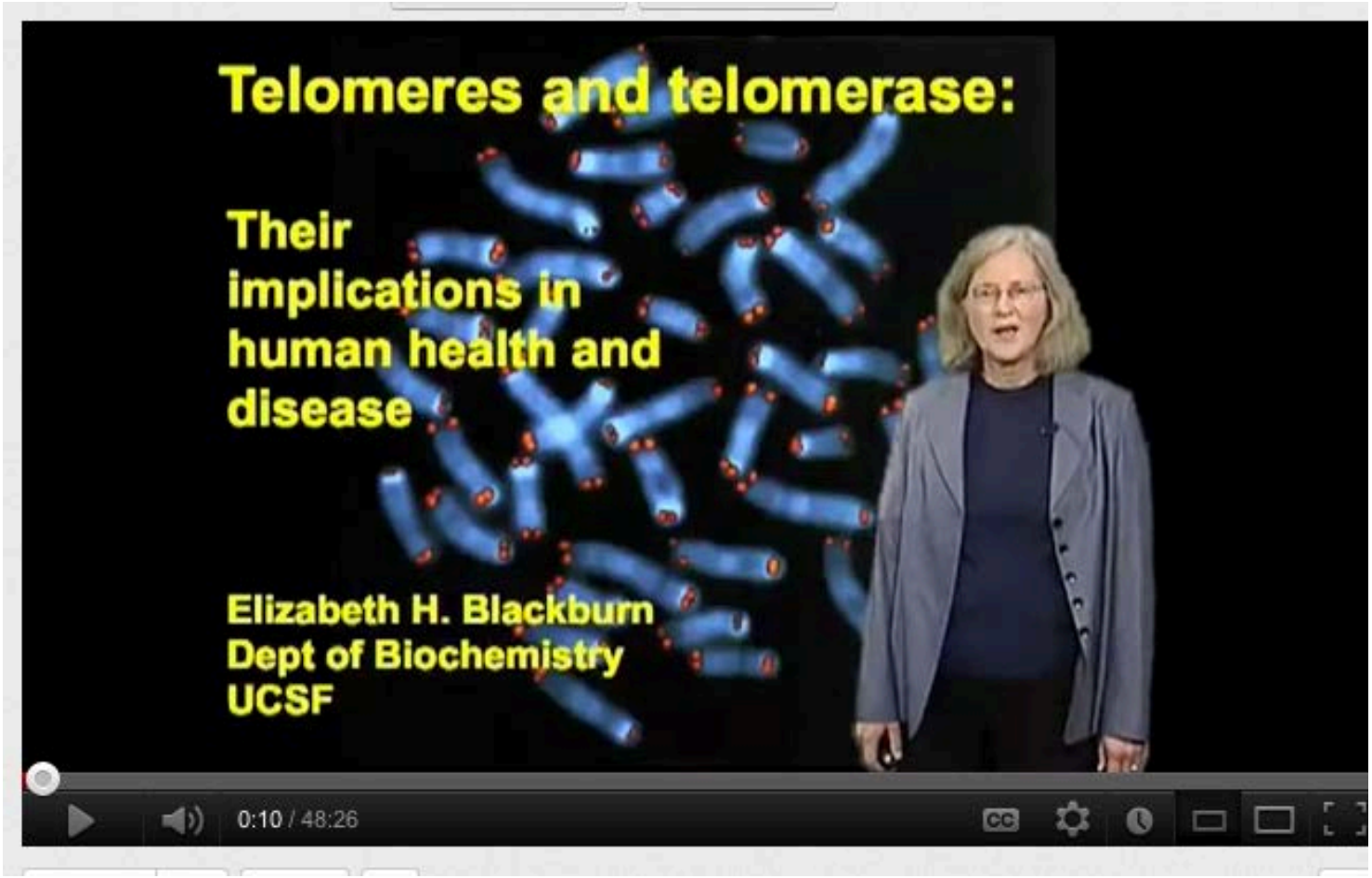


http://www.youtube.com/watch?v=5PU_jZwt8KY&feature=related

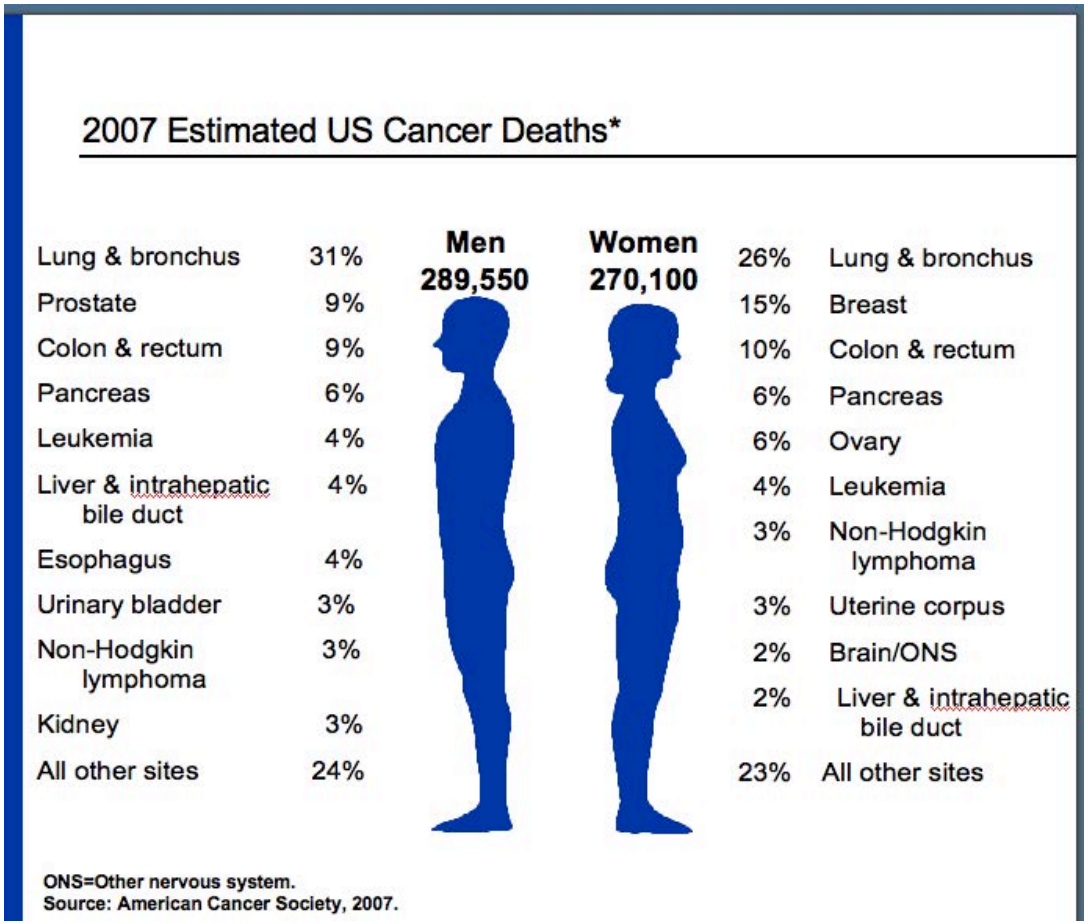
OPTIONAL

Inside cancer web site
http://www.insidecancer.org/
National Cancer Institute
http://www.cancer.gov/cancerinfo/

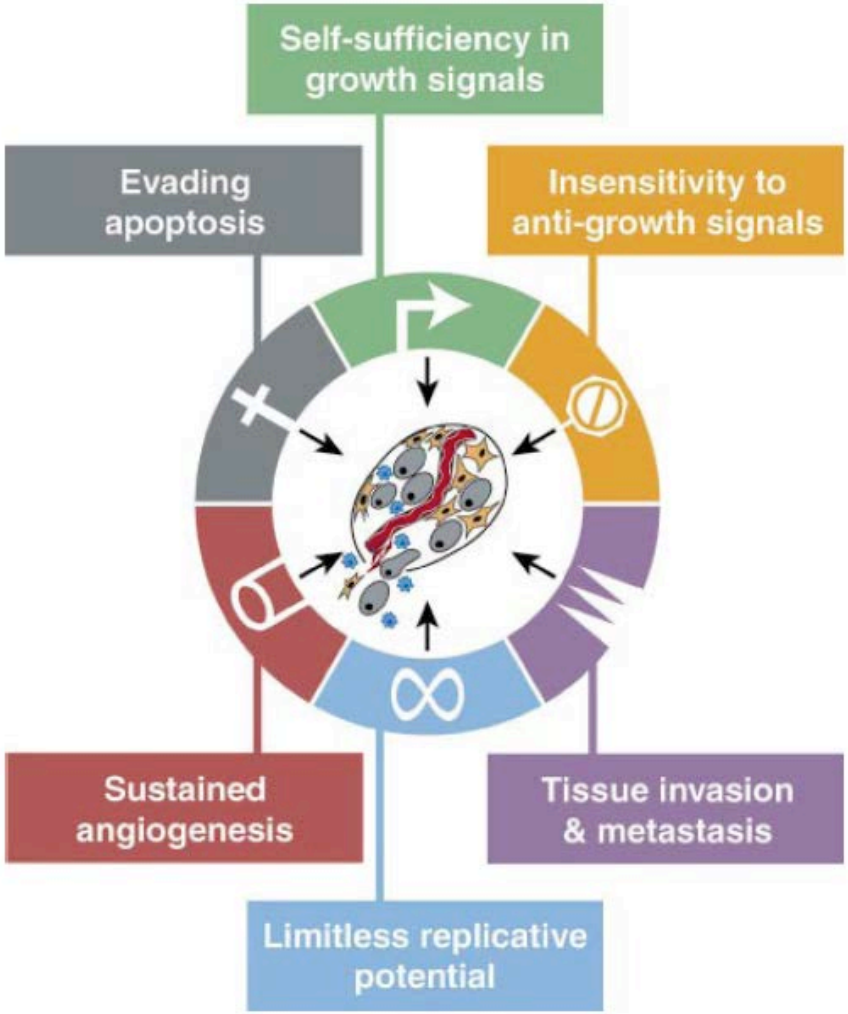
- *An adult human has somewhere around one hundred trillion* (10^{14}) *cells*
- *Metazoan tissue and organ function depend absolutely on the ability of cells to properly interact and communicate with each other*
- *In other words, somatic cells exist in a "social" setting where they need to be responsive to cues from neighboring cells*
- *Cancer cells can be thought of a rogue cells that no longer obey the rules of the social contract*

CANCER is an umbrella term used to describe a plethora of conditions characterized by unscheduled and uncontrolled cellular proliferation

These changes are due to genetic changes-mutations in genes that control these processes -- or epigenetic changes involving heritable changes in the expression of a gene



Cancer cells break most of the rules of the somatic cell "social contract"



Most, but not all cancers have acquired the same set of functional capabilities during their development, albeit through different various mechanistic strategies

Cell, Vol. 100, 57–70, January 7, 2000

See hallmarks of cancer under this link
http://www.insidecancer.org/

Cancer cells differ from normal cells in the following ways (from previous page)

1. The cells mutate so that they can dodge the cellular signals that suppress growth [or that encourage suicide of genetically abnormal cells]

2. The cells acquire their own growth-signaling pathways, independent of the external signals that normal metazoan cells are dependent on

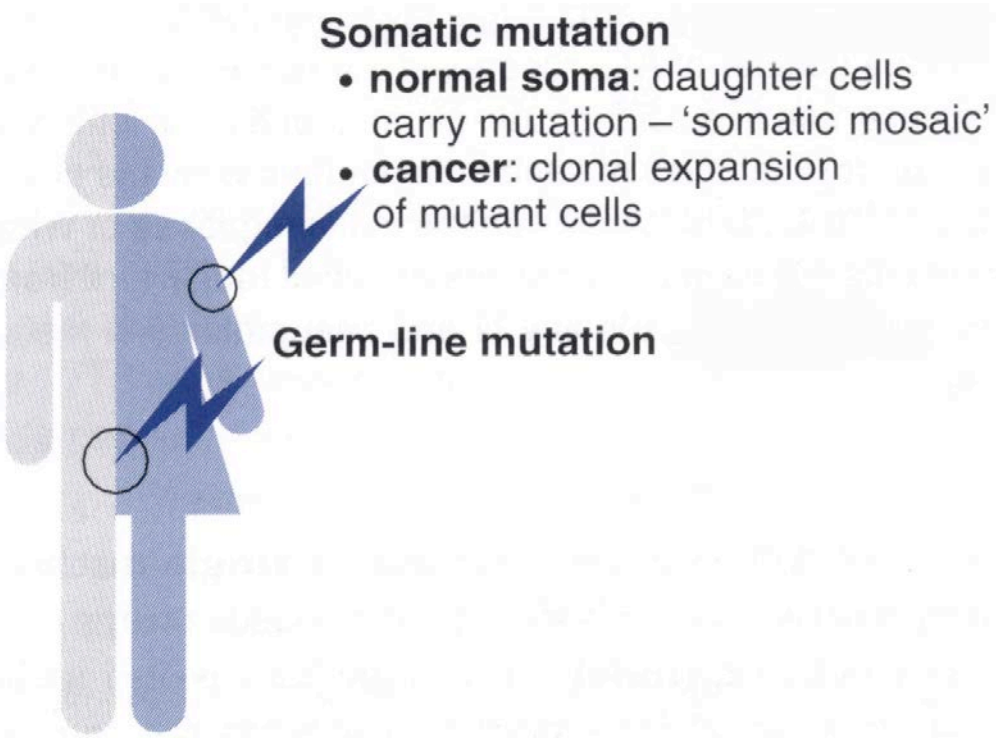
3. They develop limitless potential to proliferate: normal cells can divide only about 40-60 times before their ***telomeres*** (huh?) become so shortened that the chromosomes are damaged and the cell dies

http://learn.genetics.utah.edu/content/begin/traits/telomeres/
http://www.youtube.com/watch?v=AJNoTmWsE0s
http://www.youtube.com/watch?v=5PU_jZwt8KY&feature=related

4. Solid tumor cells create their own network of blood vessels *(to supply the growing monster with food and oxygen)*

5. Finally the most dangerous tumor cells are those that can travel to distant sites in the body (metastasis). Nine of ten cancer deaths result from metastases.

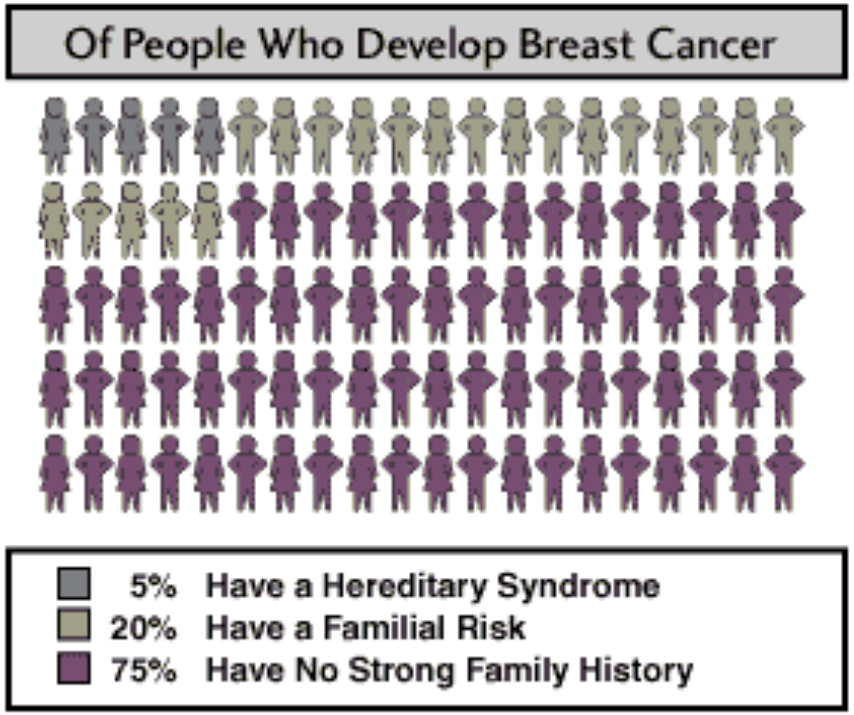
Cancer typically results from *stochastic*, *somatic cell mutations* in genes that govern and regulate the diverse aspects of growth control in multicellular organisms



- **Somatic mutations are *of course* inherited by all of the clonal descendants of the mutated cell**
- **But only germline mutations are transmitted to next-generation progeny**

Sporadic, Hereditary & Familial Cancers

http://www.geneticheath.com/G101_Hereditary_vs_Sporadic_Cancer.shtml



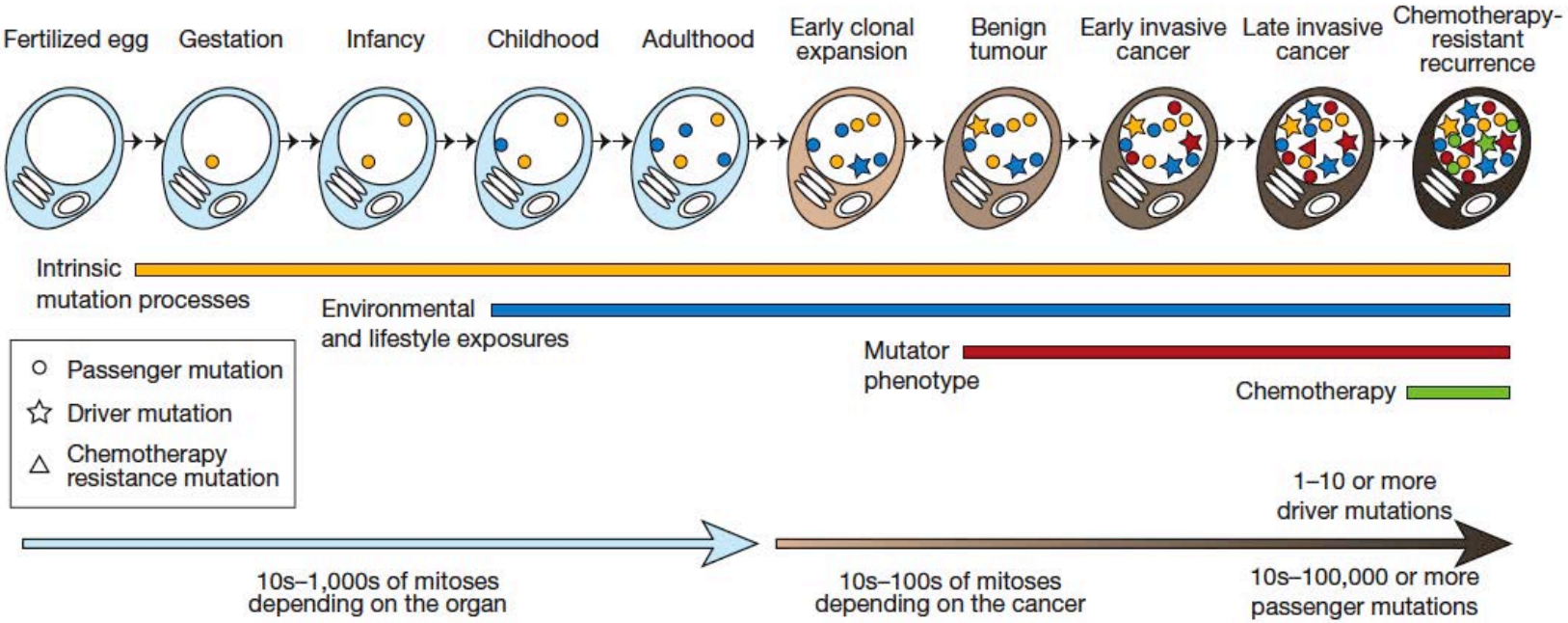
In sporadic cancer only the tumor cells have the relevant mutations. In a hereditary cancer, every cell in the body has the predisposing mutation

Most cancers are Sporadic -- no ***inherited*** cancer-causing (or predisposing) mutations are involved

Hereditary – a cancer-predisposing mutation *of strong effect is inherited* (and is present in every cell of the body); additional somatic mutations must occur before a cell becomes cancerous *(recall our discussion of retinoblastoma and breast cancer in individuals who have inherited a BRCA1 or BRCA2 mutation) [SEE also last few pages of this lecture]*

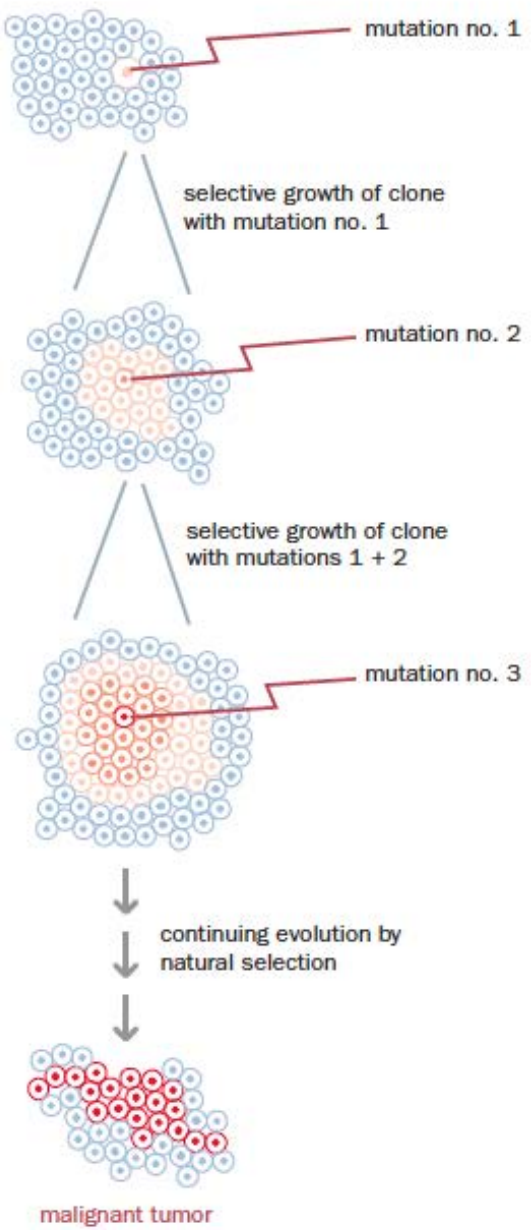
Familial – a mutation conferring a *slightly increased* cancer risk is inherited (and is present in every cell of the body); additional somatic mutations must occur before a cell becomes cancerous

The lineage of mitotic cell divisions from the fertilized egg to a single cell within a cancer showing the timing of the somatic mutations acquired by the cancer cell and the processes that contribute to them.



NATUREjVol 458j9 April 2009

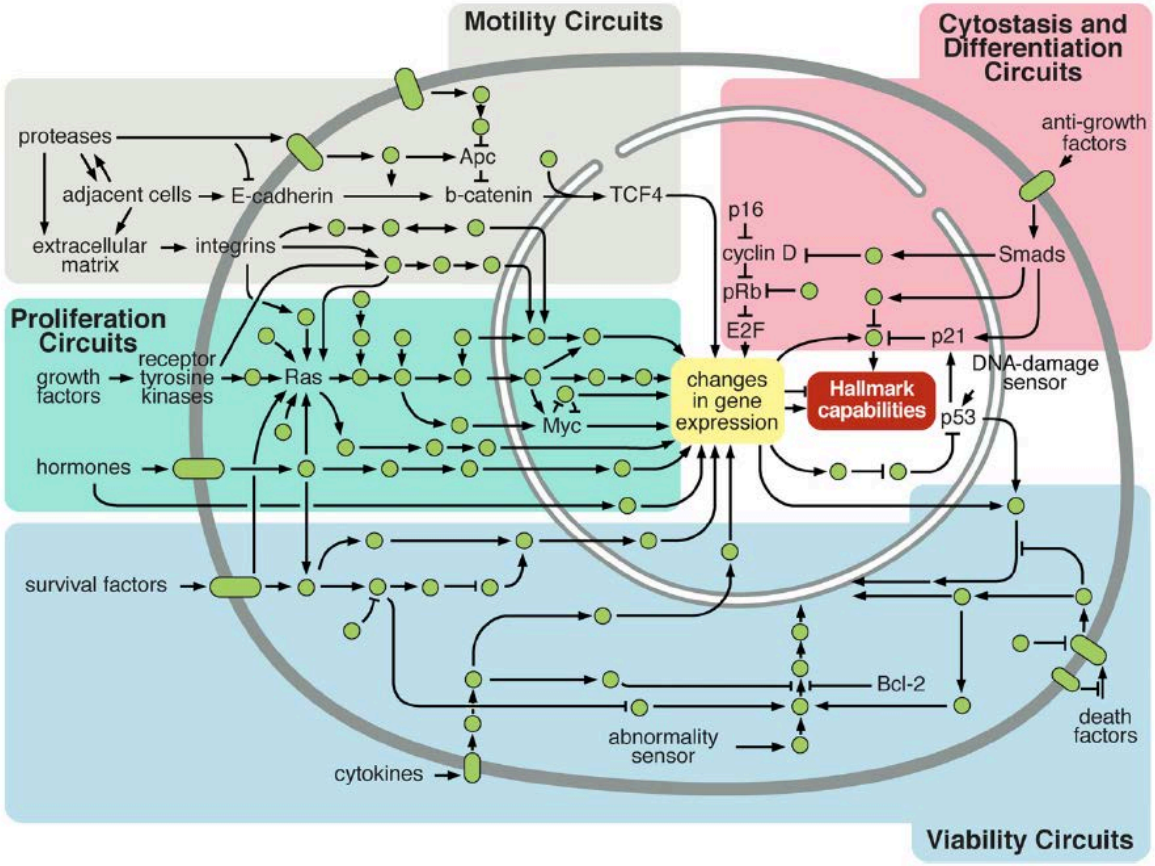
- Mutations may be acquired while the cell lineage is phenotypically normal, reflecting both the intrinsic mutations acquired during normal cell division and the effects of exogenous mutagens.
- During the development of the cancer other processes, for example DNA repair defects, may contribute to the mutational burden. ***Passenger mutations*** do not have any effect on the cancer cell, but ***driver mutations*** will cause a clonal expansion.
- Relapse after chemotherapy can be associated with resistance mutations that often predate the initiation of treatment.



Mutations in so-called driver genes confer selective growth advantage on cells

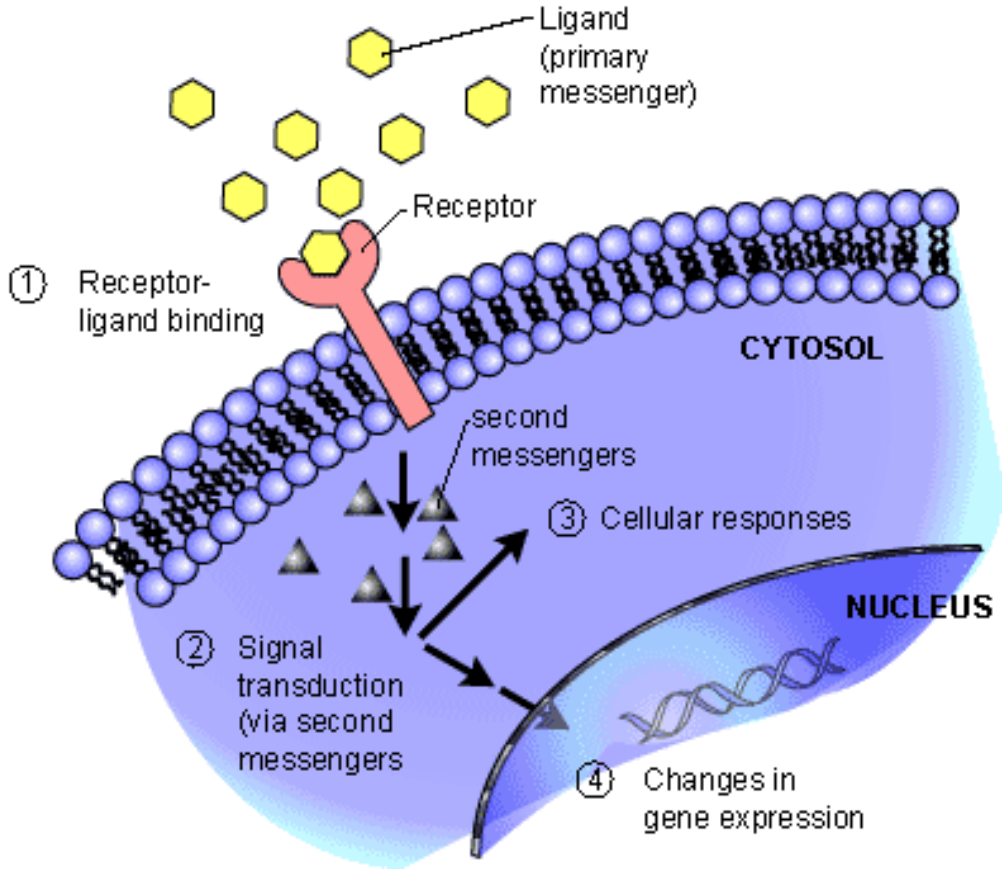
A tumor develops through repeated rounds of mutation and proliferation, giving rise eventually to a clone of fully malignant cancer cells.

The figure on the left shows the multi-stage evolution of cancer. Each successive mutation gives the cell a growth advantage, so that it forms an expanded clone, thus presenting a larger pool of targets for the next mutation



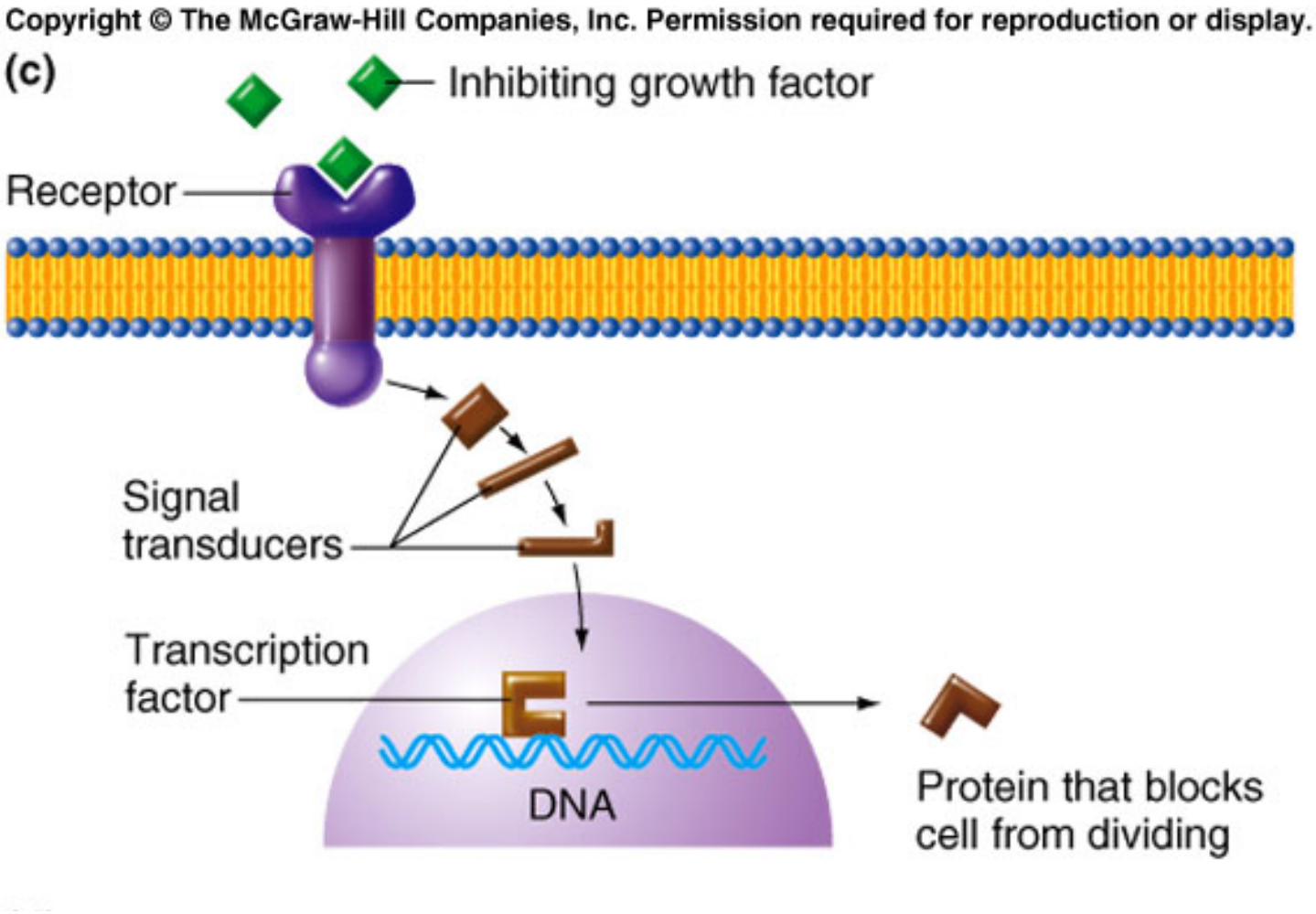
Intracellular Signaling Networks Regulate the Operations of the Cancer Cell

An elaborate integrated circuit operates within normal cells and is reprogrammed to regulate hallmark capabilities within cancer cells. Separate subcircuits, depicted here in differently colored fields, are specialized to orchestrate the various capabilities. At one level, this depiction is simplistic, as there is considerable crosstalk between such subcircuits. In addition, because each cancer cell is exposed to a complex mixture of signals from its microenvironment, each of these subcircuits is connected with signals originating from other cells in the tumor microenvironment. **Cell 144, March 4, 2011**

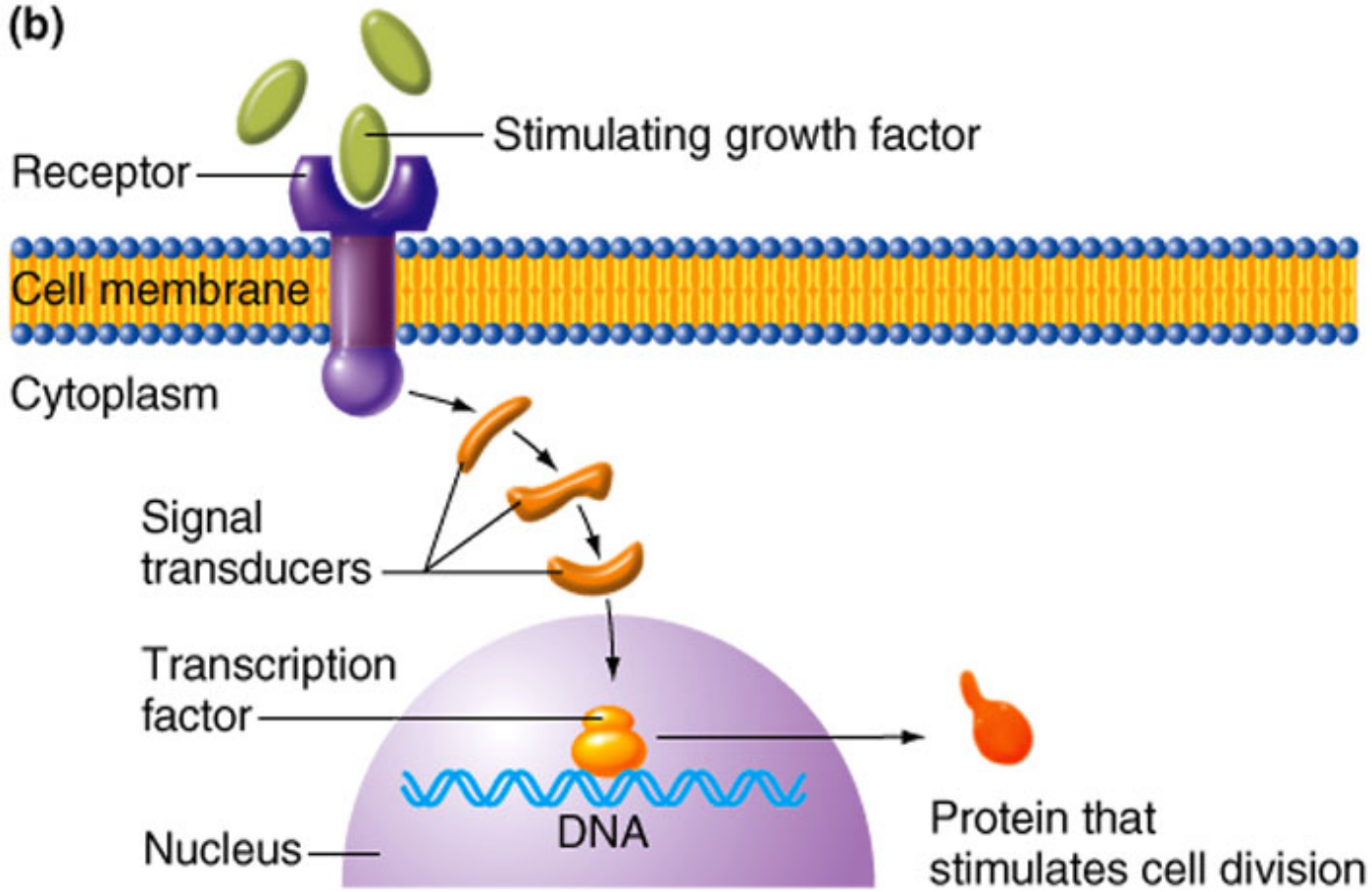


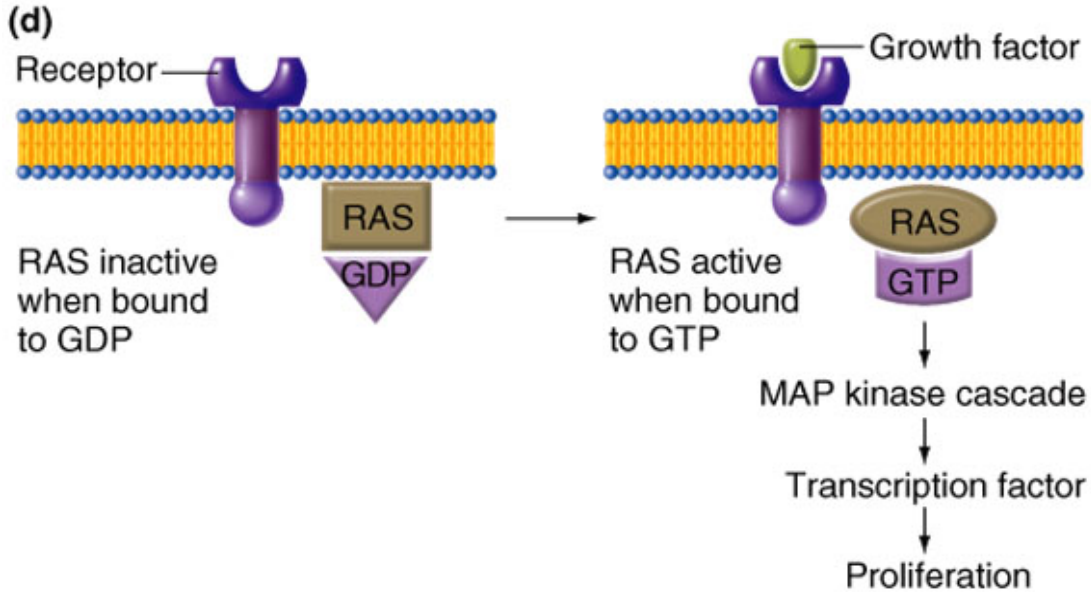
As shown in the previous figure, the rate of cell proliferation is controlled by growth promoting and growth inhibiting signal transduction pathways

What would be the effect of *loss-of-function* mutations in a growth inhibiting pathway?



What would be the effect of *loss-of-function* mutations in a growth promoting pathway?

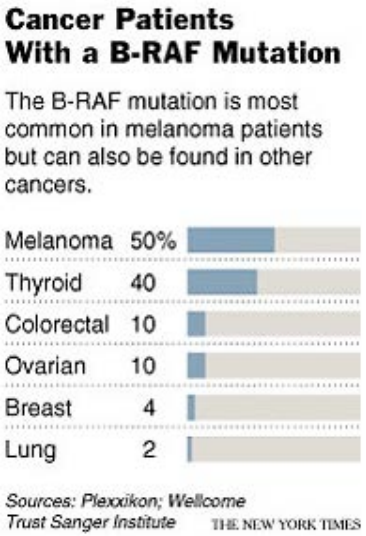




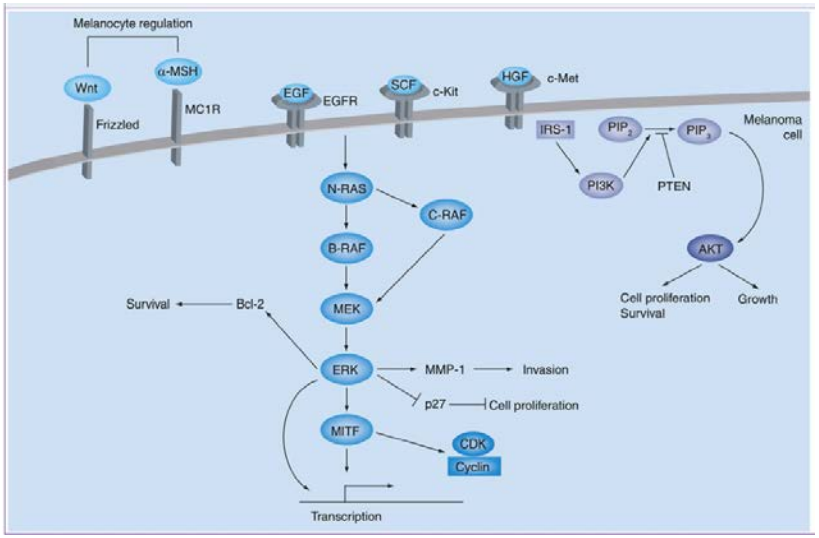
How then can mutations in a growth promoting pathway result in increased cellular proliferation?

Loss-of-function	*Gain-of-function*
• partial or complete loss of gene function	• increased level of wild-type gene product • altered function of protein: *unregulated activity of protein* • altered temporal or spatial expression of gene product
• common -- why?	• rare -- why?
• recessive or • dominant if gene is *haploinsufficient*	• dominant

TABLE 17.2 FOUR WAYS OF ACTIVATING (PROTO)-ONCOGENES		
Activation mechanism	**Oncogene**	**Tumor**
Amplification	*ERBB2* (*HER2*)	breast, ovarian, gastric, non-small-cell lung, colon cancer
	MYCN	neuroblastoma
Point mutation	*HRAS*	bladder, lung, colon cancer, melanoma
	KIT	gastrointestinal stromal tumors, mastocytosis
Chromosomal rearrangement creating a novel chimeric gene	*BCR–ABL1*	chronic myeloid leukemia (see also Table 17.3)
Translocation to a region of transcriptionally active chromatin	*MYC*	translocation to immunoglobulin heavy chain locus by t(8;14) in Burkitt lymphoma



Gain of function mutations in the BRAF oncogene are common in melanomas



See last two pages of lecture for therapeutic approaches to cancers with B-RAF mutations

- *BRAF is a protein kinase involved in the transduction of mitogenic signals from the cell membrane to the nucleus*
- *It should be "inert" until activated via ras*
- *Like an accelerator stuck to the floor, gain-of-function missense mutations in the BRAF gene result in constitutive kinase function and*
- *The mutated protein continually stimulates cells to divide without the requisite upstream signal from ras*

http://www.bio.davidson.edu/courses/immunology/Flash/MAPK.html

In principle any gene can sustain a ***gain-of-function*** *mutation.*

As with ***loss-of-function*** *mutations, whether the mutations has a dramatic phenotype or any phenotype at all depends on*

- the role of the gene in the functioning of the organism
- the sensitivity of the cell (or organism) to alterations in dosage of the gene product

Dosage levels might be especially important for:

- Genes that regulate developmental processes
- Genes that regulate cell division
- Genes that regulate physiological processes
- Any gene whose level of expression is very carefully controlled: such as an enzyme that performs a rate limiting step in an enzymatic reaction

Why is it important to make the distinction between *gain-of-function* versus *loss-of-function* mutations?

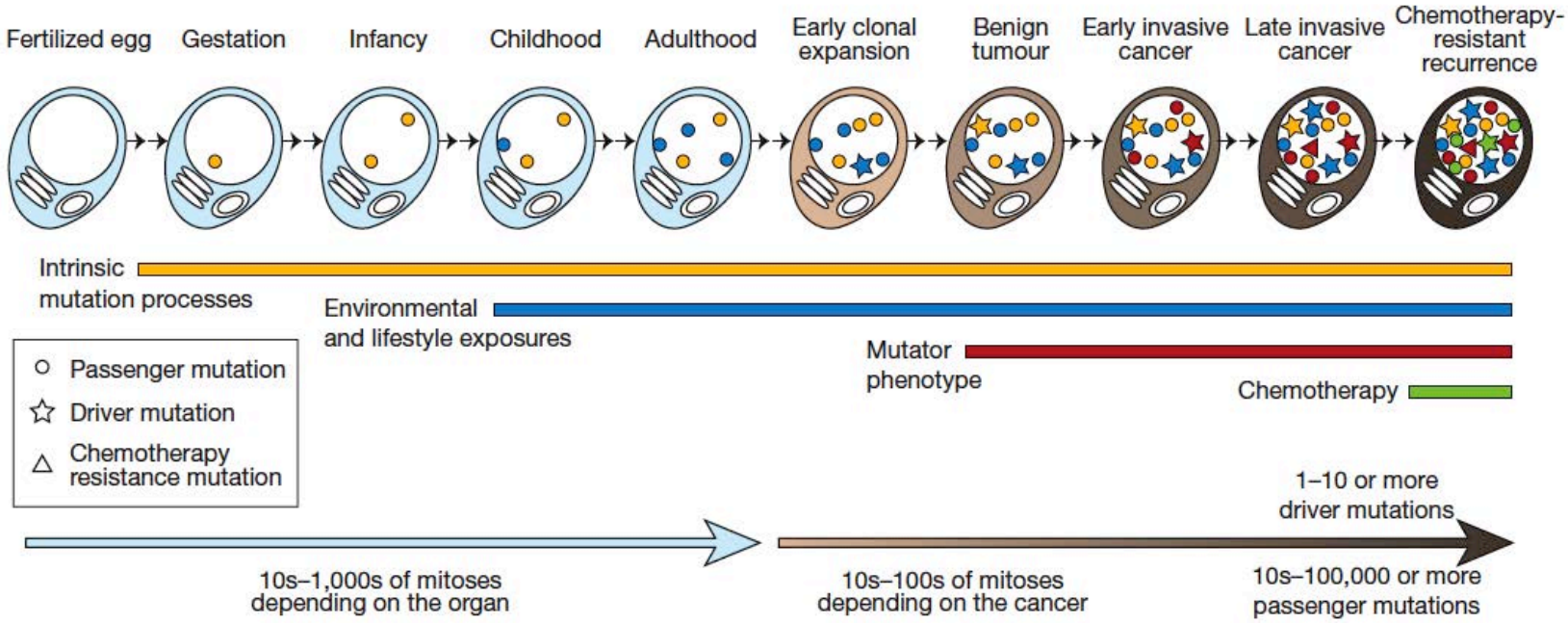
- ***Must know if a mutation is a LoF or GoF*** if you want to infer the role of the gene in the organism from the mutant phenotype

- If you want to use gene therapy to correct a genetic defect in humans, must know if the mutation results in gain or loss-of-function

- Many other reasons including predicting the phenotypic effects of mutations at the molecular/biochemical/physiological level

In addition to genes that function in growth promoting and growth inhibiting pathways, a third category of genes (not directly controlling rate of cell division) is mutated in cancer cells:

What kinds of genes might result in the mutator phenotype?



*guardians of the genome**

What specific roles would these genes have?

** These genes are sometime referred to as "mutator" genes. In this case, the gene name refers to the phenotype resulting from a loss-of-function mutation*

→ Mutations in the DNA replication and repair machinery

→ Mutations in the feedback control machinery that prevents the cell from progressing through the cell cycle with damaged DNA

→ Mutations in the machinery that direct a cell to undergo programmed cell death if its genome is severely damaged

With few exceptions cancers result from the accumulation of mutations in multiple genes in a clone of somatic cells—redo table to indicate dominance of LoF mutations*

** RETINOBLASTOMA IS ONE EXCEPTION – SEE TEXTBOOK AND ---- LECTURE NOTES*

Classes of genes mutated in cancer cells

	Proto-oncogenes (becomes oncogene when mutated)	**Tumor suppressor genes**	**Guardians of the genome**
Effect of normal gene on cell growth and division	Stimulates/ Activates	Inhibits/ Represses	No direct effect or indirect effect
Oncogenic mutation in gene	Gain-of-function increased or unregulated activity or expression of the gene or gene product (hyperactive gene or product)	Loss-of-function gene product is absent or its expression or activity is decreased	Loss-of-function
Genetic behavior of oncogenic mutation	Dominant One mutant allele is sufficient for the cancer phenotype	Recessive (dominant if gene is haploinsufficient)	Recessive
Phenotypic effect of oncogenic mutation	Increased stimulation of cell proliferation ↓ CANCER	Decreased inhibition of cell proliferation ↓ CANCER	Increased rate of mutation

Schematic Representation of the Evolution of Cancer in a Colonic Adenoma

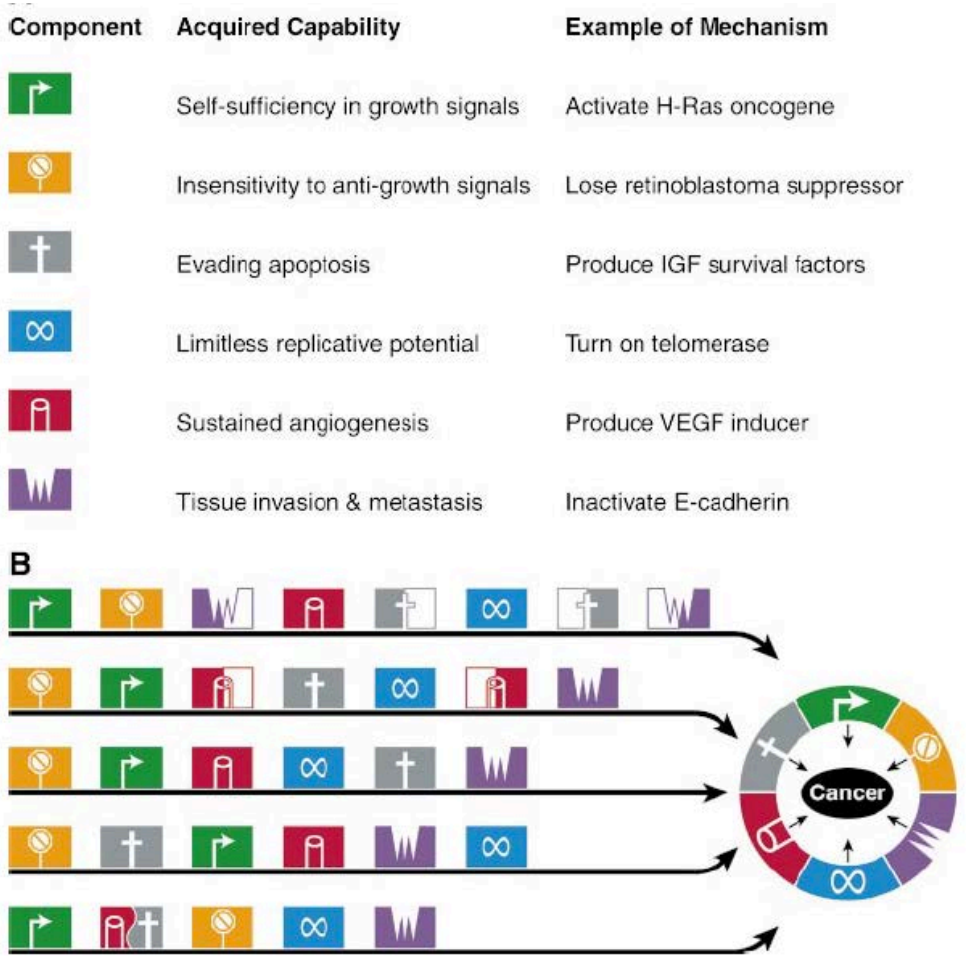
- *The adenoma grows from a population of 10^6 to 10^9 cells which accumulate mutations that drive the phenotypic changes seen in cancer cells*
- *Blue circles symbolize adenoma cells prior to accumulating the additional mutations that are the required for a typical colon cancer*
- *Green cells have acquire additional, but an insufficient number of mutations for malignancy*
- *Red indicates cells with the number of mutations required for the cancer phenotype*

What changes happen first?

- *What mutations are most important in the decades long transformation of a cell and its descendants from well-behaved tissue to invasive tumor?*
- *Is the order important? or just the accumulation of mutations?*

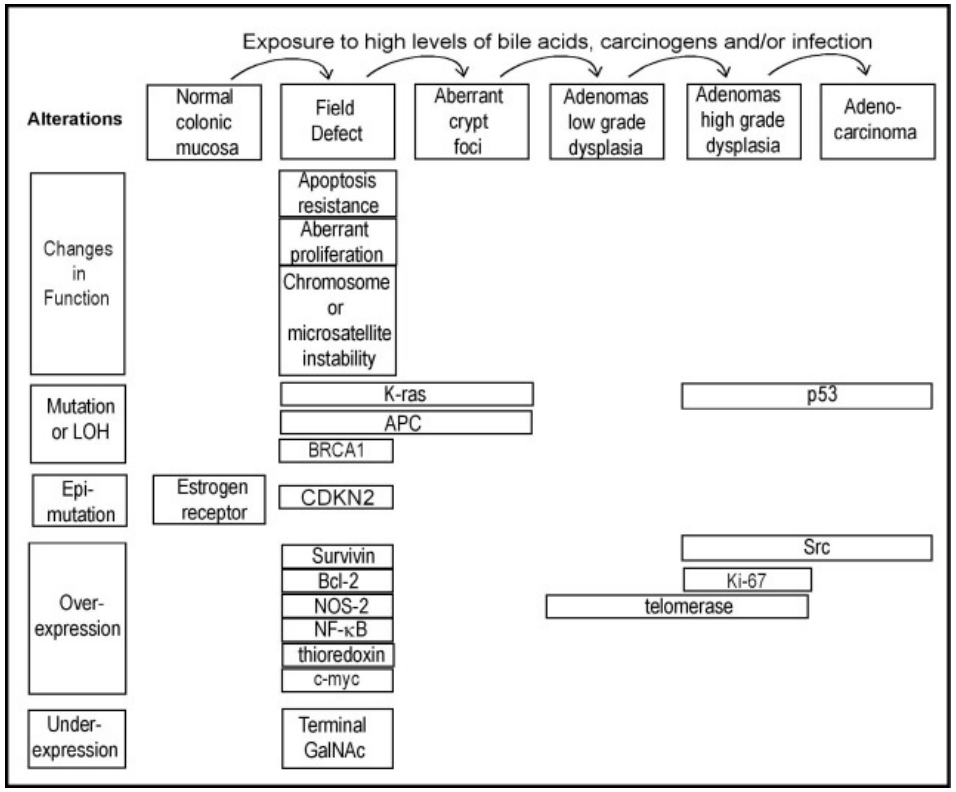
Parallel Pathways of Tumorigenesis

While we believe that virtually all cancers must acquire the same six hallmark capabilities their means of doing so will vary significantly, both mechanistically and chronologically (B). Thus, the order in which these capabilities are acquired seems likely be quite variable across the spectrum of cancer types and subtypes. Moreover, in some tumors, a particular genetic lesion may confer several capabilities simultaneously, decreasing the number of distinct mutational steps required to complete tumorigenesis. Thus, loss of function of the p53 tumor suppressor can facilitate both angiogenesis and resistance to apoptosis (e.g., in the five-step pathway shown), as well as enabling the characteristic of genomic instability. In other tumors, a capability may only be acquired through the collaboration of two or more distinct genetic changes, thereby increasing the total number necessary for completion of tumor progression. Thus, in the eight-step pathway shown, invasion/metastasis and resistance to apoptosis are each acquired in two steps.



Cell, Vol. 100, 57–70, January 7, 2000

Progression in sporadic colon cancer. Alterations are indicated at the stages in which they are first observed.



Loss-of-function = in this chart, LOH or Mutation
Gain-of-function = in this chart, Mutations (K-ras) or Overexpression

Epi-mutation = epigenetic change (ie in methylation of DNA and/or complex of DNA with histones) that effects the expression (transcription level) of a gene

untangling the roots of cancer: is the standard model always correct?

Diagrams like this mistakenly imply an inevitable progression towards cancer:

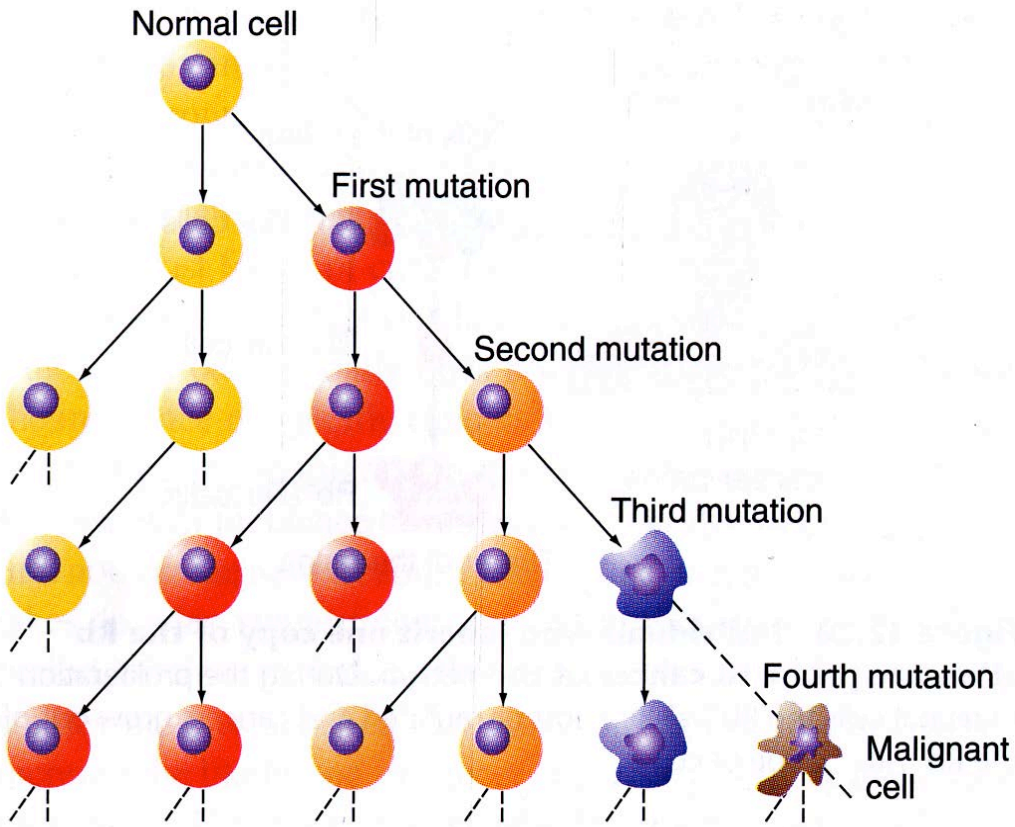
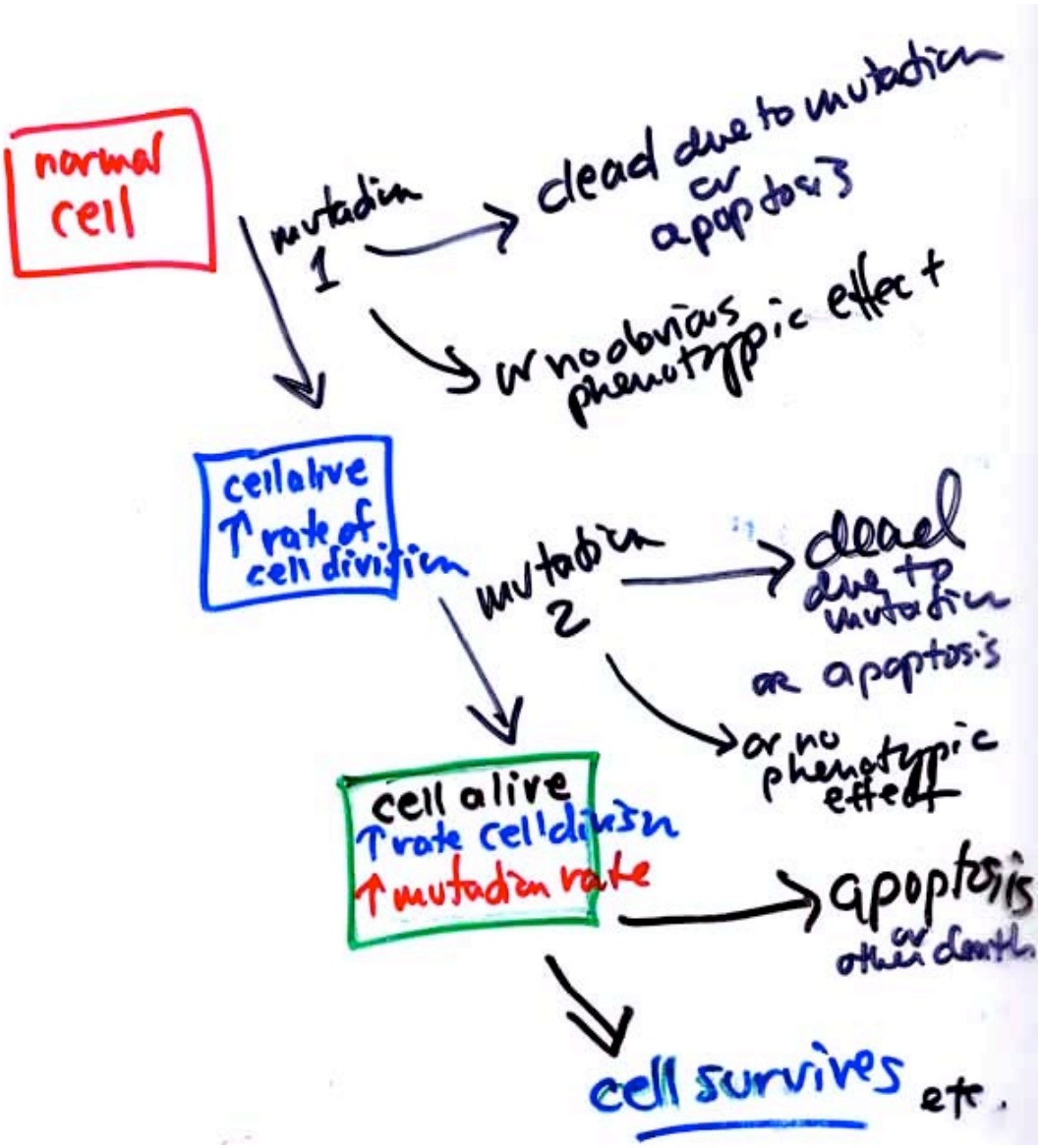


Figure 17.21 Cancer is thought to arise by successive mutations in a clone of proliferating cells.

Note: most mutations that a cell sustains will NOT hit a "cancer-causing" gene

Cancers seem to "progress" for the same reason the evolution of organisms seems to progress: *we only see the "successes" not the failures*


normal cell
mutation 1
dead due to mutation or apoptosis
or no obvious phenotypic effect
cell alive
↑ rate of cell division
mutation 2
dead due to mutation or apoptosis
or no phenotypic effect
cell alive
↑ rate cell division
↑ mutation rate
apoptosis or other death
cell survives etc.

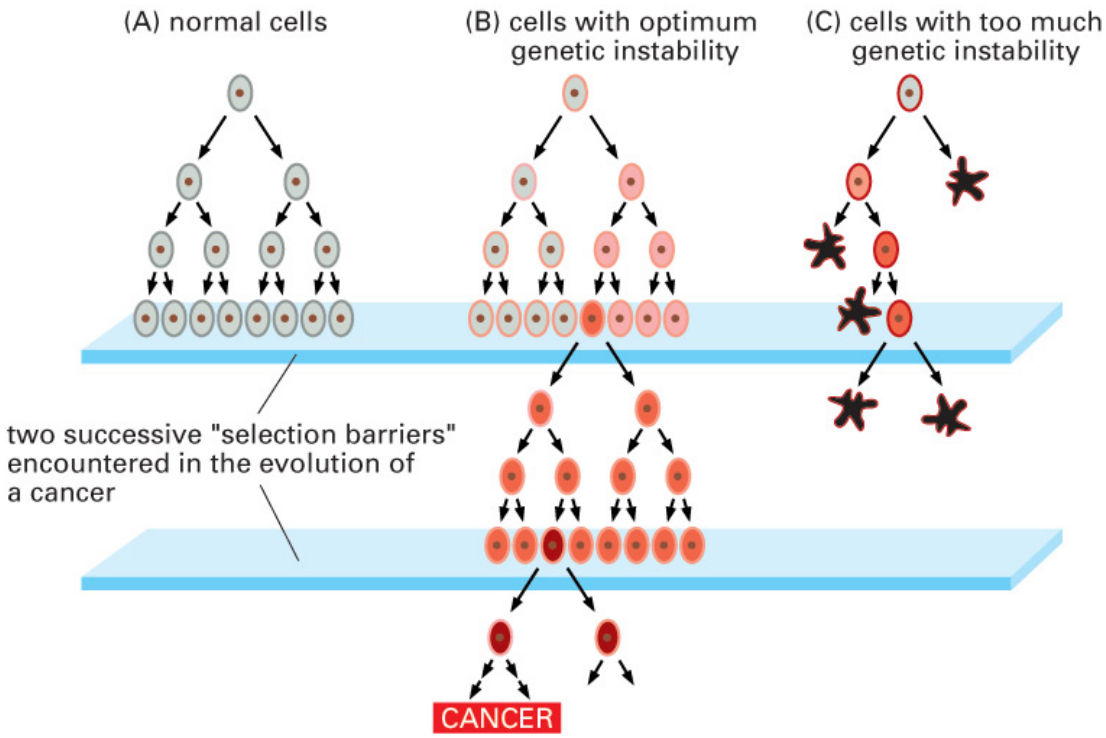


Figure 23–13. Molecular Biology of the Cell, 4th Edition.

Genetic instability and tumor production. Cells that maintain an "optimal" level of genetic instability may be the most successful in the race to form a tumor.

a) In normal cells, the intrinsic amount of genetic instability is low. When such normal cells hit a selection barrier --low levels of oxygen or a scarcity of proliferation signals, for example -- they are very unlikely to be mutable enough to produce a cell that continues to proliferate

b) In tumor cell precursors, an increased level of genetic instability makes it likely that at least one cell will contain the requisite genetic alteration to pass the selection barrier and continue the process of tumor progression. This genetic instability is retained in the lineage and can be measured in the resulting tumor.

c) If the level of genetic instability is too high, many of the cells suffer deleterious mutations and either proliferate more slowly than their neighbors or are eliminated by cell death. This excessive mutability can lead to extinction of the cell lineage.

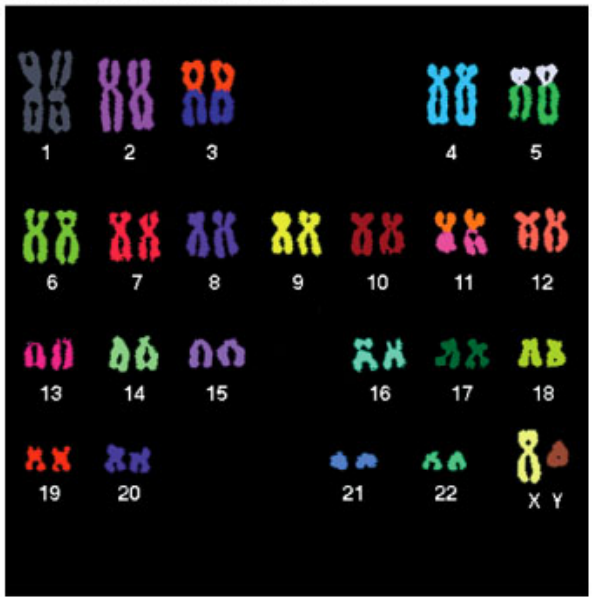
NOTE: same sort of logic can be applied to the high rate of mutation of many virus genomes

As articulated by a leading cancer researcher:

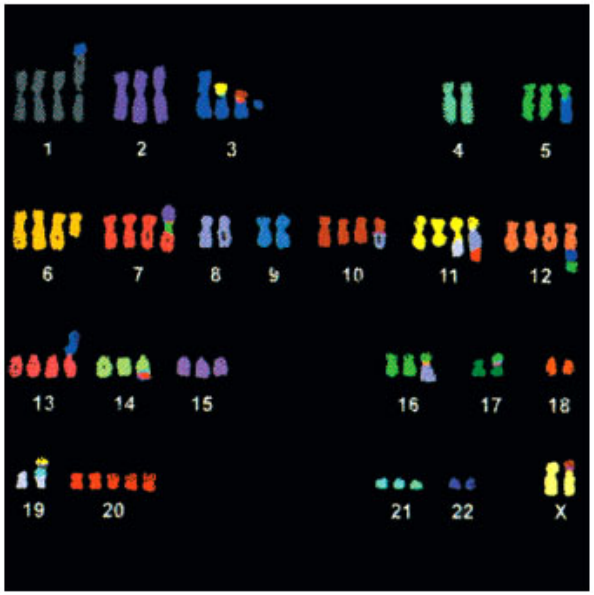
"If you look at most solid tumors in adults, it looks like someone SET OFF A BOMB in the nucleus"

Chromosome level mutations are common in cancer cells

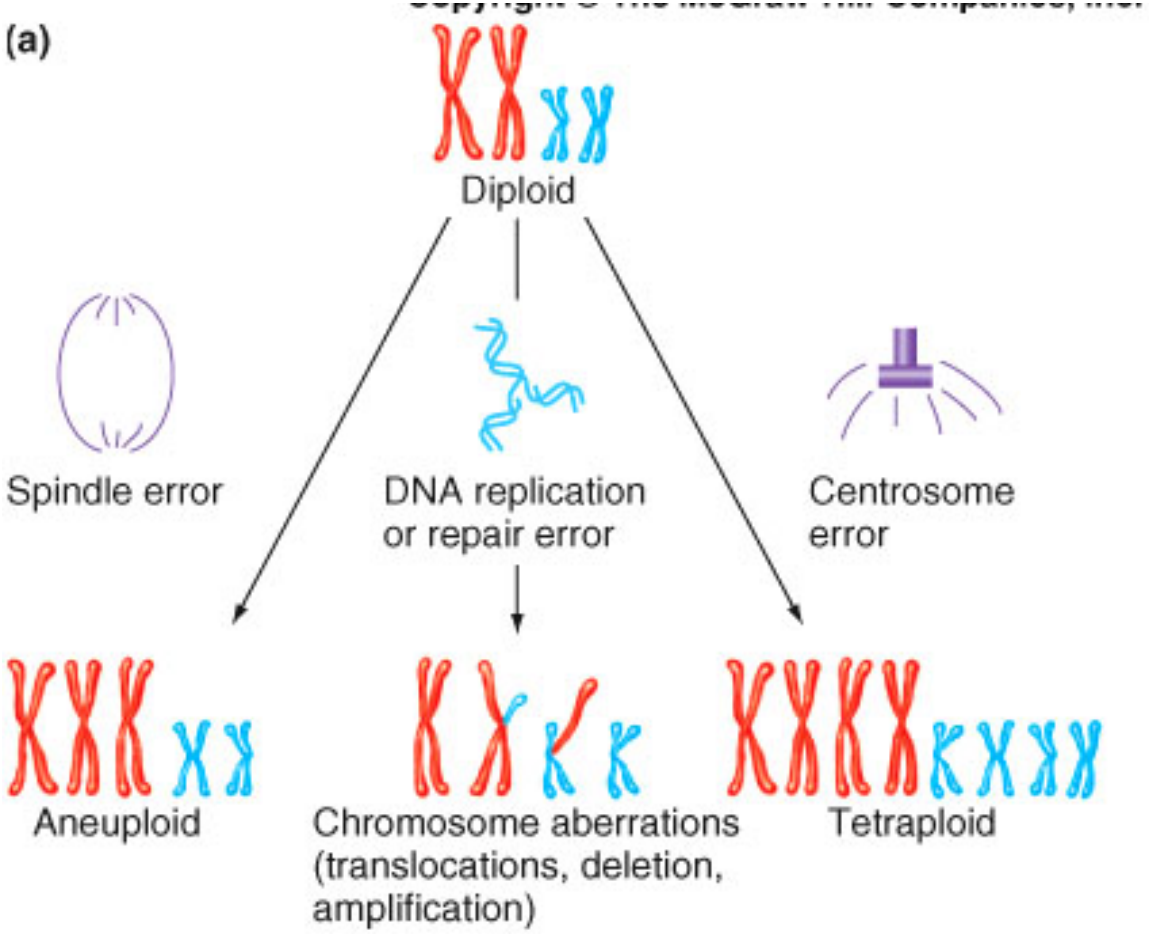
Spectral karyotyping via fluorescence *in situ* hybridization. Each chromosome is labelled with a different combination of fluorescent dyes (linked to chromosome specific sequences) and the final image is interpreted by software that colours each pixel to show which chromosome is most likely to be present at that point



TOP Panel:
Karyotype (chromosome display) of a normal cell



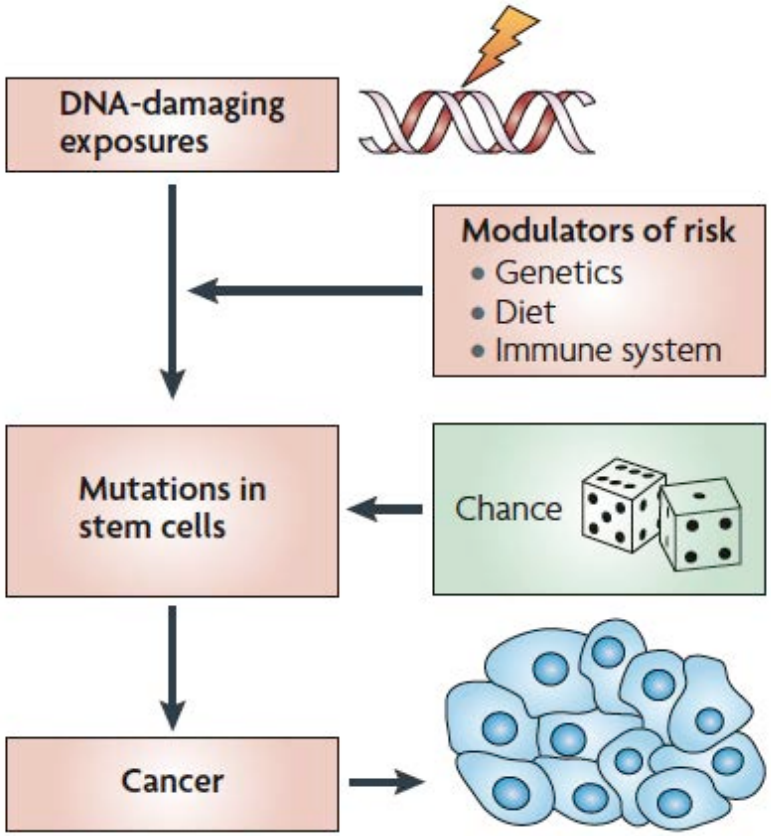
Bottom Panel:
a "bombed out" cancer cell



Three classes of errors that result in chromosomal aberrations in cancer cells:

1. Spindle errors can result in missegregation of chromosomes (non-disjunction)
2. Mistakes in DNA recombination, replication or repairs can result in large-scale chromosome mutations
3. Centrosome (MTOC) failure can result changes in cell ploidy

aneuploidy – abnormal number of individual chromosomes or chromosome segments



Themes we have seen before applied to the cancer "lottery"

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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 thereforeindiscriminate 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.

MOST cancers are sporadic: in other words are NOT due to an INHERITED mutation

Inherited cancer syndromes: families with several cases of common cancers that fall into a recognized pattern of cancer types.

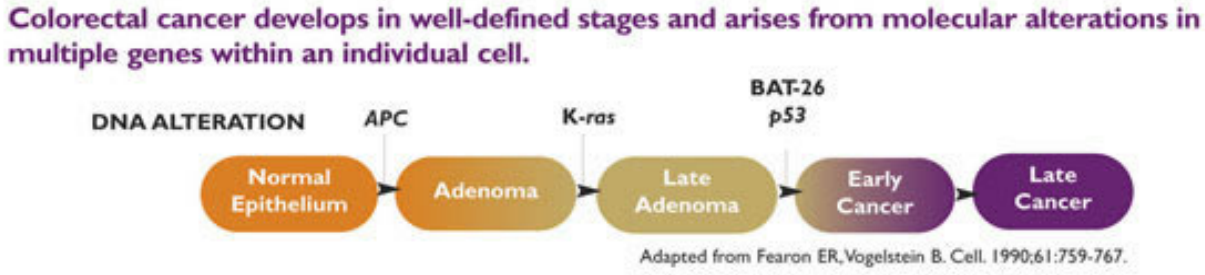
- *The spectrum of inherited cancers ranges from families with multiple cases at a young age to two to three cases at older ages.*
- *Individuals at risk for inherited cancer syndromes have received a predisposing mutation from one of their parents.*
- *These predisposing mutations are typically in guardians of the genome (see next page).*
- *In all cases additional somatic mutations must occur for the cancer "phenotype" to be expressed.*

Germline mutations (inherited from parent) predisposing individuals to cancer

Syndrome	DNA repair defect	Phenotype
Xeroderma pigmentosum	inability to repair bulky lesions that distort the DNA helix (such as UV-induced damage)	genome instability: point mutations skin cell death and skin cell cancers
Li Fraumeni syndrome (very rare) mutations in this gene also present in 50% of sporadic cancers	loss-of-function in p53 gene normal p53 gene function is to stop/slow progresion through the cell cycle in response to DNA damage and to stimulate apoptosis	multicancer syndrome: sarcomas, breast cancer, brain tumors
HNPCC	defect in post-replication mismatch repair	genome instability: point mutations colon cancer
BRCA 1 & 2	chromosome instability due to the inability to repair double-strand breaks in the DNA	genome instability: chromosome aberrations very high risk of breast cancer; increased risk of other cancers

➔ Even for a given type of cancer (i.e. colon or breast cancer), the specific genes mutated can differ from person to person although often there is a common set of genes altered in all or most of the cancers in a given tissue
➔ Furthermore, the genetic defects in cancer cells can vary within the same tumor in a given individual

➔ NONETHELESS in 85% of colon cancers, the same three genes are found mutated
➔ This observation is the basis of a DNA test for colon cancer developed by EXACT Science Corp
➔ Typically colon cancer develops slowly over several years and is the third leading cause of cancer deaths in men and women
➔ Cells from developing cancers are shed into the colon; such cells can be collected and the DNA analyzed for the three mutations common to most colon cancers



K-ras is a proto-oncogene
APC is a tumor-suppressor gene
p53 has a complex role in controlling cellular responses to DNA damage and could be considered both a tumor suppressor gene and a guardian of the genome. This gene is mutated in >50% of cancers (all types)

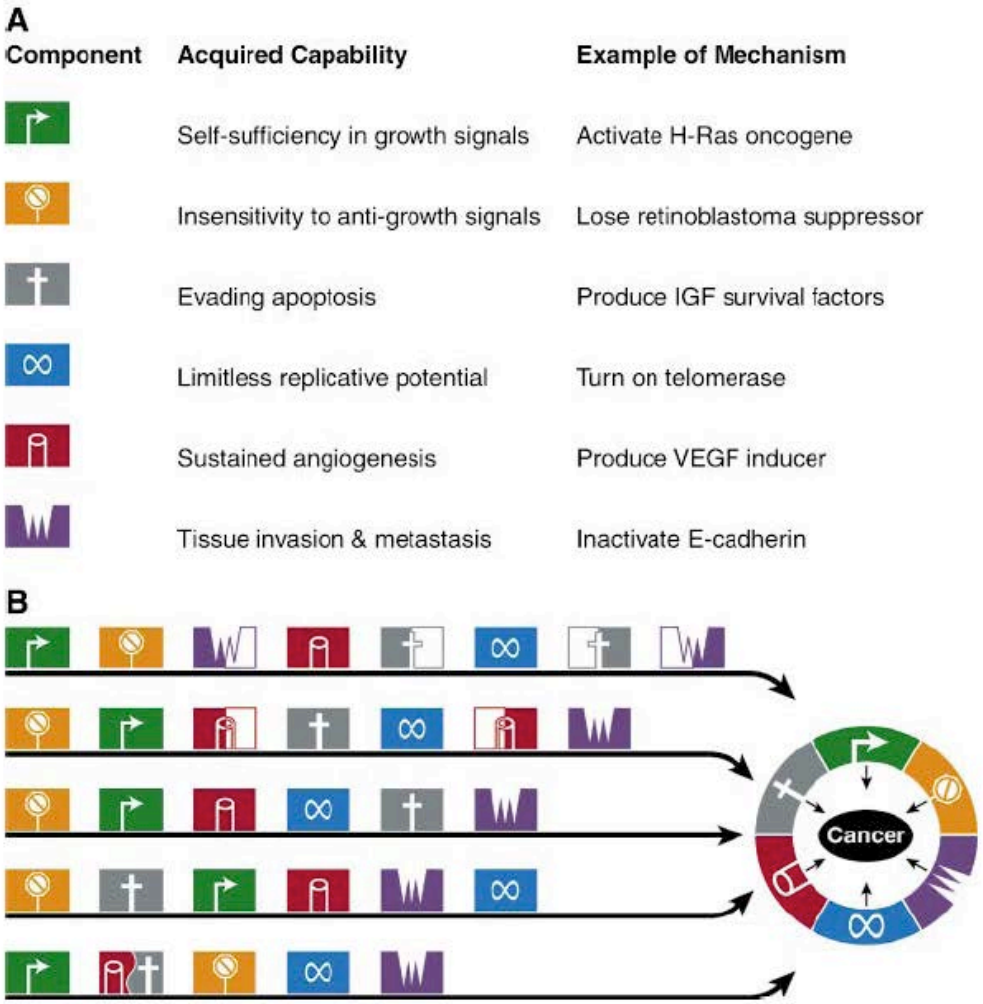


Figure 4. Parallel Pathways of Tumorigenesis

While we believe that virtually all cancers must acquire the same six hallmark capabilities (A), their means of doing so will vary significantly, both mechanistically (see text) and chronologically (B). Thus, the order in which these capabilities are acquired seems likely be quite variable across the spectrum of cancer types and subtypes. Moreover, in some tumors, a particular genetic lesion may confer several capabilities simultaneously, decreasing the number of distinct mutational steps required to complete tumorigenesis. Thus, loss of function of the p53 tumor suppressor can facilitate both angiogenesis and resistance to apoptosis (e.g., in the five-step pathway shown), as well as enabling the characteristic of genomic instability. In other tumors, a capability may only be acquired through the collaboration of two or more distinct genetic changes, thereby increasing the total number necessary for completion of tumor progression. Thus, in the eight-step pathway shown, invasion/metastasis and resistance to apoptosis are each acquired in two steps.

Cell, Vol. 100, 57–70, January 7, 2000

In February 2011 the New York Times published two articles describing a new cancer therapy that specifically targets melanomas with a BRAF driver mutation—see links below

In this type of therapeutic strategy, what matters in terms of treatment was therefore not only where a tumor originated, like the lungs or the colon, but also which set of "driver" genes was fueling its growth. Drugs that blocked the proteins that carried the genes' signals, some believed, could defuse a cancer without serious side effects.

A roller coaster Chase for a cure: doggedly testing a melanoma drug (NYT 2/22/10)
http://www.nytimes.com/2010/02/22/health/research/22trial.html?fta=y

After a long fight, drug gives sudden reprieve (NYT 2/23/10)
http://www.nytimes.com/2010/02/23/health/research/23trial.html?scp=1&sq=melanoma&st=cse

A Protein That Fuels Cancer, and a Drug to Fight It

Published: February 21, 2010

The Cancer

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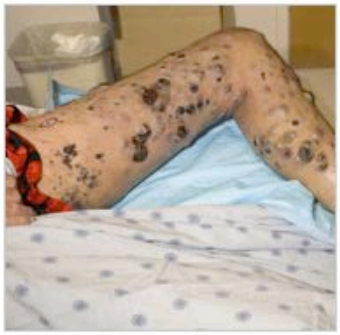

M.D. Anderson Cancer Center

ANOTHER CHANCE For patients covered in tumors, the opportunity to join a trial of an experimental melanoma drug, one said, was "like a rope you've been thrown when you're drowning, that's made just for you."

Melanoma, the aggressive skin cancer whose incidence is rising in the United States, begins in cells that produce the pigment melanin, which colors skin, hair and eyes. Most pigment cells are found in the skin, but cancer can develop in other areas where the cells are found.

More than 70,000 Americans are expected to receive a diagnosis of the disease this year, resulting in an estimated 9,000 deaths. The cancer has a high cure rate if removed early, but once it spreads to lymph nodes or to other organs, the average survival time is nine months. The average age at diagnosis of melanoma is 50.

Related

Target Cancer: A Roller Coaster Chase for a Cure (February 22, 2010)

Chemotherapy vs. Targeted Therapy

Traditional chemotherapies work by attacking fast-growing cells, both normal and cancerous. They rarely cure a cancer in its advanced stages. Targeted therapies seek to block a particular protein, among tens of thousands in each cell, that is fueling a cancer's growth.

How PLX4032 Works

Normally, a gene called B-RAF produces a protein that spurs cells to multiply only when growth is needed. But a mutation in the gene produces a protein that is defective — perpetually switched on. That leads to the rapid cell growth that characterizes cancer. The drug PLX4032 binds to the defective protein, deactivating it.