain or loss

- Comparative gene expression profiling
- Somatic chromosome transfer
Gene expression levels follow genomic copy number

four individual cases of primary colorectal carcinomas
Aneuploidy: cause or consequence of cancer?

- Most cancer cells are aneuploid (Fact)
- Chr8 duplication cause APL (Fact)
- Transgenic oncogenes initiate carcinogenesis by inducing aneuploidy (Fact)
- Cancers are clones of autonomous cells defined by individual karyotypes, much like species (Theory)
- Despite such karyotypic evidence for causality, three to six synergistic mutations, termed oncogenes, are generally thought to cause cancer (Theory)
The role of aneuploidy in promoting and suppressing tumors

A: no CIN
- Normal mitotic checkpoint
- Normal growth

B: low CIN
- Mad1^+/−
- Mad2^+/−
- CENP-E^+/−
- Slight growth advantage; modest tumor promotion

C: low CIN + tumor promotion
- Cdc20^+/−/AAA
- Bub1^+/−
- Mad2 overexpression
- Significant tumor promotion

D: high CIN
- BubR1^+/−; Apc^Min/+; Bub1^+/−; CENP-E^+/−; p19ARF^−−
- Cell death & tumor suppression

Enhancing CIN to kill tumor cells

- Elevating the frequency of chromosome mis-segregation sensitized cancer cell to low doses of taxol (Janssen et al. Proc Natl Acad Sci U S A. 2009;106(45):19108-19113.)

- Anaphase catastrophe is a target for cancer therapy: pharmacologic inhibition of cyclin dependent kinase 2 (Cdk2) combined with a microtubule inhibitor to kills tumor cells with more than 2 centrosomes (Galimberti et al. Clin Cancer Res. 2011;17(6):1218-1222.)

Cancer is an ecosystem

An ecosystem describes the physical and biological components of an environment in relation to each other as a unit.

Table 1. Contrasts between the evolution of individuals in populations and cancer cells in individuals

<table>
<thead>
<tr>
<th>Process</th>
<th>Evolution of populations</th>
<th>Evolution of cancer cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenotypic variation generated</td>
<td>Germline mutation and recombination</td>
<td>Somatic mutation</td>
</tr>
<tr>
<td>Selection</td>
<td>Owing to differential survival and reproduction; main selective agents are abiotic factors, competitors, predators and parasites</td>
<td>Epigenetic alteration</td>
</tr>
<tr>
<td>Drift</td>
<td>Stochastic changes in allele frequencies, owing to sampling error in small populations of individuals</td>
<td>Genomic instability</td>
</tr>
<tr>
<td>Inheritance</td>
<td>Genes transmitted intact barring mutation or recombination</td>
<td>Owing to differential replication and apoptosis or cellular senescence; selective pressures include intercellular competition for resources, immunosurveillance and signaling system components such as receptors and hormones</td>
</tr>
<tr>
<td>Result of process</td>
<td>Adaptation across generations</td>
<td>Asexuality; genetic and epigenetic variants inherited intact barring mutation or epigenetic alteration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Large cell population adapted to rapid growth, resulting in death of the individual</td>
</tr>
</tbody>
</table>

Cancer as an ecosystem

- **Tumor morphology and phenotypic evolution driven by selective pressure from the microenvironment.** Anderson, A.R. et al. (2006) Cell 127, 905–915
Clonal diversity increase with progression

A neoplasm acts like a single population of cells or there is a diversity of microenvironments that create different niches.

Ecology and evolution suggest various mechanisms for cancer clonal coexistence

- Mutations might be evolutionarily neutral, providing no fitness advantage, and therefore no selective sweep.
- Fitness might be density dependent, so that as a clone becomes more frequent in the population, its fitness decreases.
- This might be caused by an immune reaction (predation), one clone gaining a fitness benefit by proximity to another clone (parasitism), or pollution of its environment by metabolic byproducts.
- Niches: clones might specialize on different resources or different microenvironments, and thereby reduce their competition.
- If the environment fluctuates faster than any one clone can reach fixation, then clones adapted to the different environments could coexist in non-equilibrium.
- The total population might be expanding, therefore reducing competition for space. Which, if any, of these mechanisms are at work in neoplasms is an important open question in cancer biology.
Co-evolution of tumor cells and their microenvironment

Key:
- Red: Normal epithelial cells
- Red: Tumor epithelial cells
- Green: Fibroblasts
- Green: Cancer-associated fibroblasts
- Blue: Leukocytes

Altered microenvironment (chronic inflammation, wounding)

Basement membrane

Transformation of epithelial cells
Deregulation/mutation of genes categorized for cancer ecology

- **Caretaker**: genes that help maintain genetic integrity; their mutation can lead to microsatellite or chromosomal instability

- **Gatekeeper**: genes that regulate growth and differentiation, which include oncogenes and tumor suppressor genes

- **Landscaper**: genes that, when mutated, lead to an abnormal extracellular and intercellular environment that contributes to carcinogenesis.
<table>
<thead>
<tr>
<th>Year</th>
<th>Discovery or Event</th>
<th>Relative Survival Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1863</td>
<td>Cellular origin of cancer (Virchow)</td>
<td></td>
</tr>
<tr>
<td>1889</td>
<td>Seed-and-soil hypothesis (Paget)</td>
<td></td>
</tr>
<tr>
<td>1914</td>
<td>Chromosomal mutations in cancer (Boveri)</td>
<td></td>
</tr>
<tr>
<td>1937</td>
<td>Founding of NCI</td>
<td></td>
</tr>
<tr>
<td>1944</td>
<td>Transmission of cellular information by DNA (Avery)</td>
<td></td>
</tr>
<tr>
<td>1950</td>
<td>Availability of cancer drugs through Cancer Chemotherapy National Service Center</td>
<td></td>
</tr>
<tr>
<td>1953</td>
<td>Report on structure of DNA</td>
<td>35%</td>
</tr>
<tr>
<td>1961</td>
<td>Breaking of the genetic code</td>
<td></td>
</tr>
<tr>
<td>1970</td>
<td>Reverse transcriptase</td>
<td></td>
</tr>
<tr>
<td>1971</td>
<td>Restriction enzymes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Passage of National Cancer Cancer Act</td>
<td></td>
</tr>
<tr>
<td>Year</td>
<td>Event Description</td>
<td>Percentage</td>
</tr>
<tr>
<td>------</td>
<td>-----------------------------------------------------------------------</td>
<td>------------</td>
</tr>
<tr>
<td>1975</td>
<td>Hybridomas and monoclonal antibodies</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>Tracking of cancer statistics by SEER program</td>
<td></td>
</tr>
<tr>
<td>1976</td>
<td>Cellular origin of retroviral oncogenes</td>
<td></td>
</tr>
<tr>
<td>1979</td>
<td>Epidermal growth factor and receptor</td>
<td></td>
</tr>
<tr>
<td>1981</td>
<td>Suppression of tumor growth by p53</td>
<td></td>
</tr>
<tr>
<td>1984</td>
<td>G proteins and cell signaling</td>
<td></td>
</tr>
<tr>
<td>1986</td>
<td>Retinoblastoma gene</td>
<td></td>
</tr>
<tr>
<td>1990</td>
<td>First decrease in cancer incidence and mortality</td>
<td></td>
</tr>
<tr>
<td>1991</td>
<td>Association between mutation in APC gene and colorectal cancer</td>
<td></td>
</tr>
<tr>
<td>1994</td>
<td>Genetic cancer syndromes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Association between BRCA1 and breast cancer</td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>Sequencing of the human genome</td>
<td></td>
</tr>
<tr>
<td>2002</td>
<td>Epigenetics in cancer</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MicroRNAs in cancer</td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>First decrease in total number of deaths from cancer</td>
<td>68%</td>
</tr>
<tr>
<td>2006</td>
<td>Tumor stromal interaction</td>
<td></td>
</tr>
</tbody>
</table>
The mechanisms in maintaining cancer ecology

- autonomous
- environmental
- system
Control of chromosomal instability

Genes in genome guidance, mis-match repair
Presenter: Thanh-Trang Vo

Genes in kinetochore-microtubule dynamics
Presenter: Judy Webb

Suggested references
Tetraploidy, aneuploidy, and senescence, CIN-based therapy

Presenter: Alison McCracken

Non-heritable sources of diversity in tumor cell populations
Epithelial-mesenchymal transition (EMT)
Endothelial transdifferentiation

Presenter: Andrea Newman

Suggested references

Cancer mutator TP53 and restore of TP53 function
Presenter: Bradly Wallentine

Cause from environmental stress
Presenter: Amy Hopkin

Suggested references