CANCER: focus on tradeoffs, mismatches, evolution of causes & *somatic evolution within the body*

Evolutionary biology of cancer

SEVEN PRINCIPLES OF EVOLUTION & CANCER

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Somatic evolutionary genomics: Mutations during development cause highly variable genetic mosaicism with risk of cancer and neurodegeneration

The simplest definition is from the American Cancer Society (ACS). According to the ACS, cancer is a group of diseases characterized by uncontrolled growth and spread of abnormal cells. If the spread is not controlled, it can result in death

The Hallmarks of Cancer, all of which evolve somatically

(1) self-sufficiency in growth signals
(2) insensitivity to anti-growth signals
(3) evading apoptosis
(4) sustained angiogenesis
(5) limitless replicative potential
(6) invasion and metastasis
(7) escaping immunosurveillance
Some cancer terminology

Classification by tissue type:
- carcinoma: epithelial cell
  - 90% of all tumours derived from ectoderm (mostly) or endoderm (some)
- sarcoma: connective tissue
  - 2% of all tumours derived from mesoderm
- leukaemia: circulatory or lymphatic
  - 8% of all tumours derived from mesoderm

Classification by the type of cells:
- Adenomatous cells: ductal or glandular cells
- Squamous cells: flat cells
- Myeloid: blood cell
- Lymphoid: lymphocytes or macrophages

Cancer is many diseases with one commonality

Types of genes that undergo alterations in cancer I

(1) ONCOGENES:
- undergo dominant gains of function (e.g., increased activity or higher expression of gene product)
- often involved in stimulating cell replication (e.g., IGF2)

(2) TUMOR SUPPRESSOR GENES:
- undergo losses of function via genetic or epigenetic inactivation, such that cell survival, replication are less controlled; loss of one copy may have no or minor effects, loss of both copies is major alteration
- often involved in cell cycle regulation (e.g., RB1, CDKN1C)

NOTE:
(a) all of these genes generally have OTHER primary functions
(b) genes may be tumor suppressor or oncogene in one tissue, at one time point, NOT in other
(c) effects of such genes are subject to TRADEOFFS w/ other functions

Childhood cancers differ from adult cancers

Classification by tissue type:

MOST ADULT CANCERS
(stem cells, progenitor cells, de-differentiation, increased risk with age)

MOST CHILDHOOD CANCERS
(failures of differentiation, other losses of replication control, decreased risk with age except for osteosarcoma)

Types of genes that undergo alterations in cancer II

(1) GATEKEEPER GENES: genes that regulate growth and differentiation; include oncogenes and tumor suppressor genes

(2) CARETAKER GENES: genes that help to maintain genetic integrity; their loss of function mutations lead to
- microsatellite instability (due to mismatch repair deficiency)
- chromosomal instability (gain or loss of chromosomes or parts thereof)

(3) LANDSCAPER GENES: genes that when mutated lead to abnormal extracellular or intracellular environment that contributes to carcinogenesis

H19 gene product: normal primary function: in placenta, restricts growth and cell migration, and regulates angiogenesis under hypoxic conditions; promotes differentiation of cytotrophoblast cells; also regulates post-natal growth

ADAPTIVE FUNCTIONS
- Acts as growth restraint/tumor suppressor gene

The H19 locus acts in vivo as a tumor suppressor

The oncocalcal H19 RNA connection: Hypoxia, p53 and cancer

*If P53 suffers loss of function, then H19 acts as an oncogene in hypoxic environment of tumors

MALADAPTIVE FUNCTION

The 5′ untranslated region of the H19 transcript is transcribed and can function as a microRNA (hsa-mir-671) that targets tumor suppressor genes.

PNAS 2008

Bisch Biophys Acta 2010
**Adult Cancer Risk** Increases with Age (~40% get it, in lifetime)

due to
(1) sequential accumulation of mutations over a long time
(2) senescence-related tissue changes that can promote cancer development

**Pediatric Cancer Risk** decreases with age & parallels growth velocity; 2nd leading cause of child death in developed countries

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**Somatic evolution of cancer cell populations**

(1) Stepwise, nested generation of hierarchical among-cell genetic, epigenetic, cytogenetic diversity leading to evolution of **six hallmarks** of cancer via mutation, epimutation, chromosomal alterations; evolution in response to selective pressures including immune system, ‘competition’ between cells, ‘cooperation’ between cancer cell lineages

Origin of genomic instability, leading to much higher mutation rate

(2) Evolution of cancer cell populations in response to **therapeutic agents**

**CANCER CELLS EVOLVING BY NATURAL SELECTION**

- **Variation** in the population of cells:
  - Somatic mutations.
- **Variation amongst cells** is **Heritable**:
  - Mutations in DNA, chromosomes, methylation patterns.
- **Variation affects Reproduction and Survival of the cells**:
  - e.g., suppression of apoptosis etc.

‘ADAPTATION?’ sort of, but not in usual sense
Evolution Within a Neoplasm

Cancer cells evolve via genetic, epigenetic, genomic and cytogenetic changes in large numbers of genes

CLASSIC LINEAR MODEL: One pathway

Normal Epithelium → Hyperplastic epithelium

Me of DNA

Smad

Intermediate Adenoma → Early Adenoma

Kras

Late Adenoma → Carcinoma

Invasion and Metastasis

Linear Models of Carcinogenesis

One example of progression to cancer

One example of progression to cancer

But classic, unitary linear model fails due to high diversity of genetic, epigenetic, cytogenetic pathways whereby the hallmarks of cancer can be acquired

One example of progression to cancer

Constant population

“Advantageous” “driver” mutant (increases net proliferation of lineage) - in any number of genes; genetic, epigenetic or chromosomal
How Might Diversity Change During Progression? Genetic, Phylogenetic and Demographic Change

Subclonal phylogenetic structures in cancer revealed by ultra-deep sequencing

The results of cancer cell population-level evolution, for two patients

Other patients?
Other cancers?
Regularities, for therapeutic targets?

PNAS 2008
Population Genetics of Cancer: Rate of Evolution

What is the probability of a new cellular/genetic variant emerging and expanding in a population?

Function of:
- Mutation rate (rate of variant generation)
- Population size (numbers of mutational targets)
- Generation time (rate of turnover)
- Strength of selection (rate of clonal expansion)

EFFECTS OF GENETIC VARIABILITY ON PROGRESSION ->

Genetic Diversity Predicts Progression - Number of Clones, in Barrett’s esophagus

- Median:
  - progressors 3 (range: 1 - 9)
  - non-progressors 1 (range: 1 - 7)
- RR = 1.40 per clone (95% CI:1.13 - 1.73) p < 0.01
- Controlling for p53 LOH, aneuploidy and tetraploidy

Genetic Diversity Predicts Progression - Mean Pairwise Divergence

- Median:
  - progressors 7% (range: 0 – 54%)
  - non-progressors 0% (range: 0 – 27%)
- RR = 1.45 per 10% divergence (95% CI:1.08 - 1.95) p < 0.05
- Controlling for p53 LOH, aneuploidy and tetraploidy

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Visualizing inherited genetically-based risk ('closer to' vs 'farther from' cancer at conception)

Allele frequencies vs effect sizes of risk alleles


How evolutionary mismatches can affect cancer risk

Mismatches and female reproductive cancers I

Mismatches and female reproductive cancers II

Effects of mismatches between ancestral and current conditions on chronic disease risk

* Mismatches and female reproductive cancers I

** Mismatches and female reproductive cancers II

Table 2: Reproductive Exposures and Risk of Women's Cancer

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Risk Factors</th>
<th>Significance for cancer risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at menopause</td>
<td>10.5</td>
<td>20.8</td>
</tr>
<tr>
<td>Age at first birth</td>
<td>10.5</td>
<td>20.8</td>
</tr>
<tr>
<td>Mammography</td>
<td>10.5</td>
<td>20.8</td>
</tr>
<tr>
<td>Duration of lactation</td>
<td>10.5</td>
<td>20.8</td>
</tr>
<tr>
<td>Age at menopause</td>
<td>10.5</td>
<td>20.8</td>
</tr>
</tbody>
</table>

Table 3: Environmental Factors Affecting Risk of Women's Cancer

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Risk Factors</th>
<th>Significance for cancer risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dietary habits</td>
<td>10.5</td>
<td>20.8</td>
</tr>
<tr>
<td>Exercise</td>
<td>10.5</td>
<td>20.8</td>
</tr>
<tr>
<td>Smoking</td>
<td>10.5</td>
<td>20.8</td>
</tr>
</tbody>
</table>

* Women with a high school education beyond high school.
** For women who have never used oral contraceptives.
*** Women who had the total number of births is 21 and who survive to age 58.
Mismatches and female reproductive cancers   III

Eaton et al. 1994 QRB

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Cancer risk trades off with aging in mice

Good news! The m allele appears to confer resistance to tumors (6% vs >45%)
Bad News! The m allele appears to have a cost in terms of aging (die off sooner than p53+/+ wild types)

EXAMPLE: tradeoff between cancer and senescence mediated by effects of p53 gene

EXAMPLE: Tradeoffs between cancer risk and risks of neurodegenerative diseases

Schizophrenia, Huntington’s, Parkinson’s, Alzheimer’s

Genetic basis:

PARK2
APC
TP53
ATM, etc etc

-identify pathways

Cancer and Neurodegeneration: Between the Devil and the Deep Blue Sea

Hinda Fedor-Fineman*, Patrick B. Leaf, John Hardy, *L. Miguel Refolo, *Nicholas M. Yen

* = Corresponding author

PLoS Genetics 2010
EXAMPLE:
CHILDHOOD GROWTH - CANCER TRADEOFF

As seen, age-specific growth rate is positively associated with age-specific cancer risk in children

Childhood cancer risk positively associated with higher birth weight, faster fetal growth

See Crespi 2011 PRSLB

SELECTION ON TRADEOFFS:

- growth/cancer
- repair/proliferation/cancer
- senescence/apoptosis/cancer

'Co-option' of testis genes, pathways in carcinogenesis

Family of X-linked, primate-specific cancer/testis associated genes (CTAs), expressed in normal testis, involved in spermatogenesis, and in tumor cells, promote cancer cell growth. Roles in spermatozoa development and function, cell cycle regulation, and apoptosis. Associated with aggressiveness of skin tumors, inherited testicular and prostate cancer risk.

Kleene (2005) provides evidence that many CTAs (such as SPANX) are subject to extremely strong selection in the context of sperm production. Cancer cells dedifferentiate and take on properties of immortal male germ cells.

'Co-option' of gene expression patterns, pathways, cell/tissue phenotypes by cancer, from:

- Placenta as an initial genetic & developmental source of hallmarks of cancer, a co-option of placentally expressed pathways

- Male germ cell proliferation (cancer/testis antigens)

- Stem cells

- Childhood growth systems (IGF2, other genes) trade off with cancer risk

- Other reproductive tissues subject to rapid growth, strong selection

- Wound healing (cell migration, angiogenesis, local cell proliferation)

EXPECT TRADEOFFS OF THESE CELL, TISSUE FUNCTIONS WITH CANCER RISK

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Crespi & Summers 2005, TREE

Putative anti-cancer adaptations
(1) proportions, separation, progression of stem cells, progenitor cells, differentiated cells
(2) regenerative ability only in tissues that suffer damage
(3) stem cells kept in separate compartments, to limit initial spread via microenvironment effects
(4) cell division primarily in early fetal development, in relatively protected conditions
(5) cellular senescence and apoptosis in response to DNA damage
(6) immunosurveillance

Colon tissue architecture

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Traditional vs Targeted cancer drugs
- Traditional drugs: very toxic agents that kill all dividing cells
- Targeted drugs: small molecule inhibitors - target the specific pathways which make cancerous cells cancerous (e.g., Gleevec inhibits a tyrosine kinase)

Targeted cancer drugs
• Very effective
• Not toxic
 • However, evolution of resistance poses a problem  

Gleevec
Bcr-Abl protein
Gerlinger & Swanton 2010
Br J Cancer
Genetic, epigenetic cytogenetic clonal heterogeneity evolve during carcinogenesis
Drug treatments select for resistant clones, via different routes
Cancer may undergo remission, but recurs
Metastasis & resistance cause death

DATA: Therapies Select for Resistance Mutations

- With $10^9$–$10^{12}$ cells in a neoplasm and $10^4$ mutations, the presence of a resistance mutation is likely

- Imatinib (Gleevec) resistance:

- Gefitinib resistance:


Implications of cancer somatic evolution, variation for therapy

1) Need to personalize treatment by genotyping the cancer; identify and target the driver mutations and the expected therapy-resistance mutations

2) Genotyping must involve sampling cancer cell population diversity

3) Evolutionary responses to therapies can be monitored

4) Cancer cells can be stabilized rather than maximally killed (reducing selection for evolution of resistant lineages)

5) Genomic instability can be increased to intolerable levels

6) Adaptive immune system and cancers can be manipulated to generate immune recognition of cancer cells (1)

Interested in career in cancer biology, using evolutionary concepts and tools?

1) Learn cell biology, cancer biology

2) Learn, apply genomic and bioinformatic tools, and/or collaborate

3) Consider an MD or MD-PhD

4) Develop and apply therapies based on evolutionary principles