Conventional Medical Research

PROXIMATE
causes (how)

Disease represents breakdowns of human 'machine'

MAIN USE: uncover mechanisms, test treatments, prevention, of disease

Evolutionary Medical Research

ULTIMATE
causes (why)

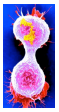
Disease risks have evolved; connect the maladaptations with adaptations

MAIN USE: theory generates testable hypotheses, indicates what data to collect

TWO APPROACHES ARE FULLY COMPATIBLE & SYNERGISTIC

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

Evolutionary biology of cancer



SEVEN PRINCIPLES OF EVOLUTION & CANCER

(1) Cancer is mediated by somatic evolution
(2) Cancer is many tissue-specific and age-associated diseases, with one commonality in uncontrolled cell replication
(3) The somatic evolution of cancer is mediated by the population-genetic forces of mutation, selection & genetic drift, in a phylogenetic, phylogeographic context
(4) Cancer is a polygenic, heritable, and environmental disease, mediated in part by mismatches between current and ancestral conditions
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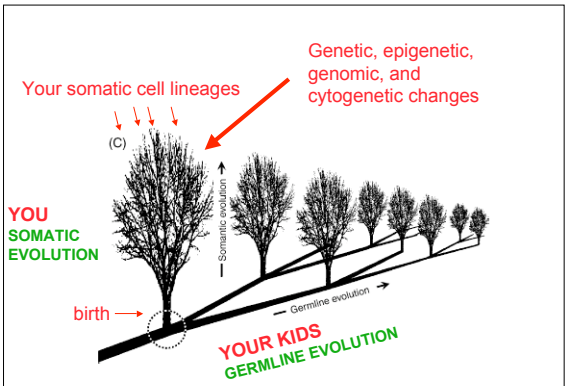
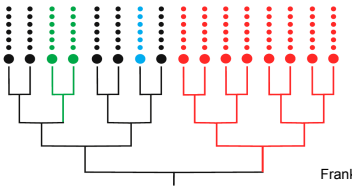


Somatic evolutionary genomics: Mutations during development cause highly variable genetic mosaicism with risk of cancer and neurodegeneration

Steven A. Frank[1]

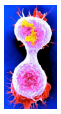
New technologies promise the ability to measure genetic mosaicism by sampling a large number of cellular genomes within an individual. The sampling of many genomes within an individual will eventually allow one to reconstruct the cell lineage history of genetic change in a single body. Somatic evolutionary genomics will follow from this technology, providing new insight into the origin and progression of disease



Frank, 2010, *PNAS*

Fig. 2. Mutational events in development occur at different stages in the exponential, branching phase of cellular expansion. In this example, the red mutation happens early, causing a significant fraction of somatic cells to carry the same mutation by descent. By contrast, the green mutation happens late in development, causing only a small fraction of somatic cells to carry the same mutation by descent. Many mutations will arise within the stem cells, each stem cell renewing only a very small fraction of all somatic cells. For example, the blue mutation is private to a single stem cell and will be confined to the small subset of somatic cells derived from that stem cell. Branching lines represent the developmental phase of cellular expansion, the large cells are stem cells, and the small cells in each line form a clone derived from their stem cell ancestor.

Evolutionary biology of cancer



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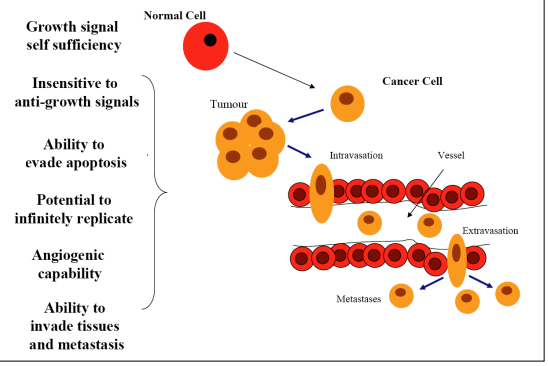
The simplest definition is from the American Cancer Society (ACS).
According to the ACS, cancer is a group of diseases characterized by ***uncontrolled growth and spread of abnormal cells***.
If the spread is not controlled, it can result in death

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

Cancer Evolution



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

Childhood cancers differ from *adult* cancers

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  epithelial cell
  90% of all tumours
  derived from ***ectoderm*** (mostly) or endoderm (some)
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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 I

(1) 'ONCOGENES'

-undergo dominant gains of function (e.g., increased activity or higher expression of gene product)

-often involved in stimulating cell replication (eg 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 (eg 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

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

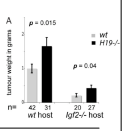
ADAPTIVE FUNCTIONS

•Acts as growth restraint/**tumor suppressor** gene

The *H19* locus acts *in vivo* as a tumor suppressor

Tomomi Yoshimizu[*1], Audrey Miroglio[*1], Marie-Anne Ripoche[*], Anne Gabory[*], Maria Vernucci[§], Andrea Riccio[§], Sabine Colnot[¶], Cécile Godard[¶], Benoît Terris[¶], Hélène Jammes[*], and Luisa Dandolo[*¶]

PNAS 2008



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

The oncofetal H19 RNA connection: Hypoxia, p53 and cancer

Imad J. Matouk[a,b,*,1], Shaul Mezan[a,1], Aya Mizrahi[a], Patricia Ohana[a], Rasha Abu-lail[a], Yakov Fellig[a], Nathan deGroot[a], Eithan Galun[b], Abraham Hochberg[a]

Bioch Biophys Acta 2010

MALADAPTATIVE FUNCTION

'Types' of genes that undergo alterations in cancer II

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

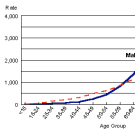
(2) CARETAKER GENES: genes that help to maintain *genetic integrity*; their loss of function mutations lead to

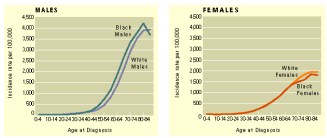
-microsatellite instability (due to mismatch repair deficiency)
-chromosomal instability (gain or loss of chromosomes or parts thereof)

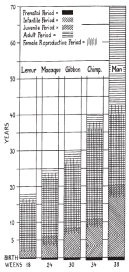
(3) LANDSCAPER GENES: genes that when mutated lead to abnormal *extracellular or intracellular environment* that contributes to carcinogenesis

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

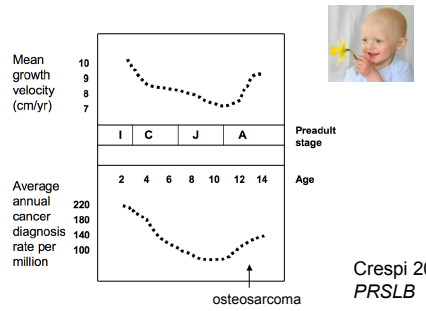






Pediatric Cancer Risk *decreases* with age & parallels growth velocity; 2nd leading cause of child death in developed countries

Figure 4. The pattern of changes in human growth velocity (adapted from Hochberg 2009) over the preadult period, in comparison to age-specific incidence of cancer (adapted from data in Ries et al. 1999).



Crespi 2011
PRSLB

Evolutionary biology of cancer

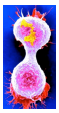


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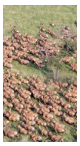
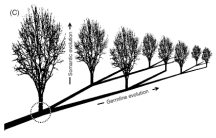
Table 1. Contrasts between the evolution of individuals in populations and cancer cells in individuals

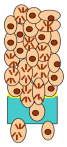
populations **cancer cells**

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

Process	Evolution of populations	Evolution of cancer cells
Phenotypic variation generated	Germline mutation and recombination	Somatic mutation Epigenetic alteration Genomic instability
Selection	Owing to differential survival and reproduction; main selective agents are abiotic factors, competitors, predators and parasites	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
Drift	Stochastic changes in allele frequencies, owing to sampling error in small populations of individuals	Stochastic changes in genetic or epigenetic allele frequencies, owing to sampling error in small populations of cells
Inheritance	Genes transmitted intact barring mutation or recombination	Asexuality; genetic and epigenetic variants inherited intact barring mutation or epigenetic alteration
Result of process	Adaptation across generations	Large cell population adapted to rapid growth, resulting in death of the individual







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

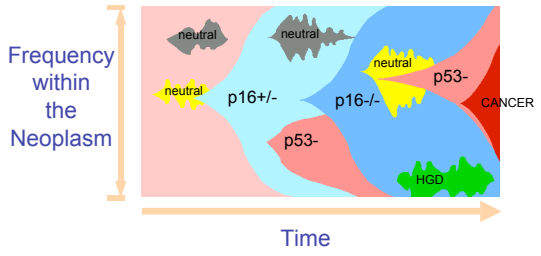
(2) Evolution of cancer cell populations in response to ***therapeutic agents***

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

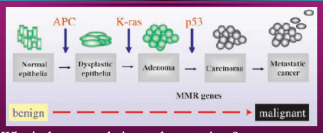


Cancer cells evolve via genetic, epigenetic, genomic and cytogenetic changes in large numbers of genes

CLASSIC LINEAR MODEL: One pathway

Normal Epithelium → APC → Hyperplastic epithelium → Me of DNA → Intermediate Adenoma → KRas → Early Adenoma → Smad 4 → Late Adenoma → p53 → Carcinoma → Invasion and Metastasis

Linear Models of Carcinogenesis



- Why is there an ordering to the mutations?
- Doesn't account for alternative carcinogenic sequences of mutations
- Obscures heterogeneity within the neoplasm
- Fails as a model:

Smith et al. (2002) PNAS 99:9433-8

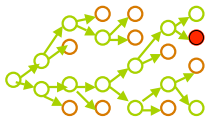
But classic, unitary linear model *fails* due to high *diversity* of genetic, epigenetic, cytogenetic *pathways* whereby the hallmarks of cancer can be acquired

One example of progression to cancer

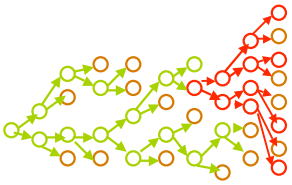
One example of progression to cancer

Constant population

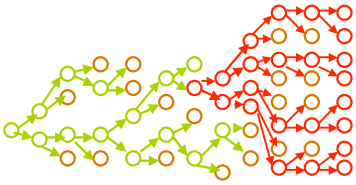
One example of progression to cancer



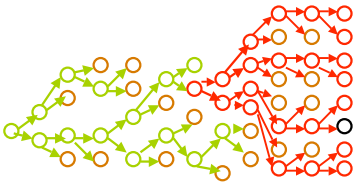
'Advantageous' 'driver' mutant (increases net proliferation of lineage) - in any number of genes; genetic, epigenetic or chromosomal



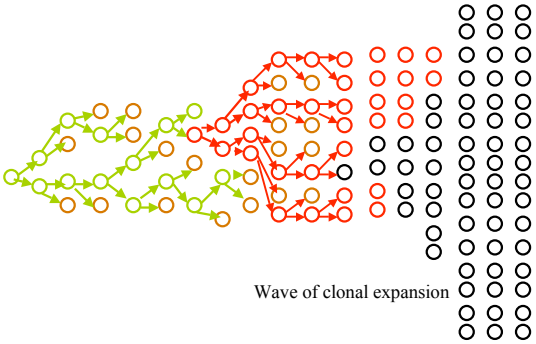
Clonal expansion



Saturation

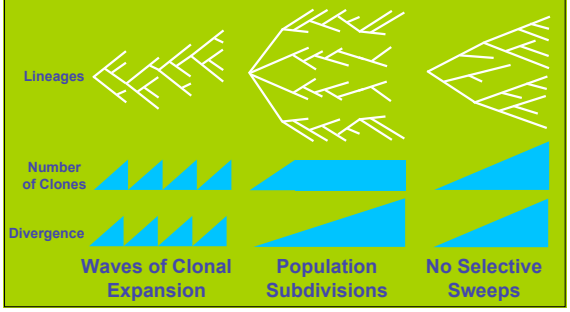


Another
'advantageous' mutant



Wave of clonal expansion

How Might Diversity Change During Progression? Genetic, Phylogenetic ***and*** Demographic Change



Subclonal phylogenetic structures in cancer revealed by ultra-deep sequencing

Peter J. Campbell*, Erin D. Pleasance*, Philip J. Stephens*, Ed Dicks*, Richard Rance*, Ian Goodhead*, George A. Follows†, Anthony R. Green†, P. Andy Futreal*‡, and Michael R. Stratton*‡§

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

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

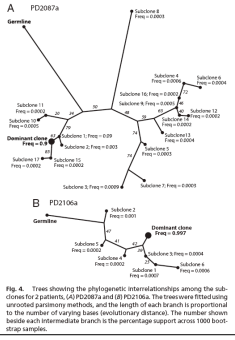
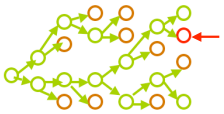


Fig. 4. Trees showing the phylogenetic interrelationships among the subclones for 2 patients, (A) PD2087a and (B) PD2106a. The trees were fitted using unrooted parsimony methods, and the length of each branch is proportional to the number of varying bases (evolutionary distance). The number shown beside each intermediate branch is the percentage support across 1000 bootstrap samples.

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)

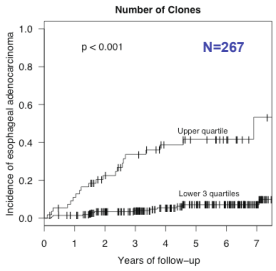
EFFECTS OF GENETIC VARIABILITY ON PROGRESSION ->

Genetic Diversity Predicts Progression - Number of Clones, in Barrett's esophagous

Carlo Maley

- 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

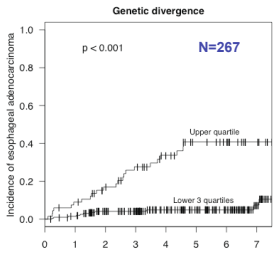
Maley et al. (2006) Nat. Gen. 38:468–73

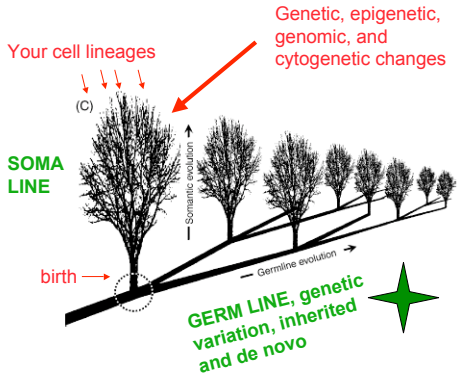


Genetic Diversity Predicts Progression Mean Pairwise Divergence

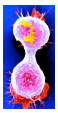
- Median:
  - progressors 7% (range: 0–54%),
  - non-progressors 0% (range: 0–27%)
- RR = 1.45 per 10% divergence
- (95% CI:1.08 - 1.95) p < 0.05
- Controlling for p53 LOH, aneuploidy and tetraploidy

Maley et al. (2006) Nat. Gen. 38:468–73





Evolutionary biology of cancer



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Genome-wide Association Studies of Cancer Predisposition

Zsofia K. Stadler MD[1], Joseph Vijai PhD[1], Peter Thom MS[1], Tomas Kirchhoff PhD[1], Nichole A.L. Hansen BS[1], Noah D. Kauff MD[1], Mark Robson MD[1] and Kenneth Offit MD, MPH[1]
[1] Clinical Genetics Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021, USA

Available online 4 September 2010.

Genome-wide association studies (GWAS) have now been performed in nearly all common malignancies and have identified more than 100 common genetic risk variants that confer a modest increased risk of cancer. For most discovered germline risk variants, the per allele effect size is small (<1.5) and the biologic mechanism of the detected association remains unexplained. Exceptions are the risk variants identified in JAK2 in myeloproliferative neoplasm and in the KITLG gene in testicular cancer, which are each associated with nearly a 3-fold increased risk of disease. GWAS have provided an efficient approach to identifying common, low-penetrance risk variants, and have implicated several novel cancer susceptibility loci. However, the identified low-penetrance risk variants explain only a small fraction of the heritability of cancer and the clinical usefulness of using these variants for cancer-risk prediction is to date limited. Studies involving more heterogeneous populations, determination of the causal variants, and functional studies are now necessary to further elucidate the potential biologic and clinical significance of the observed associations.

Heritabilities 10-50% depending on form of cancer

Galvan et al. 2010 Trends Genet.

-Many common alleles of small effect found by GWAS
-Small % of heritability 'explained' so far
-Rare variants being studied now
-High genetic heterogeneity likely
-Epigenetics virtually unstudied
-Gene x Env't interactions unstudied

Hematology/Oncology Clinics of North America Volume 24, Issue 5, October 2010, Pages 973-996

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

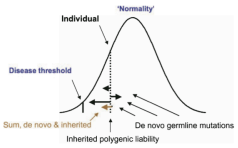


Figure 1 Polygenic disease risk for a given individual can be depicted as a combination of risk owing to alleles inherited from parents (inherited polygenic liability), and risk owing to new mutations (de novo germline mutation). Somatic mutation during development is also likely to be important, but has yet to be studied in detail.

Allele frequencies vs effect sizes of risk alleles

Crespi 2011, Evol. Appl.

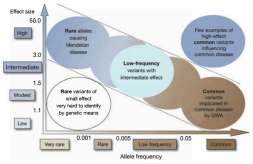


Figure 2 The frequency spectrum of human disease risk alleles includes alleles at all frequencies from rare to common, with effect sizes from high to low, with the relative importance in risk of different variants yet to be ascertained. From Manolio et al. (2009).

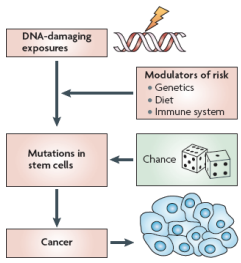


Figure 1 | **The cancer lottery.** The process of tumorigenesis is essentially a lottery. Epidemiologists might see this as less than 100% penetrance of disease in a group of highly exposed individuals; for example, only one in ten persistent high level smokers develop lung cancer. There is a biological rationale for this. Cancer can only emerge if a relevant gene is functionally mutated in a relevant cell. One per cent of our genes might be 'relevant' in this context, along with perhaps 0.1% of our cells. Exogenous or endogenous genotoxic exposures are almost entirely blind to gene or cellular functions, and are therefore indiscriminate with respect to these criteria. What we see in cancer clone mutants must be distilled or selected from a huge sea of noise — as in evolution (through germ-cell mutation) itself. Genetics: inherited allelic variation, for example, in genes and signal networks that underpin functions such as detoxification, DNA repair and immune recognition. Diet: the pattern of intake of total calories plus particular ingredients (for example, antioxidants and folates) coupled with energy usage through physical activity. Immune system: for example, surveillance against viruses.

Genetic PLUS Environmental impacts; showing importance of *chance* mutational events

Greaves 2007 *Nat Rev Cancer*

How evolutionary mismatches can affect cancer risk

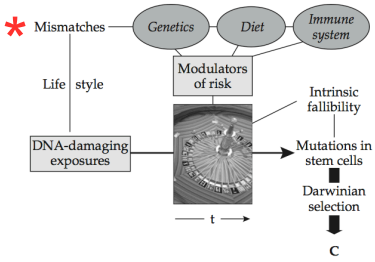


Figure 21.2 The cancer lottery: an evolutionary heritage. Proximate mechanisms as in Fig. 21.1. Addition of causal mechanisms involving evolutionary mismatches and intrinsic fallibility. t = time.

Greaves 2008

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

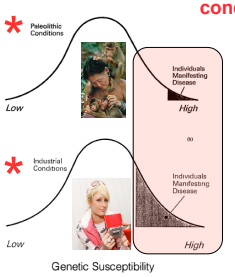


FIG. 1. GENES, LIFESTYLE, AND CHRONIC DEGENERATIVE DISEASE

The genetic susceptibility of current humans, for any given chronic degenerative disease, is similar to that of our preagricultural, but anatomically modern, ancestors. The interaction between current lifestyle factors and ancient genetically determined biology, however, produces far greater disease expression in today's affluent nations.

Eaton et al. 1994 *QRB*

Mismatches and female reproductive cancers I


TABLE 2

Reproductive Experience and Risk of Women's Cancers

	Reproductive contrasts		Significance for cancer risk		
	Hunter-gatherers	Americans	Breast	Endometrium	Ovary
Age at menarche	16.1	12.5	+	+	
Age at first birth	19.5	24.0 (all) 26.5 (educated*)	+		
Menarche to first birth time elapsed, years	3.4	11.5 (all) 14.0 (educated*)	+		
Duration of lactation per birth	2.9 years	3.0 months	+		+
Completed family size***	5.9	1.8	+	+	+
Age at menopause	47	50.5	+	+	
Total number of ovulations (see text for calculations)	160	450**			+

* Women with at least some education beyond high school.
** For women who have not used oral contraceptives.
*** Mean number of live births in women who survive to age 50.

Eaton et al. 1994 *QRB*

Mismatches and female reproductive cancers II


TABLE 3

Extrareproductive Factors Affecting Risk of Women's Cancers

	Hunter-gatherers	Typical Americans
Dietary fat, % energy	20	36*
Dietary fiber, *g/d*	100	15
Maximal O_2 consumption, ml/kg/min**	51.8	42.5
Triceps skinfold, mm	9.6***	17.0

* 36% in 1985–1986; 41% in 1977–1978.
** VO_2 max is a measure of aerobic (endurance) fitness. The values are for young men; women's data are unavailable, but believed comparable.
*** Australian Aborigines, 9.4; Tanzanian Hadza, 9.8.
Sources: Abbie, 1963; Eveleth and Tanner, 1976; Hiernaux and Boedhi Hartono, 1980; Eaton et al., 1988; Committee on Diet and Health, National Research Council, 1989.

Eaton et al. 1994 *QRB*

Mismatches and female reproductive cancers III

TABLE 4
Estimated Cumulative Relative Cancer Risk to Age 60 (see Appendix)

	Breast	Epithelial ovarian	Endometrial
Paleolithic hunter-gatherers*	1	1	1
Americans with 10 years COC use	114**	6.9	75
Americans who have not used COCs	114	24	240

* About 9% of hunter-gatherers reach age 60 and beyond (Howell, 1979).
** See Mann (1990) for a discussion of this relationship.
The computations used to derive this table are generated by a modification of Pike's model (Pike et al., 1983; Pike, 1987; see Appendix). The underlying assumptions are detailed in the original papers.

Eaton et al. 1994 *QRB*

SIMILARITIES OF PROSTATE AND BREAST CANCER: EVOLUTION, DIET, AND ESTROGENS

DONALD S. COFFEY

TABLE I. *Correlation coefficient of age-adjusted prostate cancer incidence with other cancers in 21 countries*

Cancer	Coefficient
Breast	0.81
Endometrium	0.78
Ovary	0.71
Colon	0.64
Rectum	0.40

Data adapted from Endocrinol Rev[4] *and* Cancer Causes Control.[5]

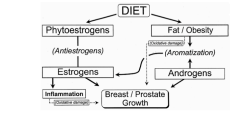


FIGURE 1. *Diet, fat, and hormones are combined in a unifying model indicating how they might affect the development of breast and prostate cancer. The diet, besides presenting carcinogens such as those formed in burned meat, also provides phytoestrogens, which can serve as weak antiestrogens affecting the hormonal status of the natural estrogens. Natural estrogens are made from aromatization of androgens that occur primarily in fat tissues. Fats also produce oxidative damage, as does inflammation, which is driven by estrogens. Phytoestrogens prevent the development of prostate inflammation.*

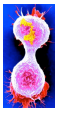
TABLE II. *Cancer comparison in the United States*

Feature	Breast	Prostate
Benign disease	High	High
Inflammation	Low?	High
Incidental cancer, microscopic (early onset)	High (yes)	High (yes)
Malignant cancer		
Incidence	184,200	180,400
Deaths	41,200	31,900
Deaths/incidence	0.22	0.18
Deaths/100,000 (age adjusted)	25.4	25.6
Lifetime risk	12.6%	19.8%
% Inherited	≈10%	≈10%
Gonads required	Yes	Yes
Metastasize to bone	High	High
Osteoblastic	Moderate	High
Hormonal therapy	Yes	Yes

Data adapted from Cancer Facts and Figures, 2000.[3a]

Urology 2001

Evolutionary biology of cancer



SEVEN PRINCIPLES OF EVOLUTION & CANCER

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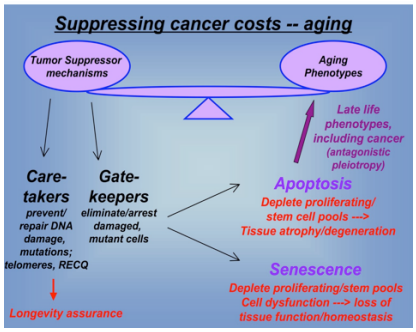
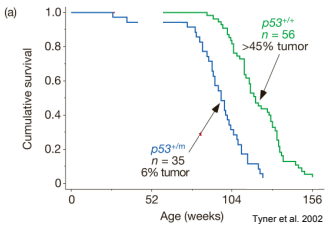
(7) Cancer cell populations evolve in response to therapies

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



Judy Campisi, UC Berkeley

Cancer risk trades off with aging in mice



p53 alleles in this mouse strain:

\+ = wild type
\- = loss of function
m = mutation

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: Tradeoffs between cancer risk and risks of neurodegenerative diseases

Schizophrenia, Huntington's, Parkinson's, Alzheimer's

Abstract: Cancer and neurodegeneration are often thought of as disease mechanisms at opposite ends of a spectrum; one due to enhanced resistance to cell death and the other due to premature cell death. There is now accumulating evidence to link these two disparate processes. An increasing number of genetic studies add weight to epidemiological evidence suggesting that sufferers of a neurodegenerative disorder have a reduced incidence for most cancers, but an increased risk for other cancers. Many of the genes associated with either cancer and/or neurodegeneration play a central role in cell cycle control, DNA repair, and kinase signalling. However, the links between these two families of diseases remain to be proven. In this review, we discuss recent and sometimes as yet incomplete genetic discoveries that highlight the overlap of molecular pathways implicated in cancer and neurodegeneration.

Genetic basis:

PARK2
APC
TP53
ATM, etc etc
->identify pathways

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

Hélène Plun-Favreau[1]*, Patrick A. Lewis[1], John Hardy[1], L. Miguel Martins[2], Nicholas W. Wood[1]*
1 Department of Molecular Neuroscience, UCL Institute of Neurology, London, United Kingdom, 2 Cell Death Regulation Laboratory, MRC Toxicology Unit, Leicester, United Kingdom

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

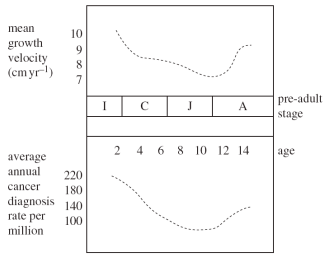


Figure 2. The pattern of changes in human growth velocity (adapted from [48]) over the pre-adult period, in comparison to age-specific incidence of all paediatric cancers (adapted from data in [49]).

SELECTION ON TRADEOFFS:

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

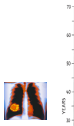
Rapid cell proliferation

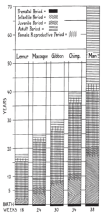
DNA repair

Apoptosis

Senescence, Lifespan

Cancer risk, rates



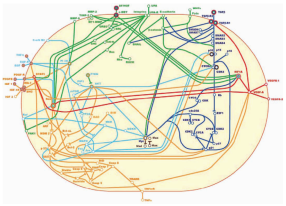


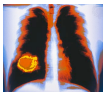
Placenta as 1° genetic & developmental source of hallmarks of cancer;
Co-option of placentally expressed pathways

Molecular circuits shared by placental and cancer cells, and their implications in the proliferative, invasive and migratory capacities of trophoblasts

Ferretti et al. 2006
Hum Rep Update

C.Ferretti[1,2], L.Bruni[1,2], V.Dangles-Marie[1], A.P.Pecking[3] and D.Bellet[1,3,4]





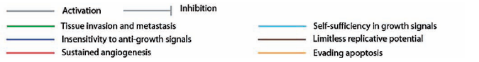


Figure 3. Schematic map of major signalling pathways (molecular circuitries) that may be shared by both trophoblastic and malignant cells so as to acquire six traits important for malignant growth: tissue invasion and metastasis (green), insensitivity to growth-inhibitory (antigrowth) signals (dark blue), sustained angiogenesis (red), self-sufficiency in growth signals (light blue), limitless replicative potential (brown) and evasion of programmed cell death (apoptosis) (orange) (Hanahan and Weinberg, 2000; Hahn and Weinberg, 2002). This figure simplifies complex interacting regulatory networks. Casp, caspases; CDK, cyclin-dependent

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

The *SPANX* gene family of cancer/testis-specific antigens: Rapid evolution and amplification in African great apes and hominids

Natalay Kouprina[1], Michael Mullokandov[1], Igor B. Rogozin[2], N. Keith Collins[3], Greg Solomon[3], John Otstot[3], John I. Risinger[4], Eugene V. Koonin[2], J. Carl Barrett[4], and Vladimir Larionov[1,4]

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.

'**HIJACKING' of gene expression, functions, networks** → sperm function
→ cancer risk

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

-Placentation

-Male germ cell proliferation (cancer/testis antigens)

Stem cells

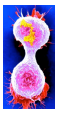
Childhood growth systems (IGF2, other genes) trade off with cancer risk

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

Evolutionary biology of cancer



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Box 2. Optimal tissue architecture for cancer suppression

Recent theoretical studies have suggested crucial roles for three different aspects of tissue architecture in controlling the initiation and progression of cancer via mutated gatekeeper and caretaker genes [75–81].

First, the separation of tissues into long-lived rarely dividing stem cells and short-lived transit cells might represent an important anticancer adaptation [75]. Such separation might enable transit cells to be removed (i.e. shed) before they accumulate enough mutations to become cancerous. The division of cells into compartments consisting of stem cells and differentiated cells, with gradual replacement of differentiated cells, creates a 'linear process' that might have evolved as a mechanism to reduce the risk of cancer [75].

Second, theoretical analyses indicate an optimal stem cell:transit cell ratio within compartments [76]: too high a ratio increases the risk of dangerous mutations accumulating in stem cells, whereas too low a ratio decreases the ability of the stem cells to replace mutant transit cell lineages within compartments. Cancerous mutations are also more likely in longer stem-cell lineages [77], a problem that could be ameliorated via two hypothesized means of tissue renewal [78]: (i) a pool of quiescent proto-stem cells might contain a single dividing cell to replace each lost transit cell lineage, with the dividing stem cell replaced by a new cell from the pool [78]; and (ii) a compartment could be divided into a hierarchical series of stages, with an ultimate stem cell lineage that rarely divides and a series of lineages descending from it that divide with progressively greater frequency [78].

Third, the separation of tissues into different compartments also limits the initial spread of cancer clones, and the number of cells in compartments has conflicting influences on the within-compartment fixation of gatekeeper and caretaker genes [79–81]. In large compartments, caretaker mutations are at a competitive disadvantage owing to the negative effects of genomic instability, but gatekeeper mutations that enhance cellular replication can increase in a deterministic fashion (Figure Ia). By contrast, in small compartments, caretaker mutations might more easily be fixed by drift, and gatekeeper mutations are more readily lost (Figure Ib). Depending upon the parameters of the models, there might be an optimal compartment size that minimizes the local risk of cancer [81].

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

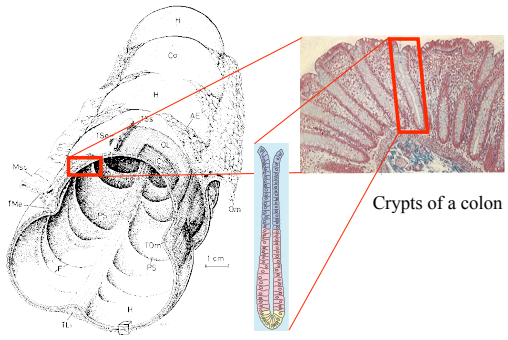
(4) cell division primarily in early fetal development, in relatively protected conditions

(5) cellular senescence and apoptosis in response to DNA damage

(6) immunosurveillance

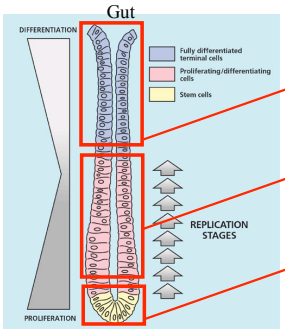
Crespi & Summers 2005, *TREE*

Colon tissue architecture



Crypts of a colon

Colon tissue crypt architecture

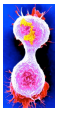


Differentiated cells get shed off into the lumen

Proliferating cells divide symmetrically and differentiate

Stem cells replenish the tissue; asymmetric divisions

Evolutionary biology of cancer



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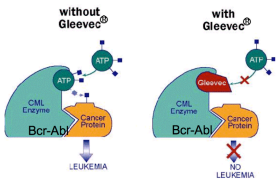
Traditional vs Targeted cancer drugs

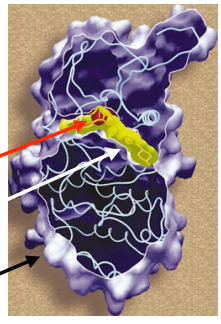
-Traditional drugs: very toxic agents that kill all dividing cells

-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 *Mutation*



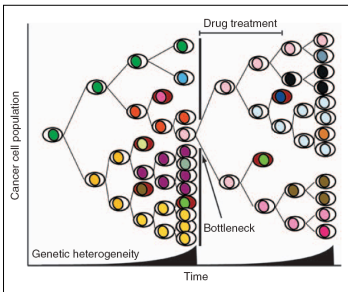


Figure 1 Schematic view of tumour heterogeneity during tumour progression and treatment. Acquired mutations in daughter cells of a single founder cell (left) promote diversion into subclones (different colours reflect different clones). Some new mutations lead to accelerated growth (for example yellow and orange clones). Fitness reducing mutations lead to negative selection (cells with brown cytoplasm). Drug treatment leads to selective survival of a drug resistant clone (pink) and generates an evolutionary bottleneck that reduces genetic heterogeneity transiently. Heterogeneity is re-established rapidly through acquisition of mutations by daughter cells of the resistant clone.

Genetic, epigenetic cytogenetic clonal heterogeneity evolve during carcinogenesis

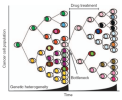
Drug treatments select for *resistant clones*, via different routes

Cancer may undergo remission, but recurs

Metastasis & resistance cause death

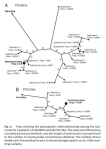
Gerlinger & Swanton 2010
Br J Cancer

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:
  - Point mutations in the kinase domain of BCR-ABL – *Gorre & Sawyers. Curr. Opin. Hematol. 9:303-7 (2002)*
  - Mutation present before therapy – *Roche-Lestienne & Preudhomme. Sem. Hematol. 40:80-2 (2003)*
- **Gefitinib** resistance:
  - EGFR mutation – *Kobayashi et al. NEJM 352:786-92 (2005)*
  - MET amplification – *Engelman et al. Science 316:1039-43 (2007)*
- **5-fluorouracil** resistance: TYMS amplification –
  - *Wang et al. PNAS 101:3089–3094 (2004)*

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 (**!**)

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