Mutations and cancer

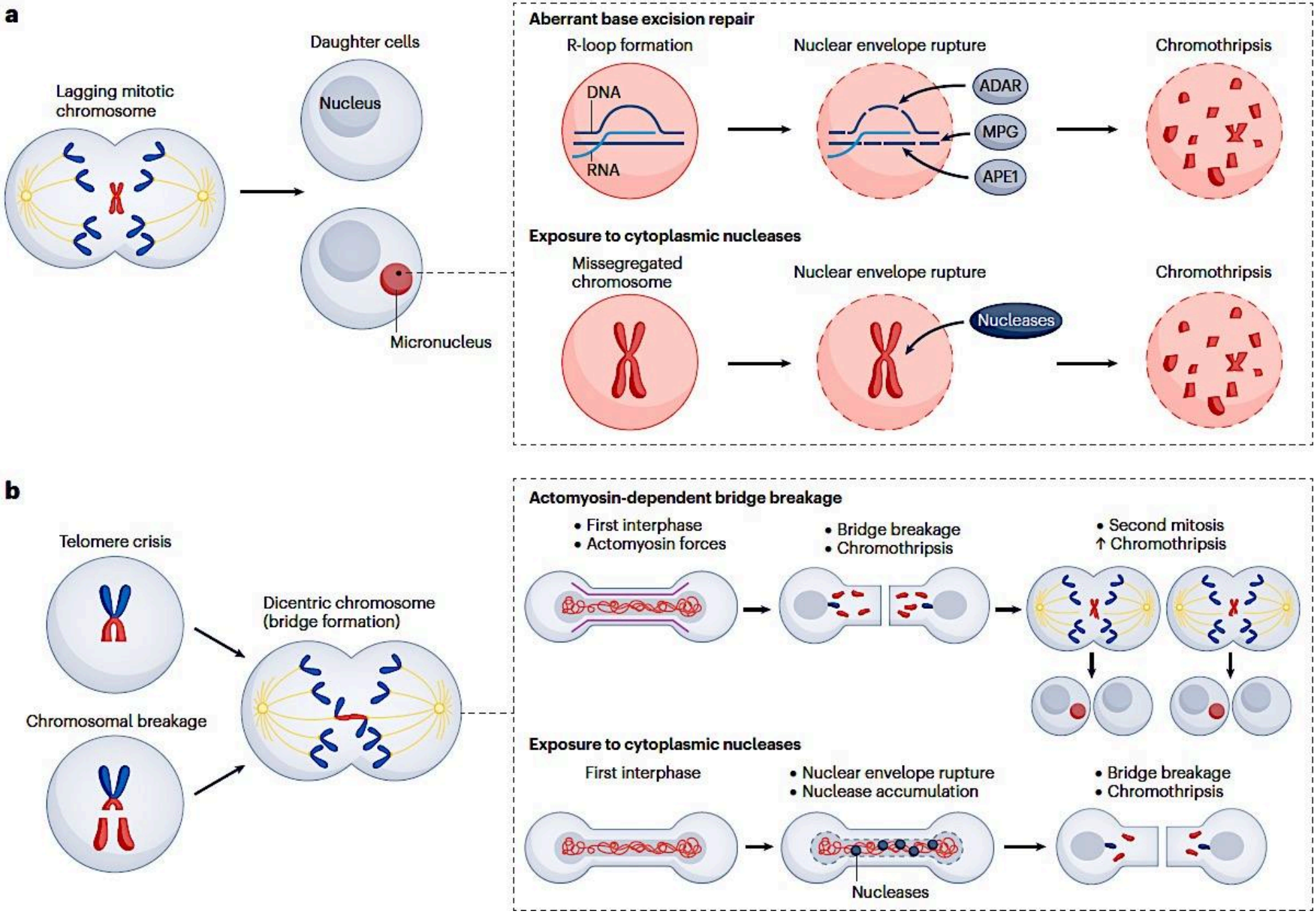
$3x10^{13}$ cell in human body

10^{11} cell divisions (DNA replication events)/day

The mutation rate per nucleotide/DNA replication event is 10^{-9}

Every possible single nucleotide mutation occurs in our genome hundreds of times each day.

Mitotic recombination can convert heterozygous cells into homozygotes. Rates range from 10^{-2} - 10^{-4} per individual/ generation


a
Lagging mitotic chromosome
Daughter cells
Nucleus
Micronucleus
Aberrant base excision repair
R-loop formation
DNA
RNA
Nuclear envelope rupture
ADAR
MPG
APE1
Chromothripsis
Exposure to cytoplasmic nucleases
Missegregated chromosome
Nuclear envelope rupture
Nucleases
Chromothripsis
b
Telomere crisis
Chromosomal breakage
Dicentric chromosome (bridge formation)
Actomyosin-dependent bridge breakage
• First interphase
• Actomyosin forces
• Bridge breakage
• Chromothripsis
• Second mitosis
↑ Chromothripsis
Exposure to cytoplasmic nucleases
First interphase
• Nuclear envelope rupture
• Nuclease accumulation
• Bridge breakage
• Chromothripsis
Nucleases

Genetic Alterations in Cancer

- **Mutations**
  - -Missense
  - -Nonsense
  - -Frameshift
  - -Splicing
  - -Promoter
  - -Activation
- **Deletions**
- **Rearrangements**
- **Amplifications**
- **Epigenetic Events (Methylation)**

Mutations: alterations in the DNA sequence

Substitutions
Deletions
Additions

Inversions
Translocations
Duplications

mobile DNA insertions

Mutations may have their effects in trans or cis, depending on whether they affect protein coding regions (trans acting factors) or regulatory sequences that affect the synthesis, splicing, stability or translation of these protein coding regions (cis acting sequences).

null alleles $\frac{\text{null}}{\text{null}} = \frac{\text{null}}{\text{Deficiency}} = \frac{\text{Deficiency}}{\text{Deficiency}}$

hypomorph $\frac{\text{hypomorph}}{\text{hypomorph}} > \frac{\text{hypomorph}}{\text{Deficiency}} > \frac{\text{Deficiency}}{\text{Deficiency}}$

hypermorph hypermorph $\frac{\text{hypermorph}}{\text{hypermorph}} > \frac{\text{hypermorph}}{+} > \frac{\text{hypermorph}}{\text{Deficiency}}$

neomorph neomorph $\frac{\text{neomorph}}{\text{neomorph}}$ The neomorph phenotype does not revert towards wildtype in trans to a deficiency. $\frac{\text{neomorph}}{\text{Deficiency}}$

haploinsufficient The haploid dose of the wildtype gene product is not sufficient to rescue normal function.

antimorph $\frac{\text{antimorph}}{+} < \frac{\text{Deficiency}}{+} <$ antimorph$/+/+$

Strange alleles of the lac repressor, lacI. LacI is a tetramer. laci^{d} mutants do not bind to the operator = laci-
Dominant to wildtype. Interaction with wildtype subunits in a partial diploid prevents any tetramers that contain laci^{d} subunits from binding DNA.

Ectopic expression at inappropriate time or in inappropriate place

Spontaneous

Induced

chemicals

ionizing radiation

Transitions:

purine to purine or pyrimidine to pyrimidine changes

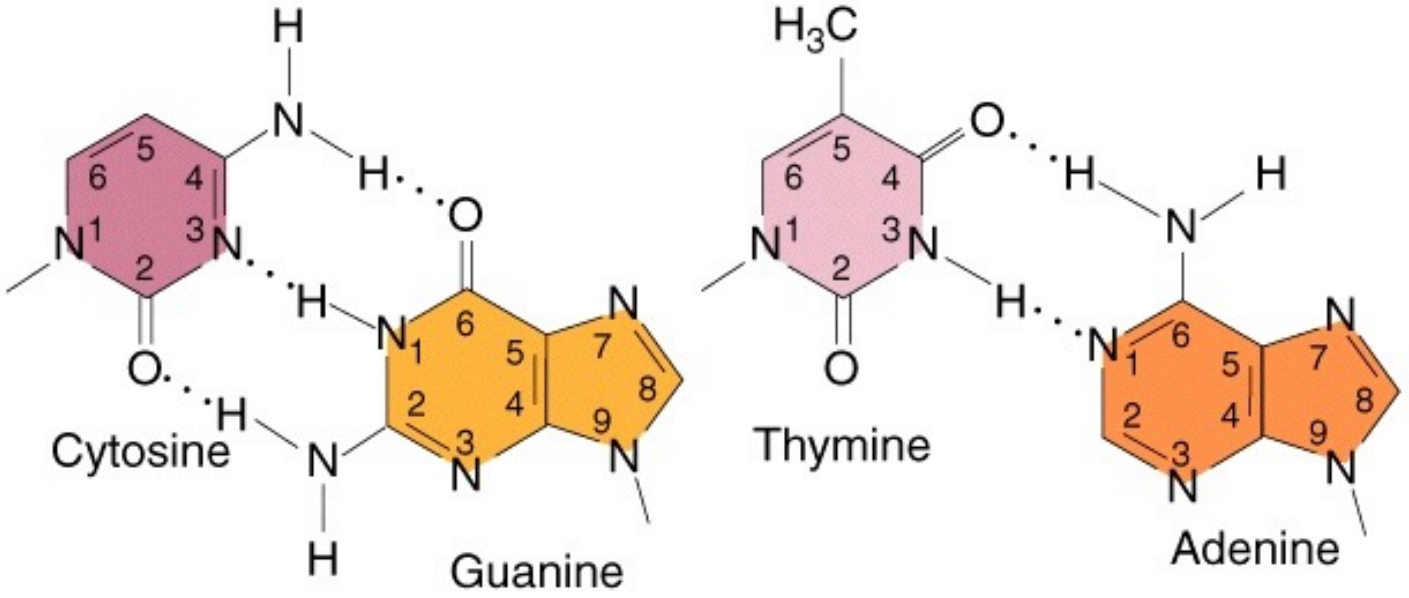
Transversions:

purine to pyrimidine or pyrimidine to purine changes

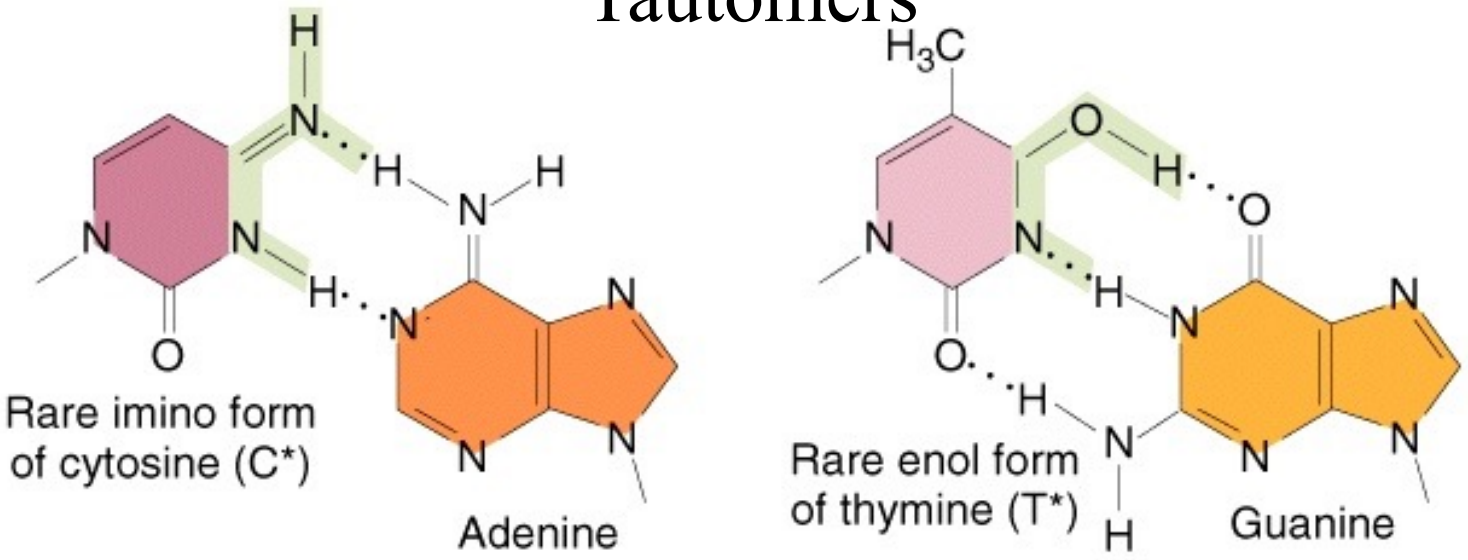
purines = guanine and adenine

pyrimidines = cytosine, thymine and uracil

Normal base pairing

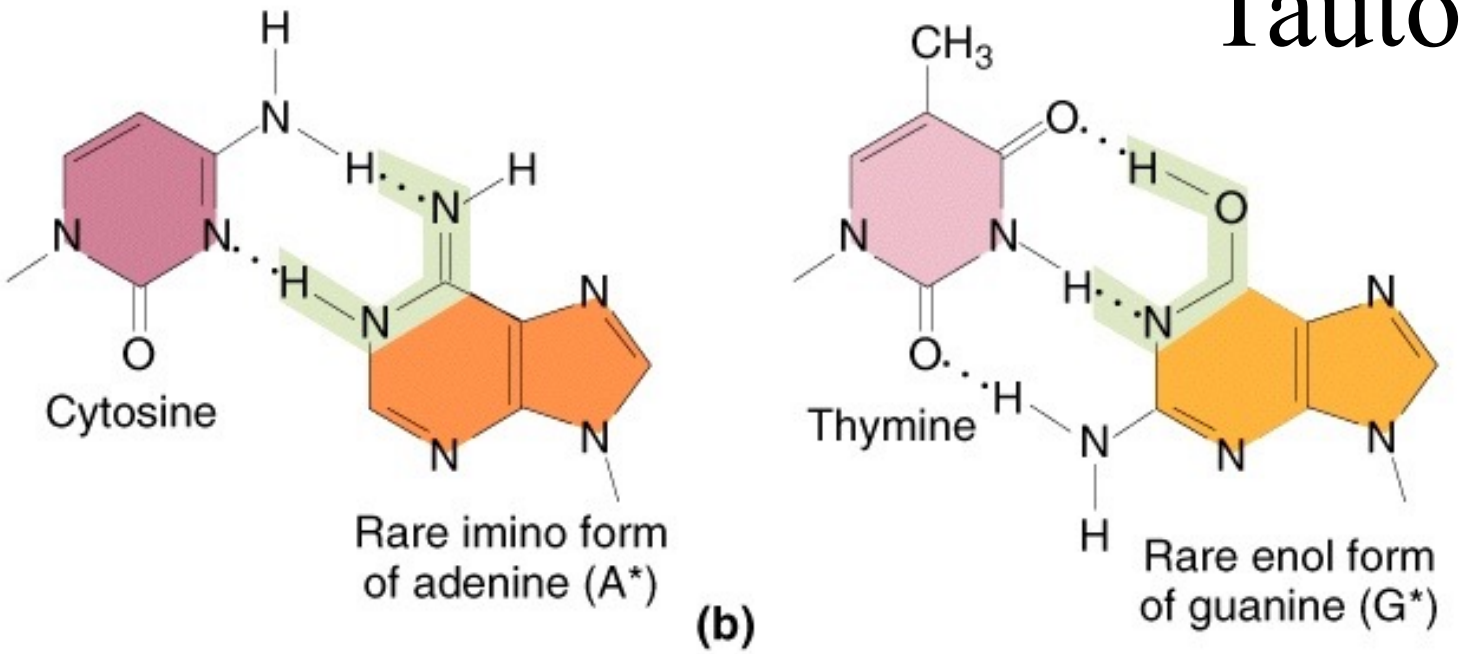


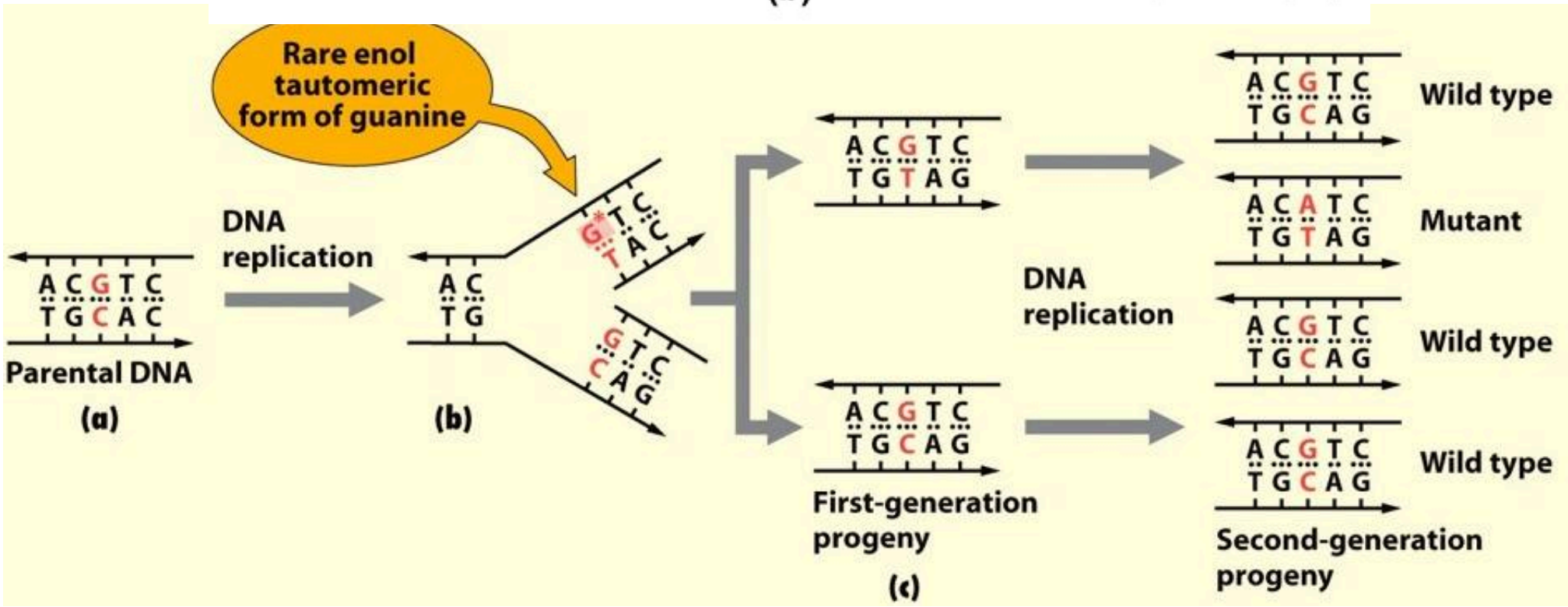
Tautomers



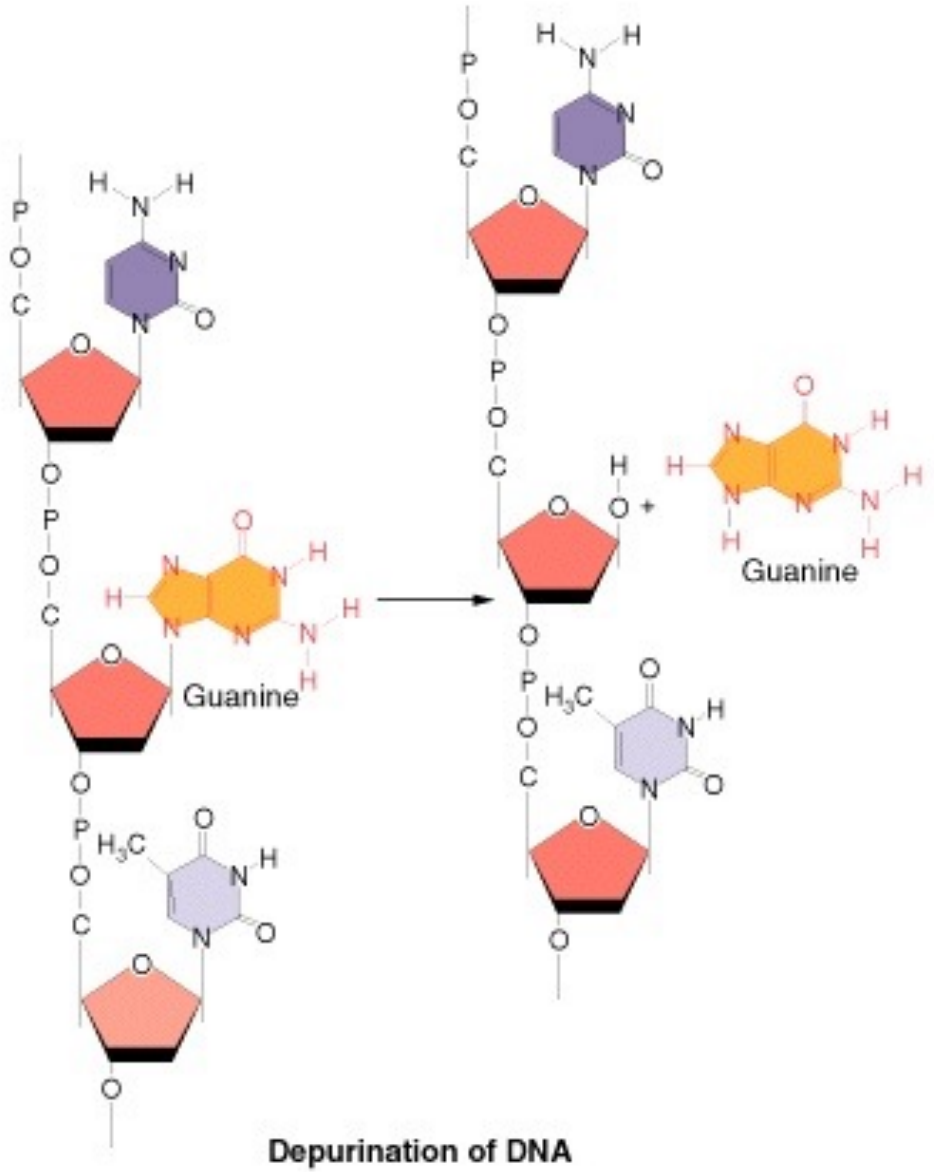
(a)

Tautomers

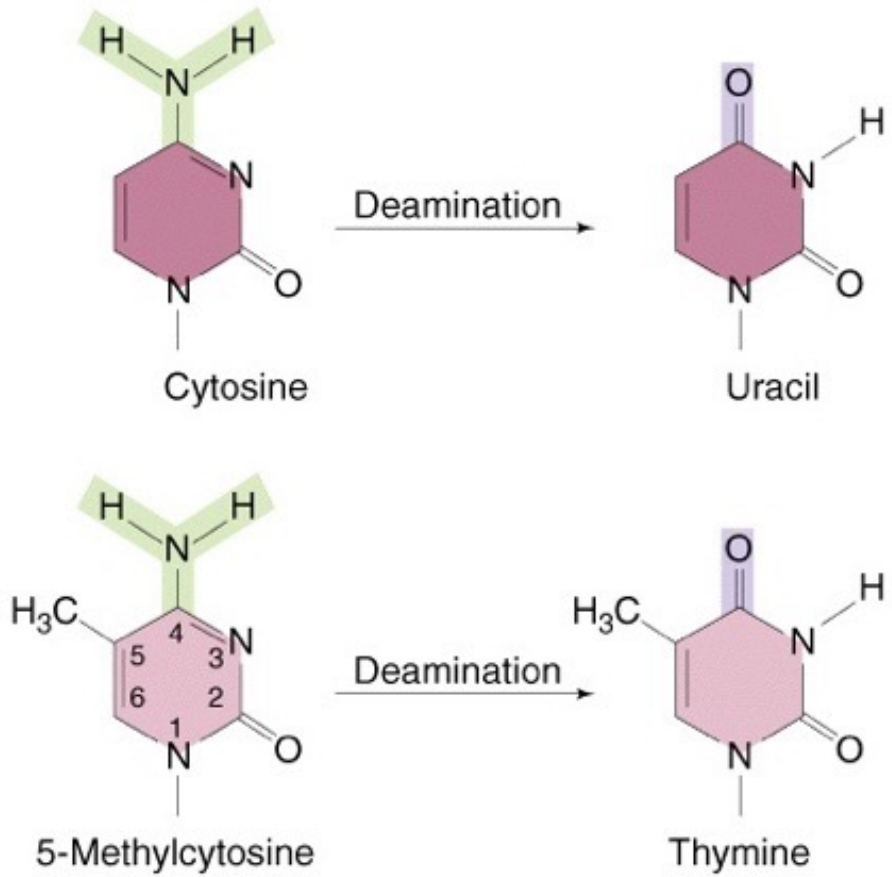

Cytosine
Rare imino form of adenine (A*)
Thymine
Rare enol form of guanine (G*)
(b)


Rare enol tautomeric form of guanine
DNA replication
Parental DNA
(a)
(b)
DNA replication
First-generation progeny
(c)
Wild type
Mutant
Wild type
Wild type
Second-generation progeny

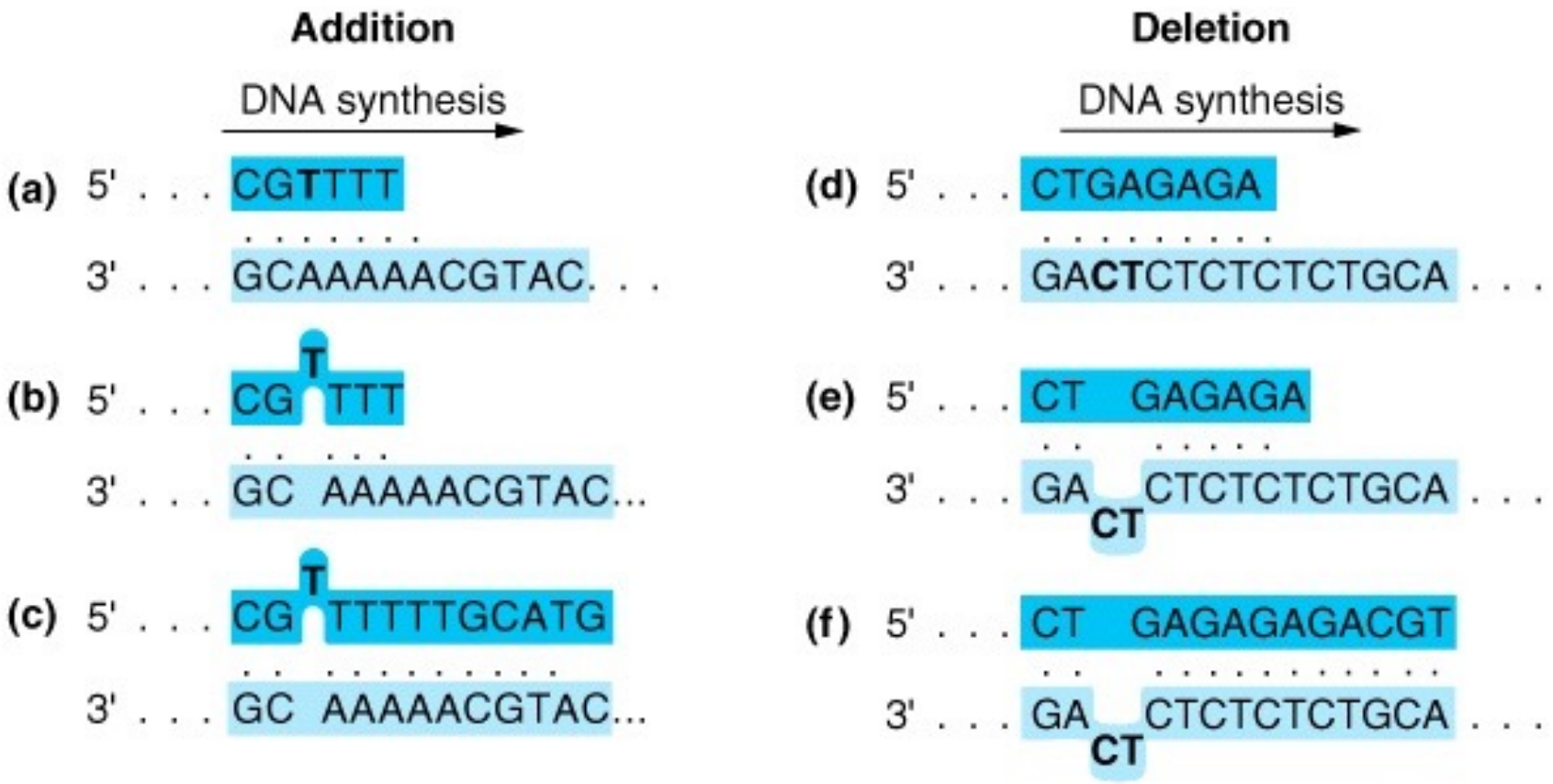
Depurination and deamination lead to spontaneous mutations



Depurination of DNA

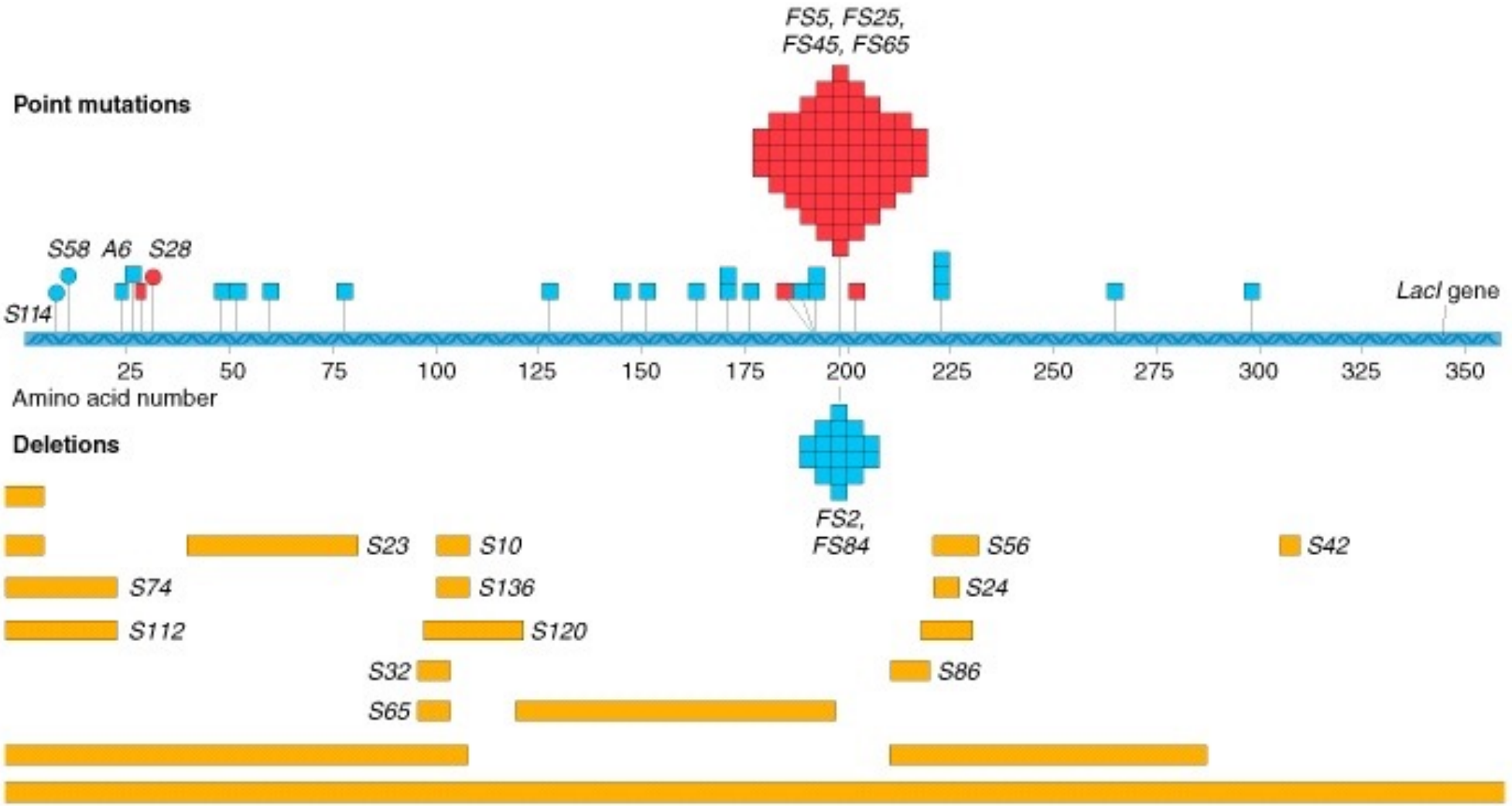


Slippage during replication of repeated nucleotides can lead to addition or deletion of nucleotides.



Certain positions are hotspots for spontaneous mutations.

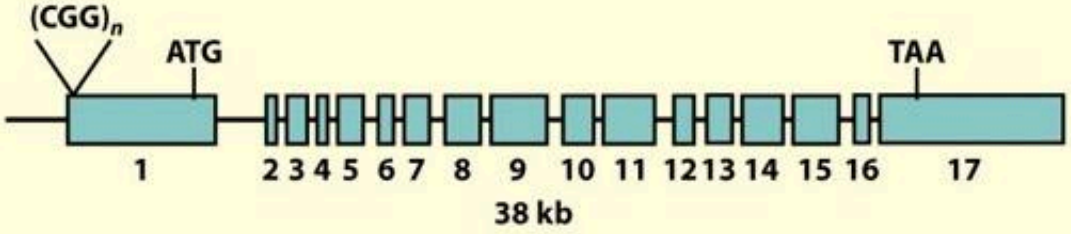
Mutations in the *E. coli lacI* gene



Some hotspots are positions with repeated DNA, and mutations result from lost or duplication of repeat.

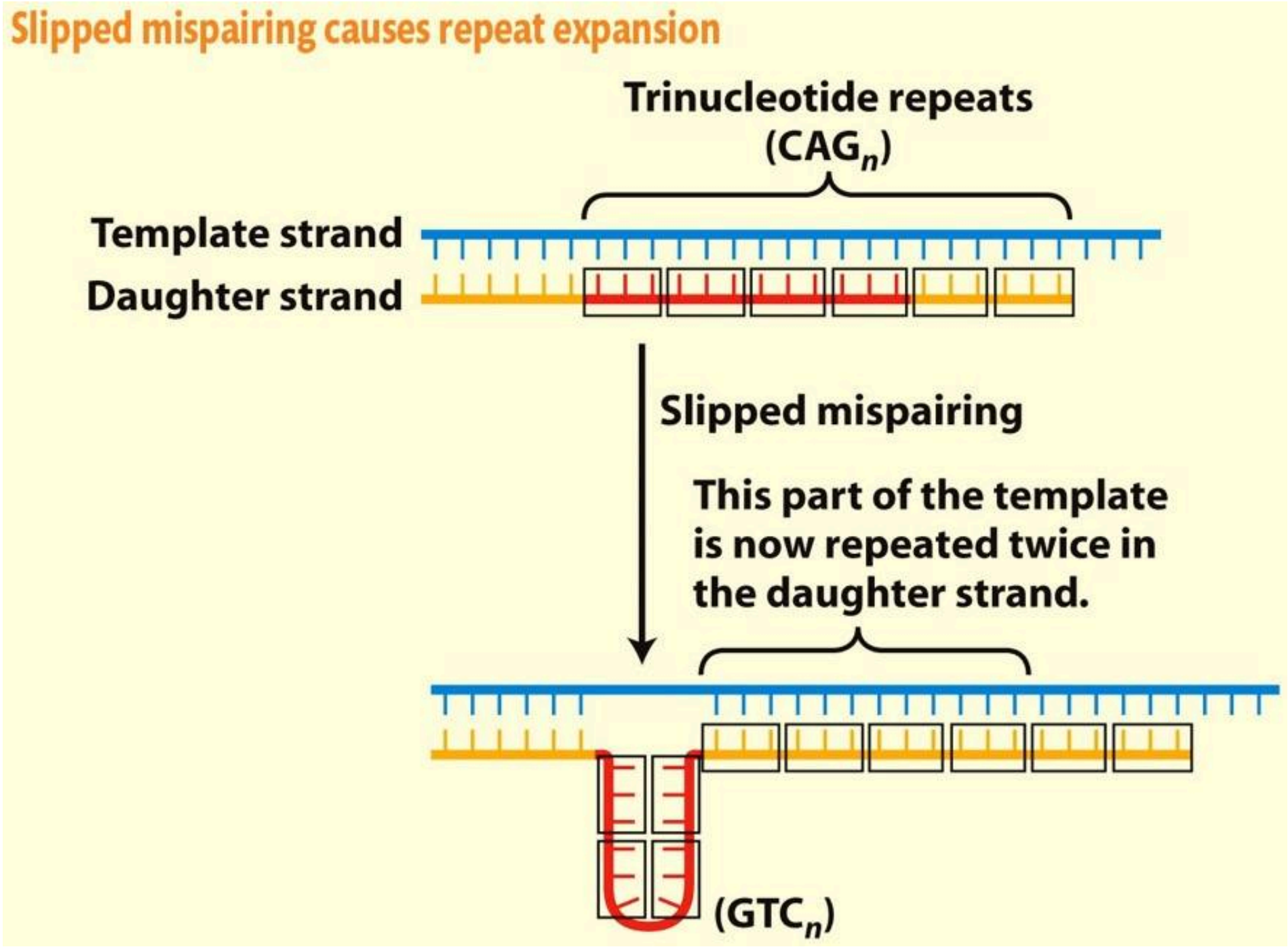
Trinucleotide repeats in the *FMR-1* gene hinder transcription

(a)



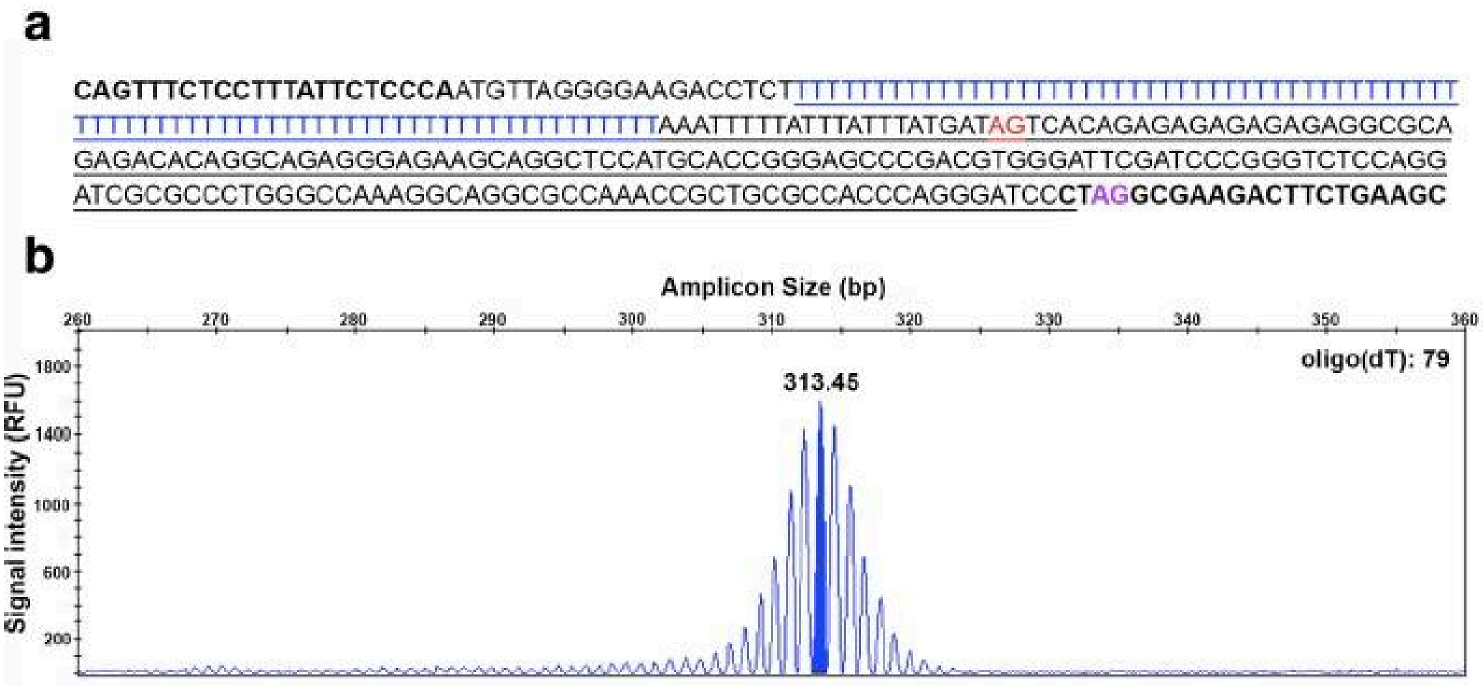
(b) *FMR-1* gene	Phenotype	Transmission	Methylation	Transcription
Normal $(CGG)_{6-59}$ ATG ...	Normal	Stable	No	Yes
Premutation $(CGG)_{60-200}$ ATG ...	Largely normal	Unstable, prone to expansion	No	Yes
Full mutation $(CGG)_{>200}$ ATG ... X	Affected	Unstable	Yes	No

Anticipation


Slipped mispairing causes repeat expansion
Trinucleotide repeats
(CAG$_n$)
Template strand
Daughter strand
Slipped mispairing
This part of the template
is now repeated twice in
the daughter strand.
(GTC$_n$)

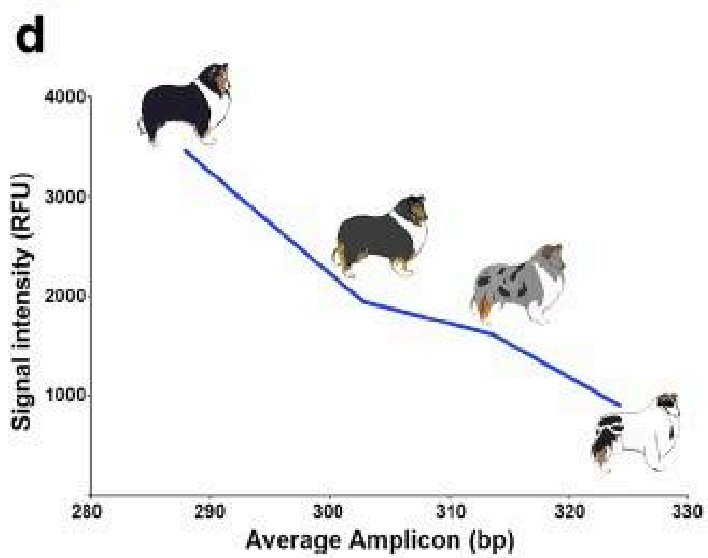
The inconstant genome: Somatic mosaicism

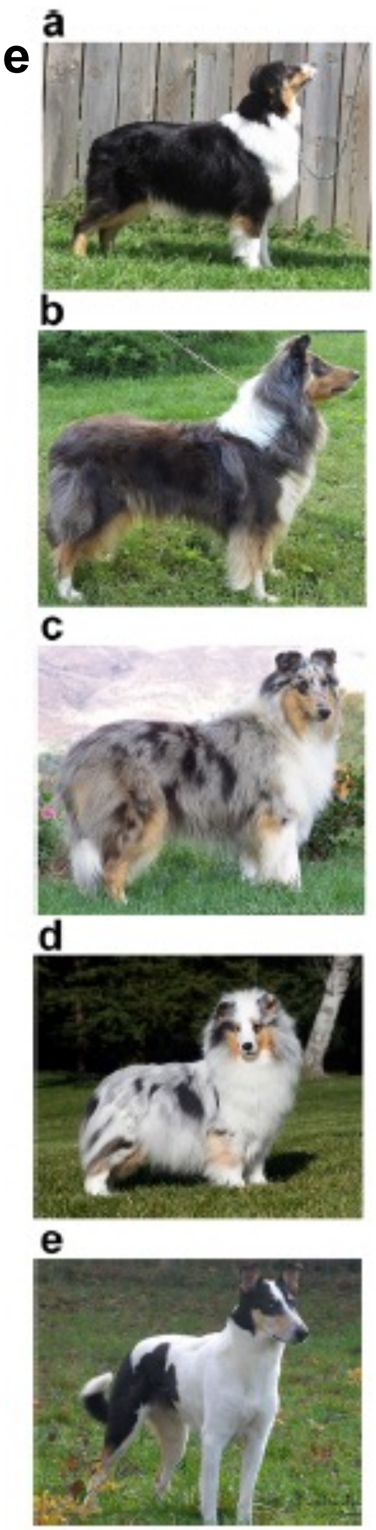
Different alleles of a single gene cause this variation in coat color

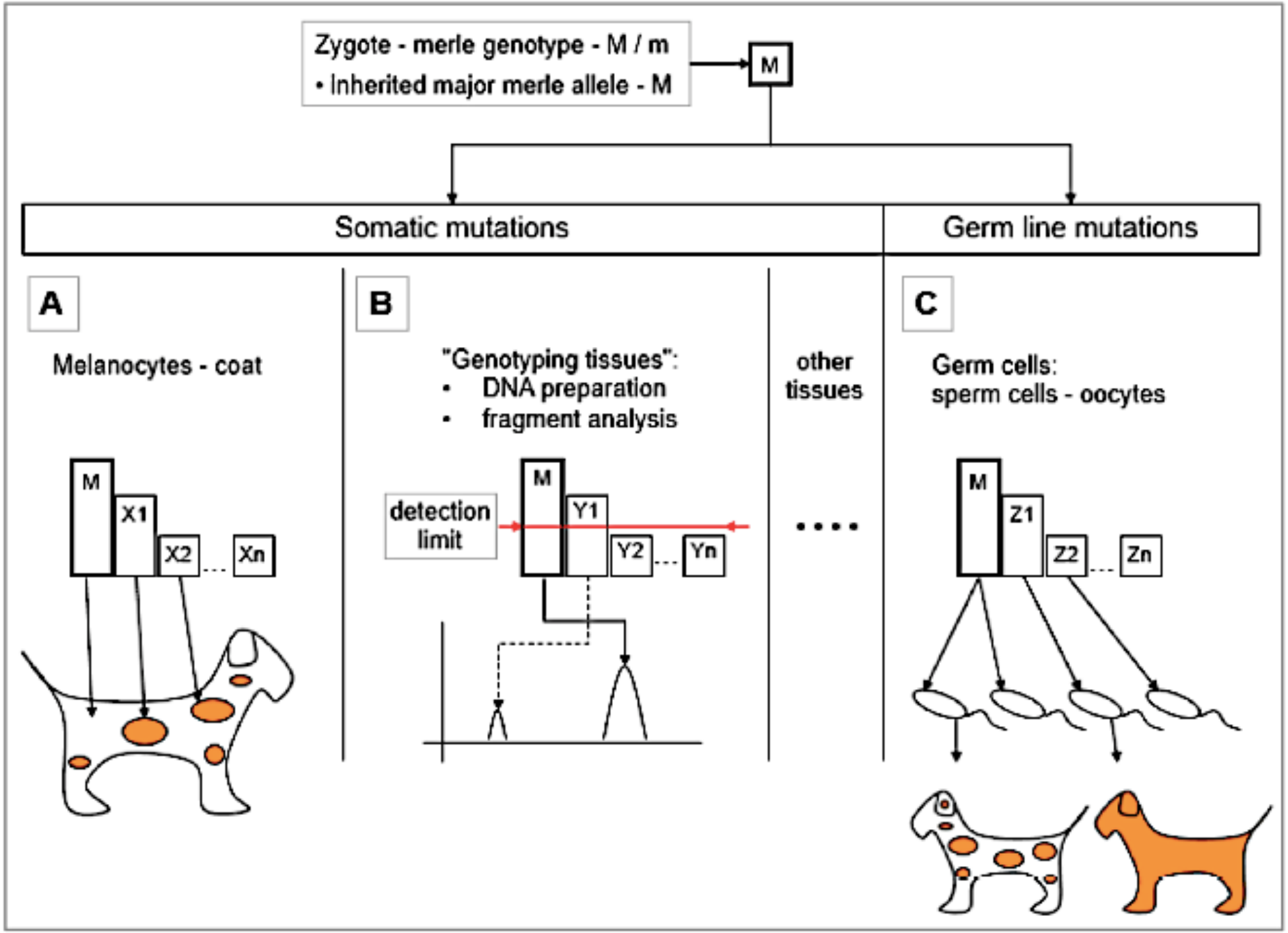


c

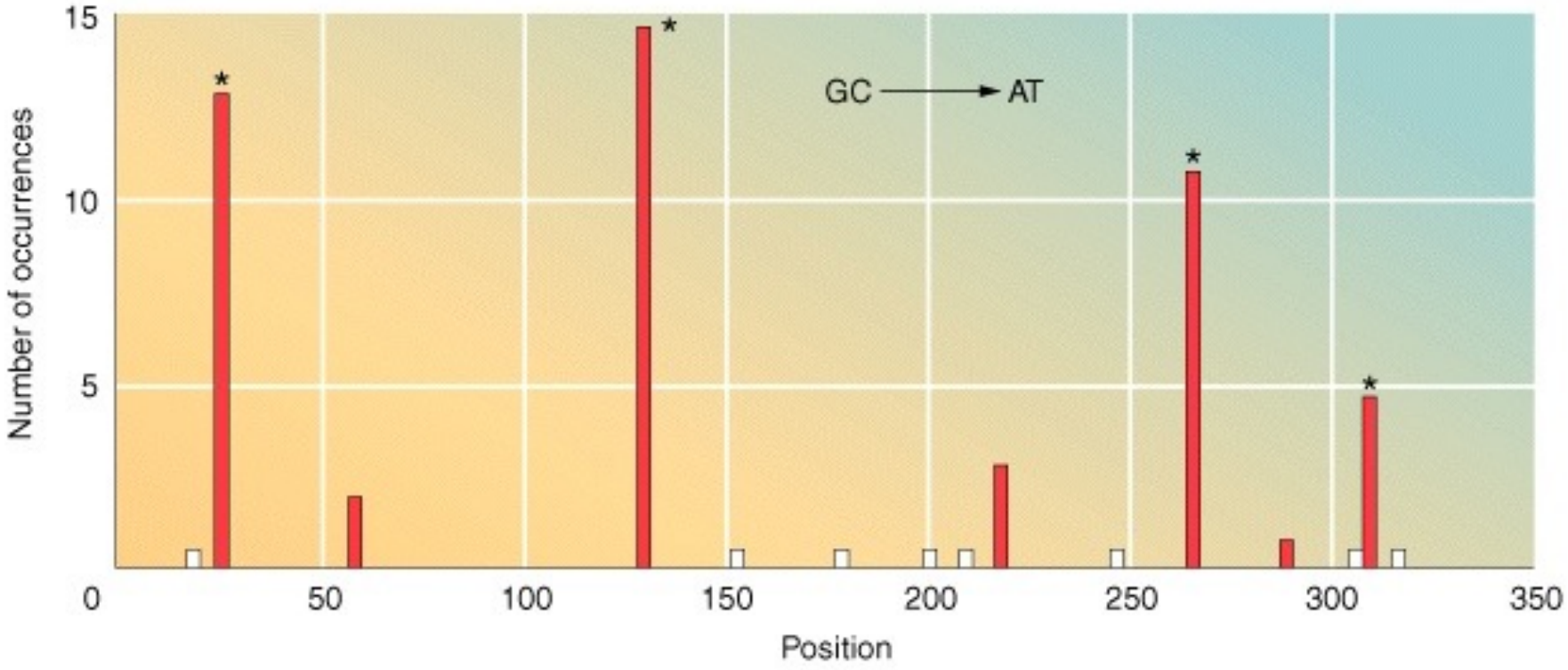
Phenotype	Oligo(dT) (bp)	Replicates	Average Amplicon (bp)	Standard Deviation (bp)
Cryptic	54	11	287.88	0.04
Dilute	69	9	302.79	0.09
Standard	80	11	313.64	0.23
Harlequin	90	10	324.24	0.34

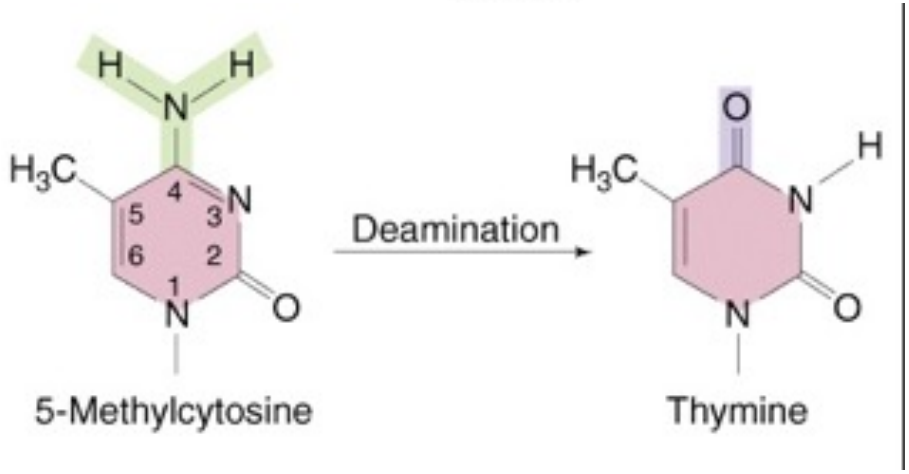




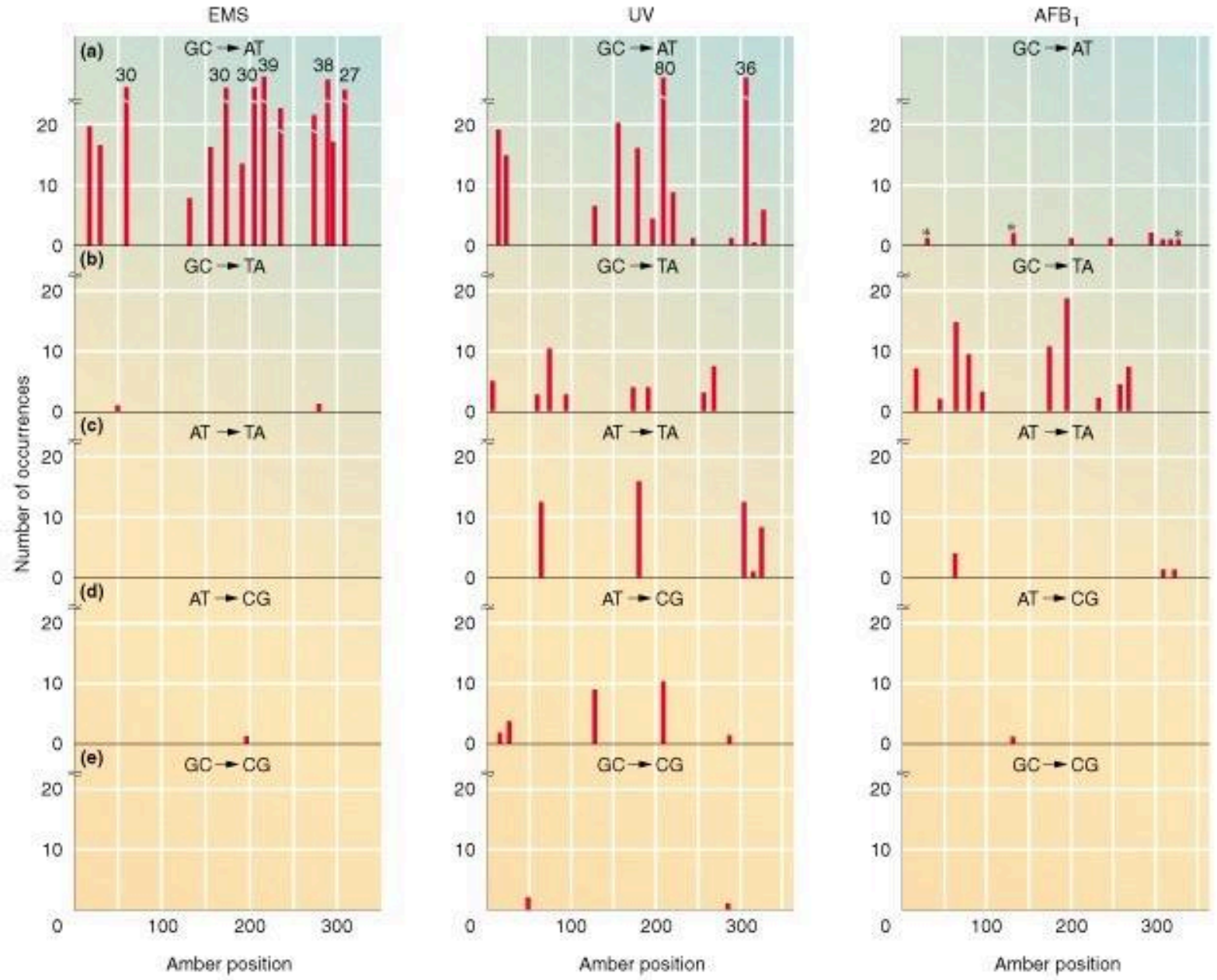

Zygote - merle genotype - M / m
• Inherited major merle allele - M
M
Somatic mutations
Germ line mutations
A
Melanocytes - coat
M
X1
X2
Xn
B
"Genotyping tissues":
• DNA preparation
• fragment analysis
detection limit
M
Y1
Y2
Yn
other tissues
C
Germ cells:
sperm cells - oocytes
M
Z1
Z2
Zn

lacI sites that result from 5-methyl cytosine can generate nonsense mutations.



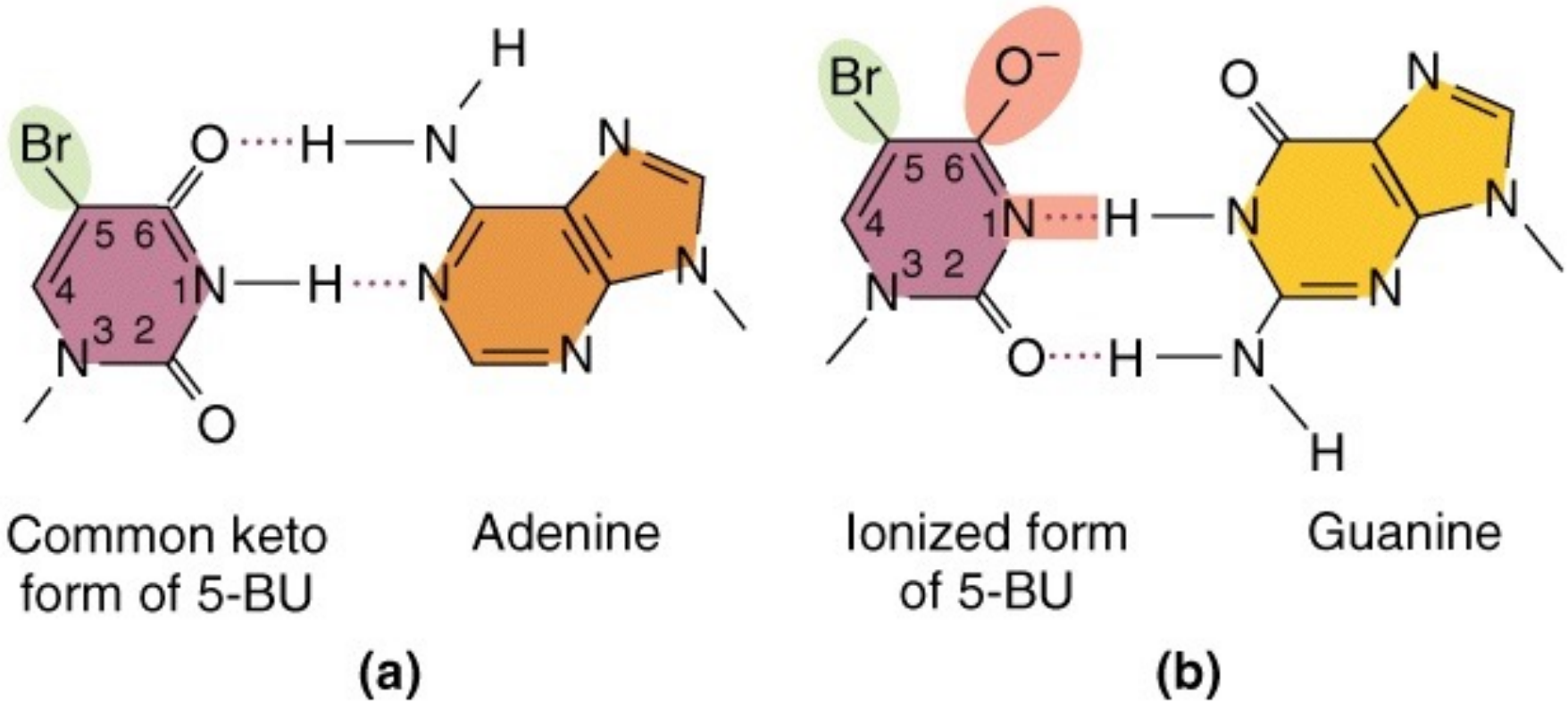


Different mutagens have different specificities.

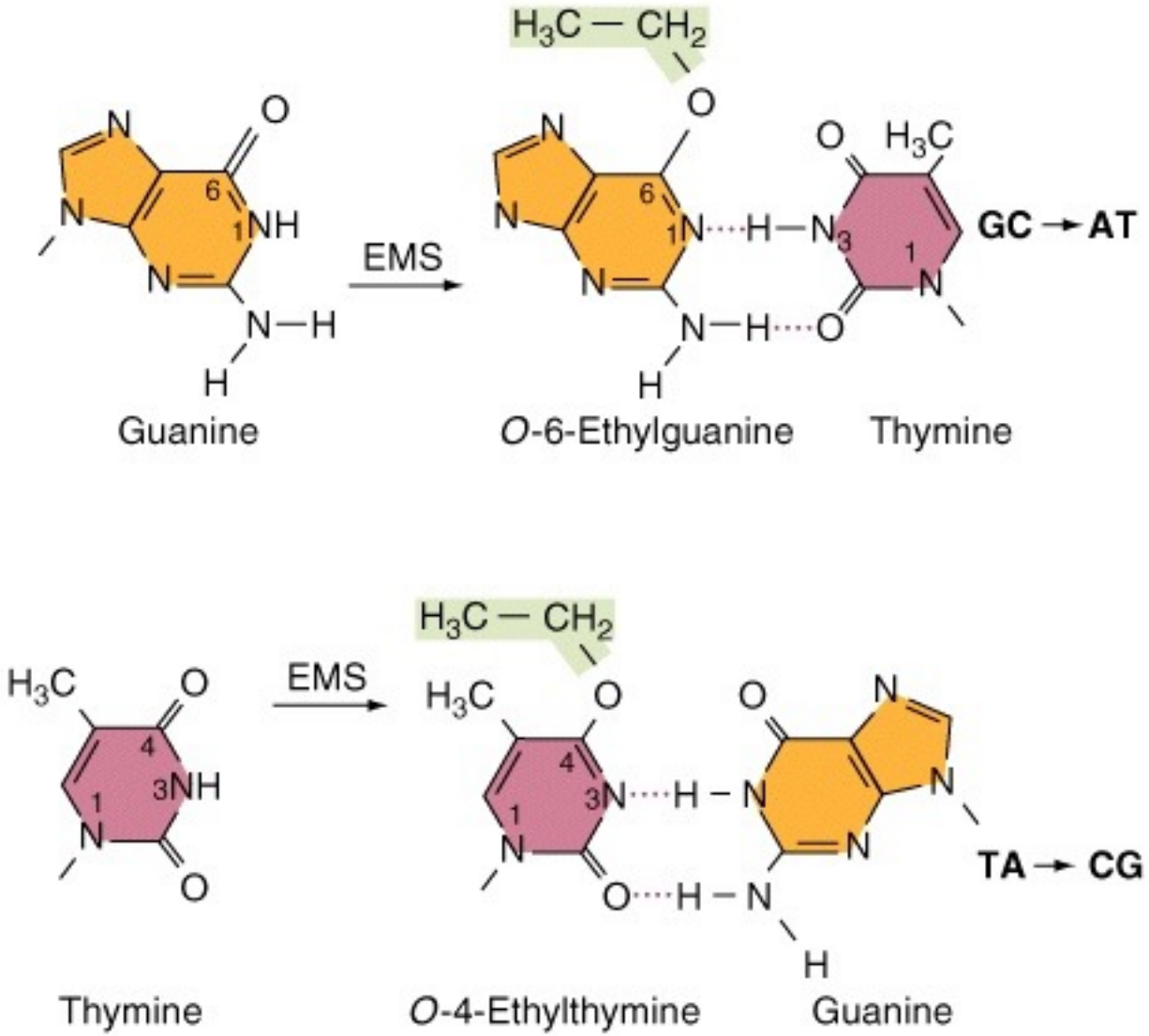


Chemical mutagens

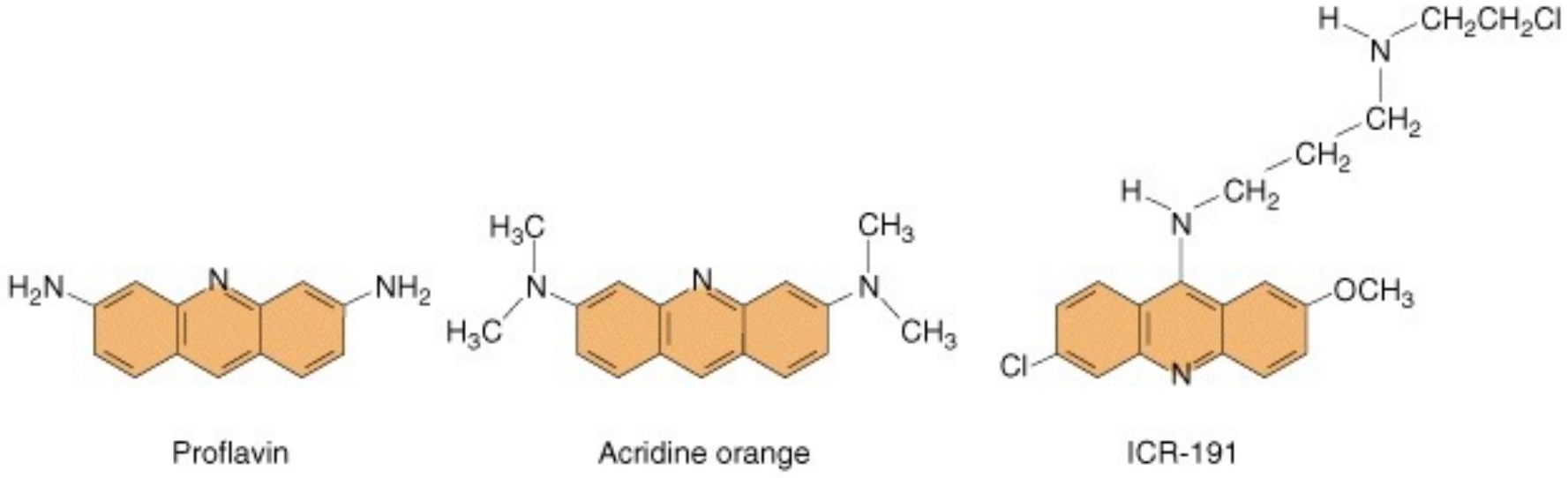
1. Base analogs: incorporated into DNA instead of normal bases, but have different pairing properties.



2. Alkylating agents: add alkyl groups to bases, and change pairing specificity.

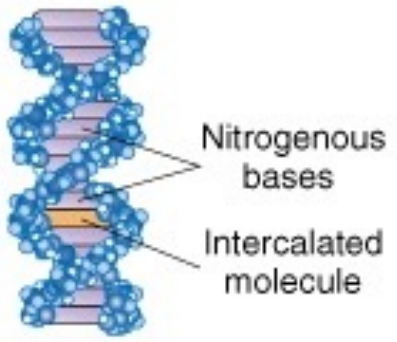


3. Intercalating agents: mimic base pairs and intercalate between stacked bases. Result in single nucleotide deletions and insertions.



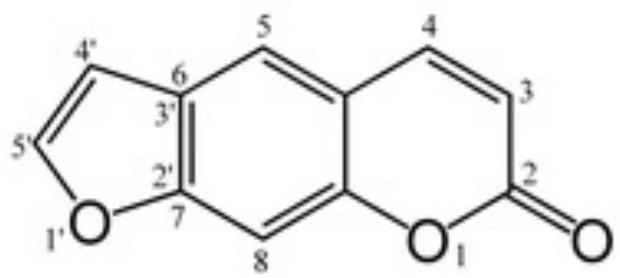
Proflavin Acridine orange ICR-191

(a)



(b)

Psoralens intercalate into DNA and form inter-strand crosslinks on UV exposure



Arch Dermatol. 1990 Oct;126(10):1334-6.

Severe phototoxic burn following celery ingestion.

Phytophotodermatitis from celery among grocery store workers.

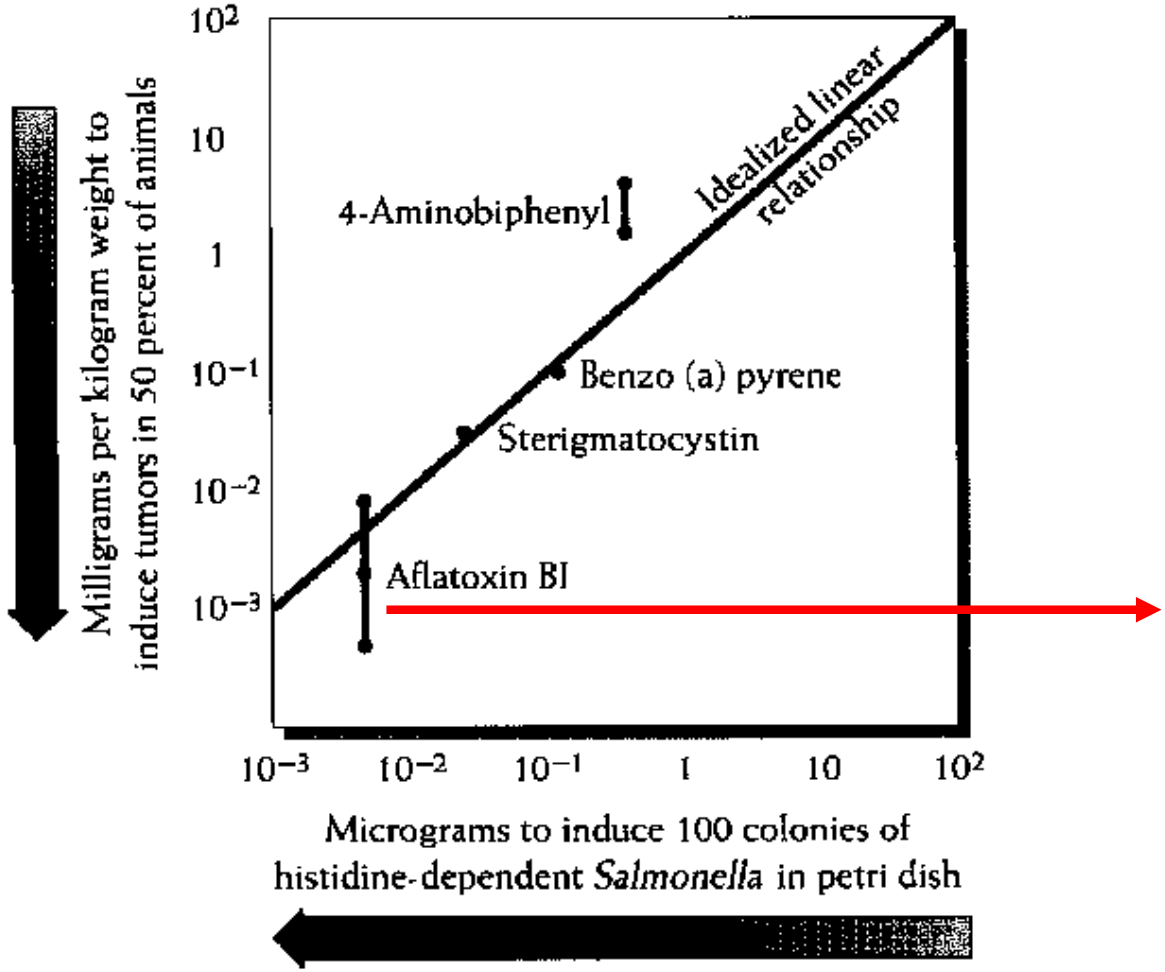
Seligman PJ, Mathias CG, O'Malley MA, Beier RC, Fehrs LJ, Serrill WS, Halperin WE.

Division of Surveillance, Hazards Evaluations and Field Studies, National Institute for Occupational Safety and Health, Cincinnati, OH 45226.

Abstract

We detected 19 cases of phytophotodermatitis during a cross-sectional epidemiological investigation of two Oregon grocery stores that were part of the same supermarket chain. Outdoor sunlight exposure during the workshift and tanning salon use were identified as risk factors; the most severe cutaneous reactions tended to occur among tanning salon users. Although both stores carried the same brands and varieties of produce, all 19 cases occurred among employees of one store, which had held a celery sale coincident with the outbreak, resulting in a quadrupling of the usual volume of celery sold. We found elevated psoralen levels in two of three celery samples obtained from the affected store; cutaneous provocation tests with trimmed surfaces of these celery samples produced phototoxic reactions. Preliminary experiments with one brand of celery have demonstrated psoralen levels as high as 25 micrograms/cm2 of trimmed surface. These observations suggest that clinical phytophotodermatitis among grocery store workers may be caused by healthy celery and results from a complex interaction of exposure variables, including ultraviolet radiation from tanning salon use, frequency of handling celery, celery brand, and sporadic elevation of psoralen content from environmental stresses.

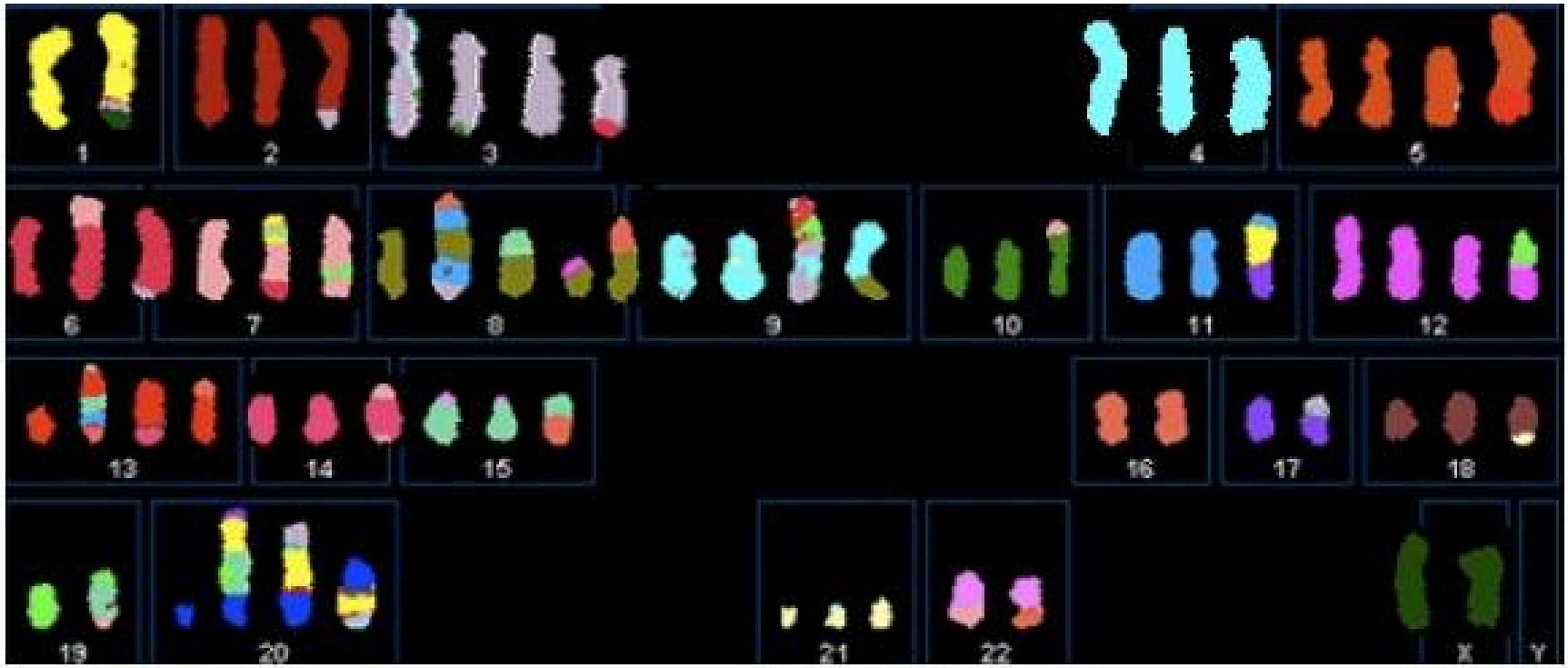
Mutagens are often carcinogens. Aflatoxin B1 a toxin produced by fungi that infect a number of crops, including peanuts, is a very potent mutagen. For commercial suppliers, ALL peanuts are scanned for evidence of fungal infection. What about your local, farmers market organic peanut butter???



The mutagenic potency of four test compounds (horizontal axis) plotted against their carcinogenic potency when fed to laboratory rodents (vertical axis).

The breakage-fusion-bridge cycle created following a DS break can give rise to gross aneuploidy. This will include chromosomes that have lost homozygosity in specific regions

Gross Chromosome Instability



http://www.path.cam.ac.uk/

SKY Paint of MCF7 Breast Tumor Cell Line

Breakage-fusion-bridge cycle + chromothripsis

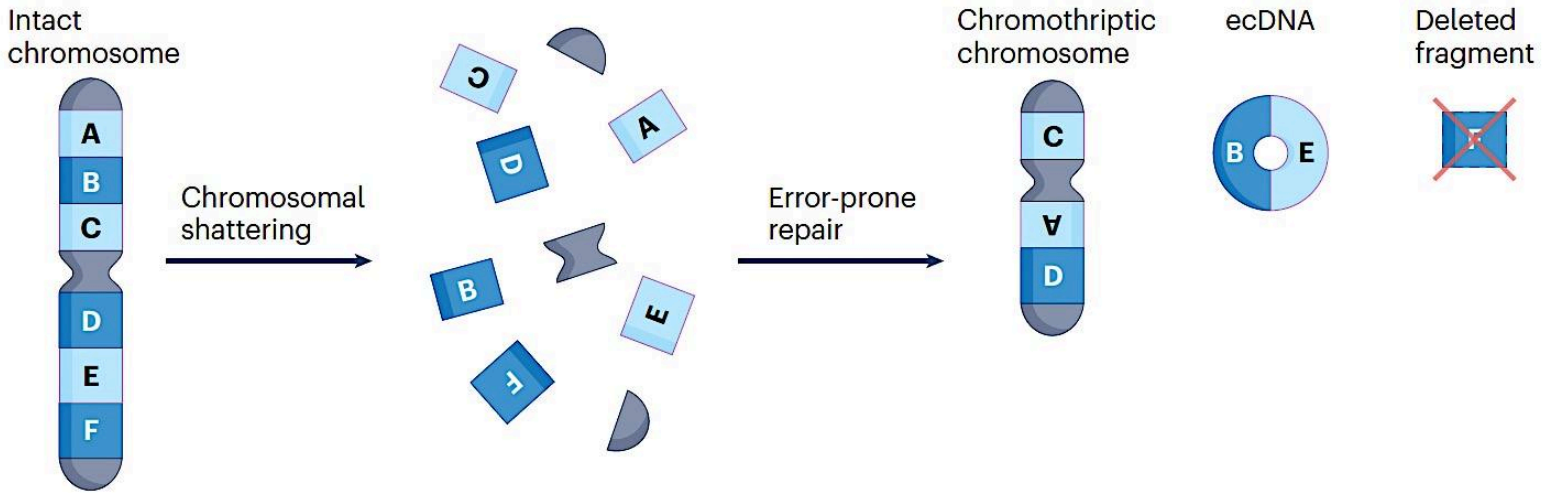
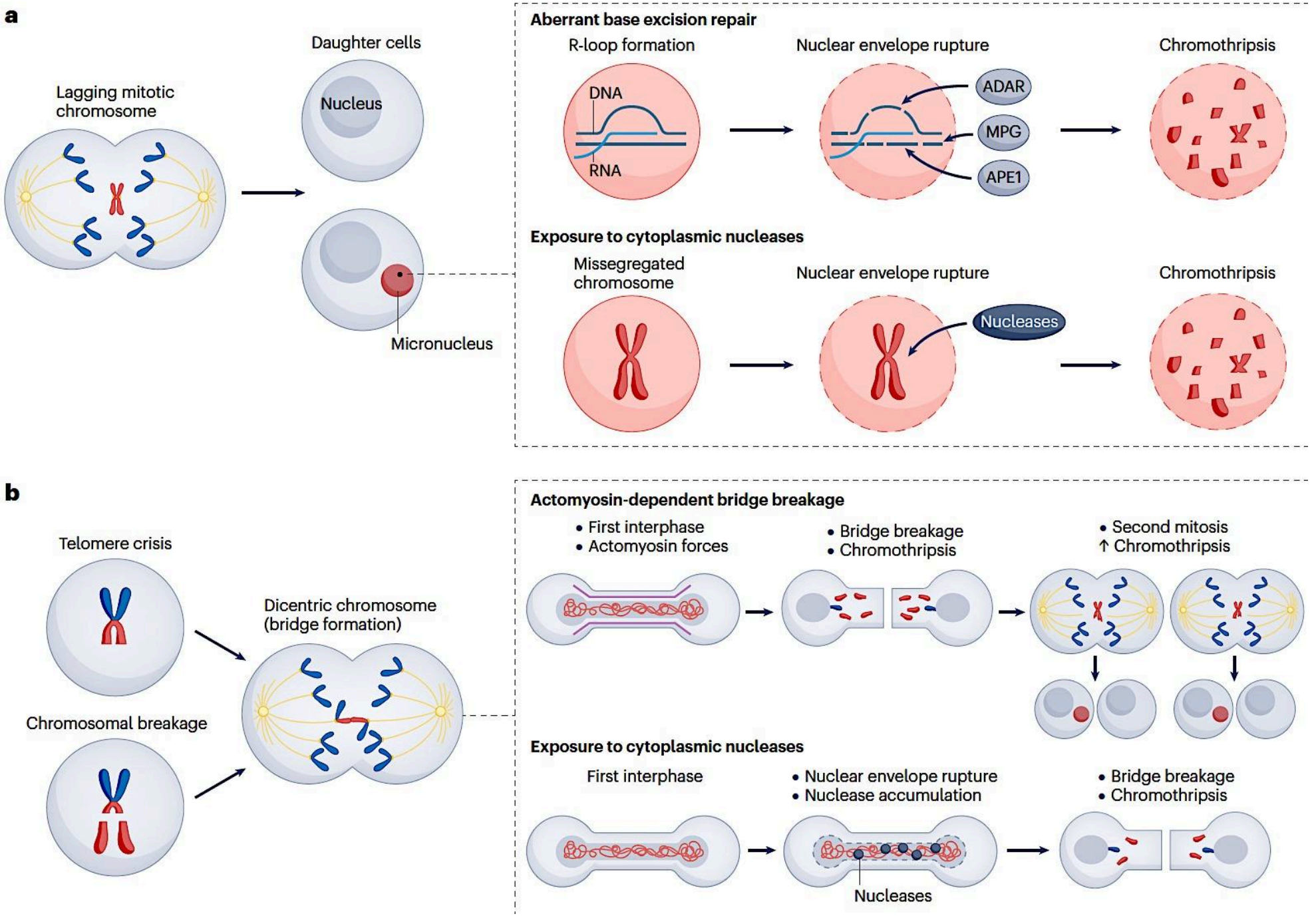


Fig. 3 | Mechanistic models of chromothripsis due to DNA damage. a, A lagging mitotic chromosome results in the formation of a micronucleus, which can undergo chromothripsis via two potential mechanisms. Aberrant base excision repair50 is initiated by the formation of R-loops (RNA–DNA hybrids) resulting from collisions between the DNA replication fork and the transcription apparatus. In this model, the recruitment of adenine deaminase acting on RNA (ADAR) enzymes to R-loops leads to DNA strand editing, which converts deoxyadenosine into deoxyinosine. Deoxyinosine in R-loops is then converted into abasic sites by the recruitment of DNA-3-methyladenine glycosylase (MPG). Finally, apurinic/apyrimidinic endonuclease 1 (APE1) acts on these abasic sites to cleave the phosphodiester backbones and generate single-stranded DNA nicks, whose conversion into double-stranded DNA breaks could ultimately lead to chromothripsis. Alternatively, rupture of the nuclear envelope directly exposes DNA to cytoplasmic nucleases, which could potentially lead to chromothripsis. b, Telomere crisis or chromosomal breakage can result in the formation of a dicentric chromosome and lead to the formation of chromosome bridges. In this model, chromosomal shattering occurs via either actomyosin-dependent bridge breakage31 or exposure to cytoplasmic nucleases. Cytoplasmic actomyosin forces (purple lines) induce the initial bridge breakage, after which chromothripsis accumulates in daughter cells. During the next cell division, chromosomes that originate from broken bridges become missegregated and generate micronuclei, which in turn undergo additional chromothriptic events. Exonuclease 3′ exonuclease 1 (TREX1) accumulates on the bridge DNA after rupture of the nuclear envelope and leads to the generation of single-stranded DNA nicks and ultimately chromothripsis29

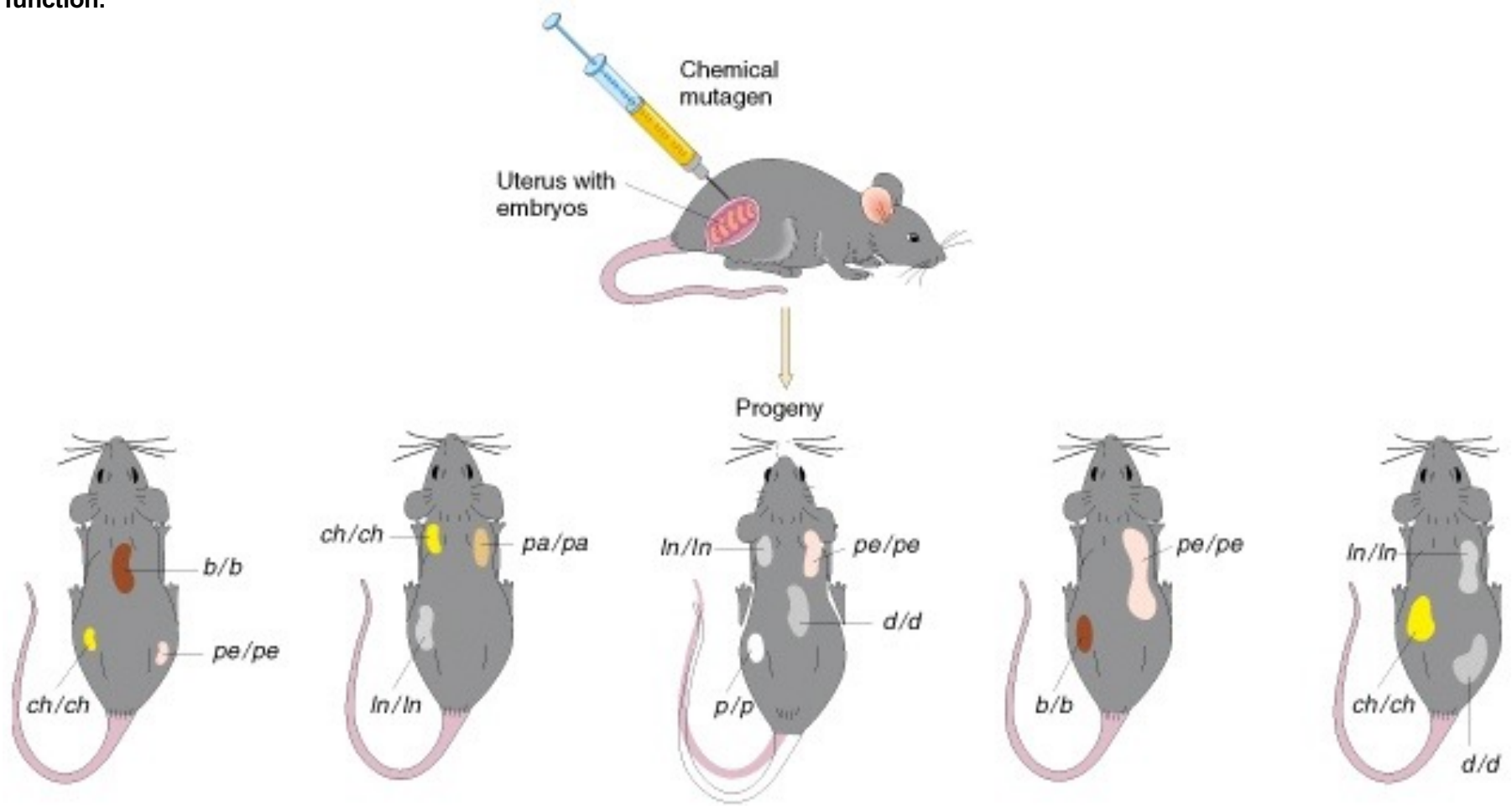
Mechanisms of chromothripsis



1. The specific locus test

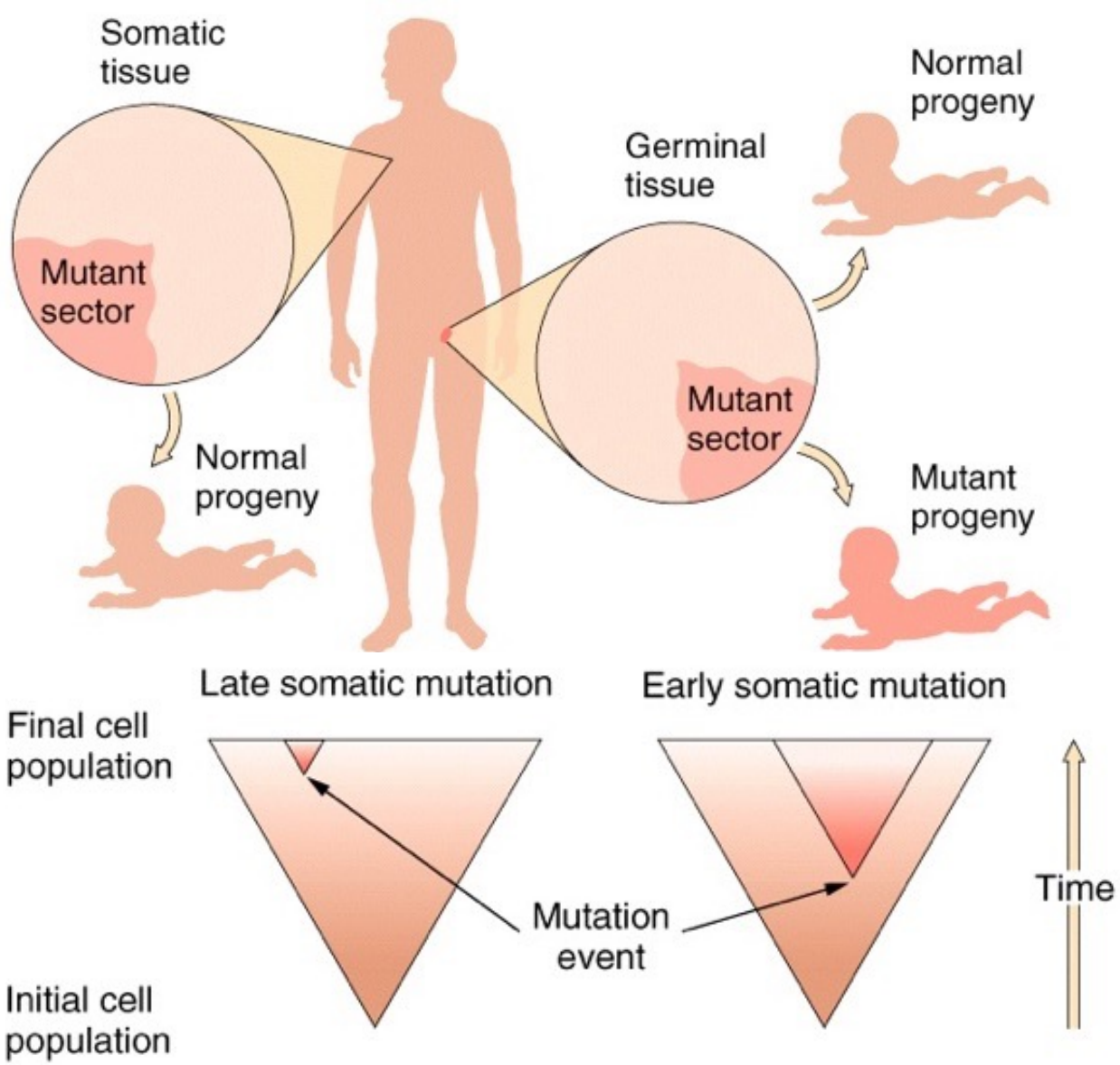
A. organism based tests

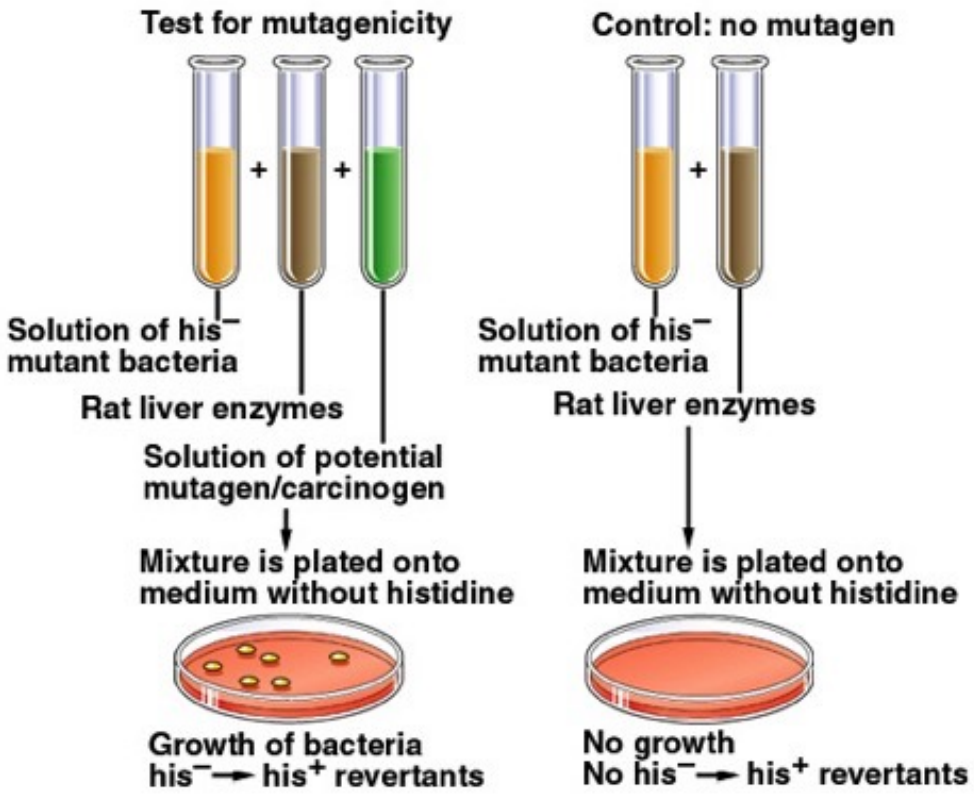
Parents homozygous for the markers listed are mated, giving rise to a female with offspring that are heterozygous at each of these loci. In the absence of loss-of-function mutations at any of these loci her offspring will all look wildtype. The combination of mitotic recombination and spontaneous mutation rate is given by the frequency of progeny with clones of homozygous mutant coat color. Increases above this background, in response to environmental stimuli, give a measure of mutagenicity. The use of multiple loci provides a way of averaging out problems associated with the fact that genes have different sizes, and that some are more sensitive than others to mutation-induced alteration In function.

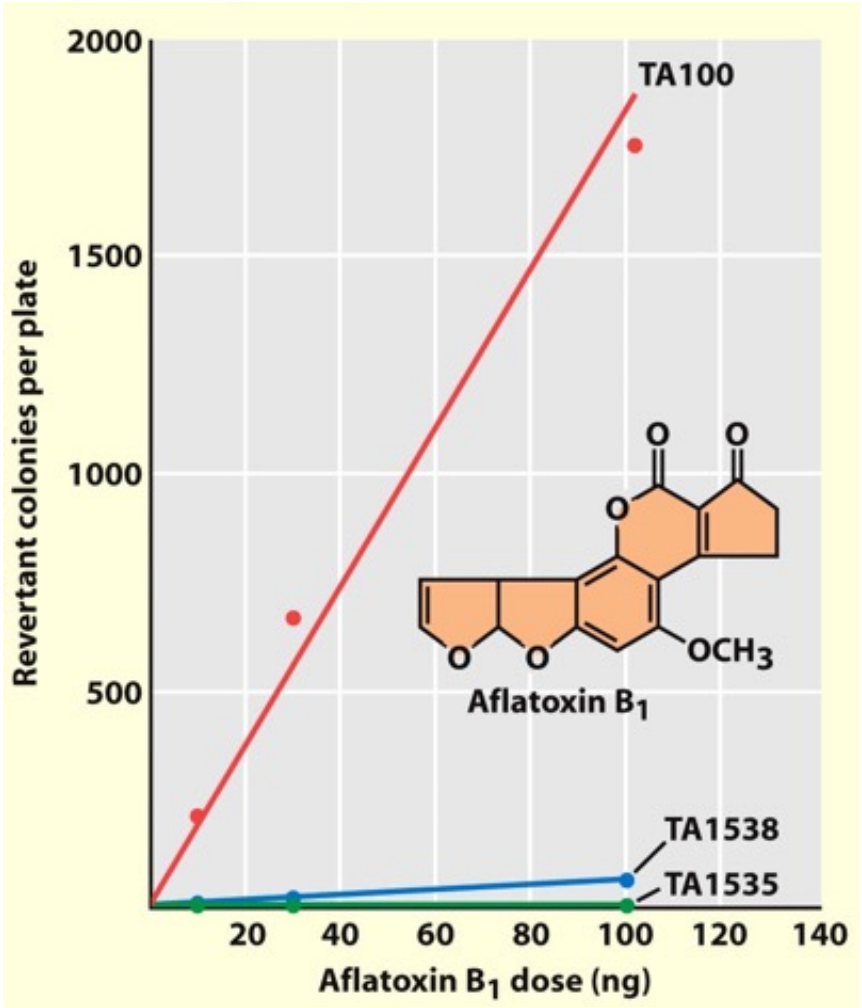


Genotype of progeny is *In/In⁺ • pa/pa⁺ • b/b⁺ • ch/ch⁺ • p/p⁺ • d/d⁺ • pe/pe⁺*
Phenotype of progeny is wild type with mutant sectors

Somatic mutations are not passed on to the next generation because they do not involve cells that give rise to gametes. Germline mutations can be passed on, depending on whether the gamete participating in fertilization carries the mutant allele. The earlier a mutation is induced during the life of an organism, the larger the mutant patch of tissue is likely to be, given that these cells will undergo more rounds of cell division.







TA100 sensitive to base pair substitution, TA1535 and TA1538 sensitive to reversion through frameshift

A compound to be tested is mixed with cells of a histidine- auxotrophic bacterial strain. (Auxotrophic means that because of the his- mutation the bacteria cannot survive in the absence of histidine.) This particular auxotroph contains several different nonfunctional variants of the mutated histidine biosynthesis gene. These are mutated in different ways, such that different kinds of mutagens are likely to revert one or the other of the mutant proteins back to wildtype, thus allowing growth of the cell in the absence of histidine. A compound to be tested is mixed with cells of the his- strain, and with a solution of rat liver enzymes. The liver enzymes are added because in the body these enzymes may convert nontoxic molecules into mutagens during transit through the liver. The mixture is then plated on a petri dish without histidine, Only colonies that are his+ revertnats will be able to grow. Comparison with the control that lacks mutagen provides an indication as to whether the compound is mutagenic.

Mutations and cancer

10^{13} cell in human body

10^{11} cell divisions (DNA replication events)/day

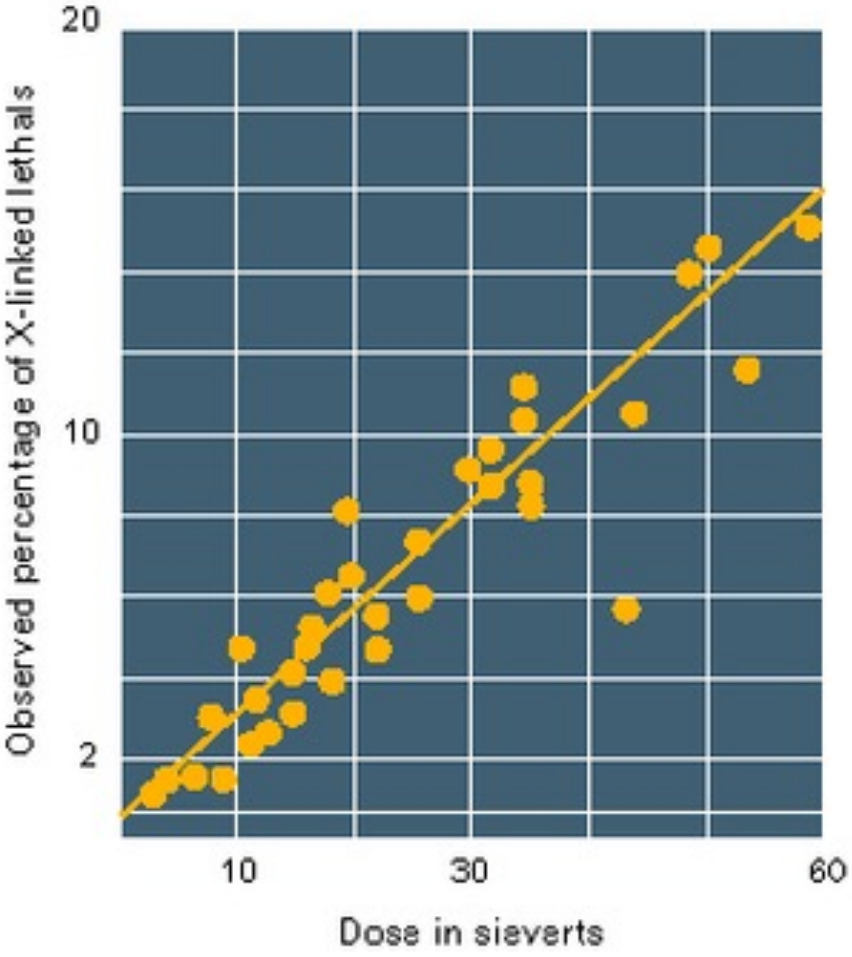
The mutation rate per nucleotide/DNA replication event is 10^{-9}

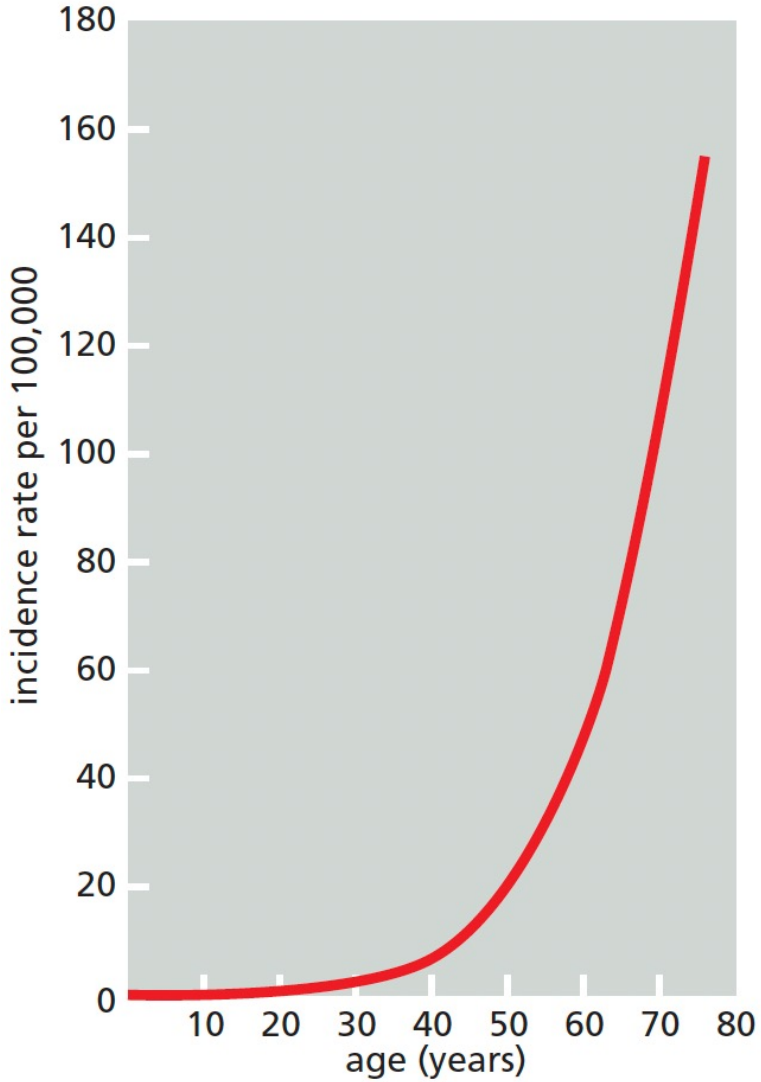
Every possible single nucleotide mutation occurs in our genome hundreds of times each day.

Mitotic recombination can convert heterozygous cells into homozygotes. Rates range from 10^{-2} - 10^{-4} per individual/ generation

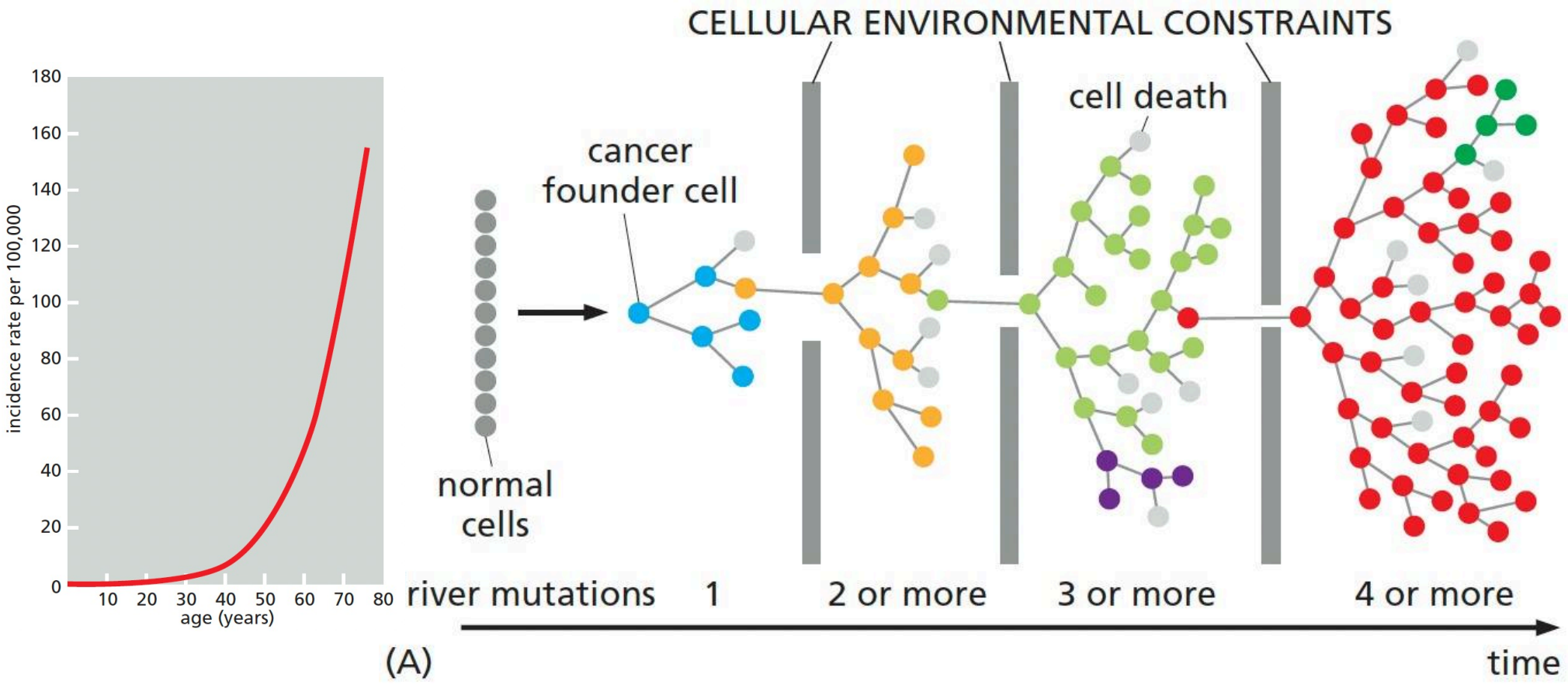
Cancer as a genetic disease

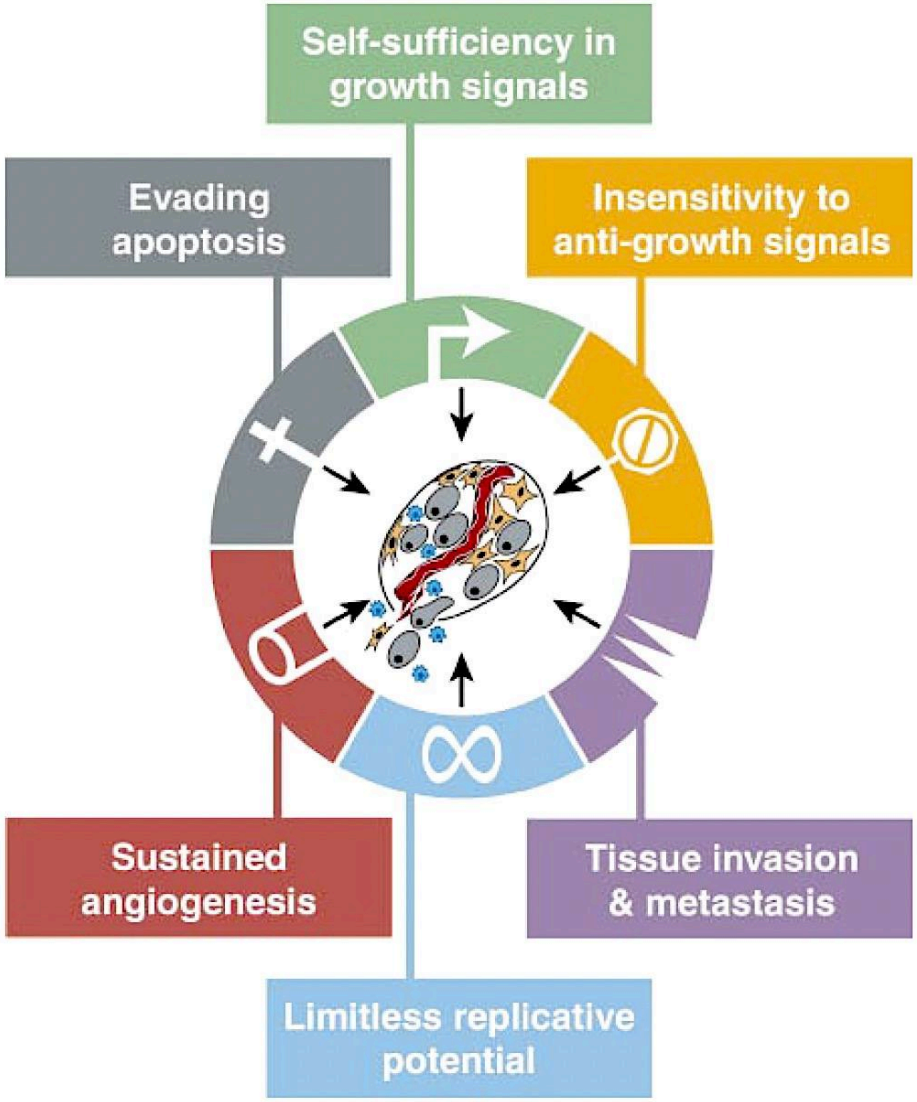
The figure on the left shows that the frequency of lethal mutation induction (which is related but not equivalent to the total mutation rate) is roughly a linear function of radiation dose. In contrast, the incidence of most cancers (on right) is highly nonlinear, increasing dramatically with age. Why???



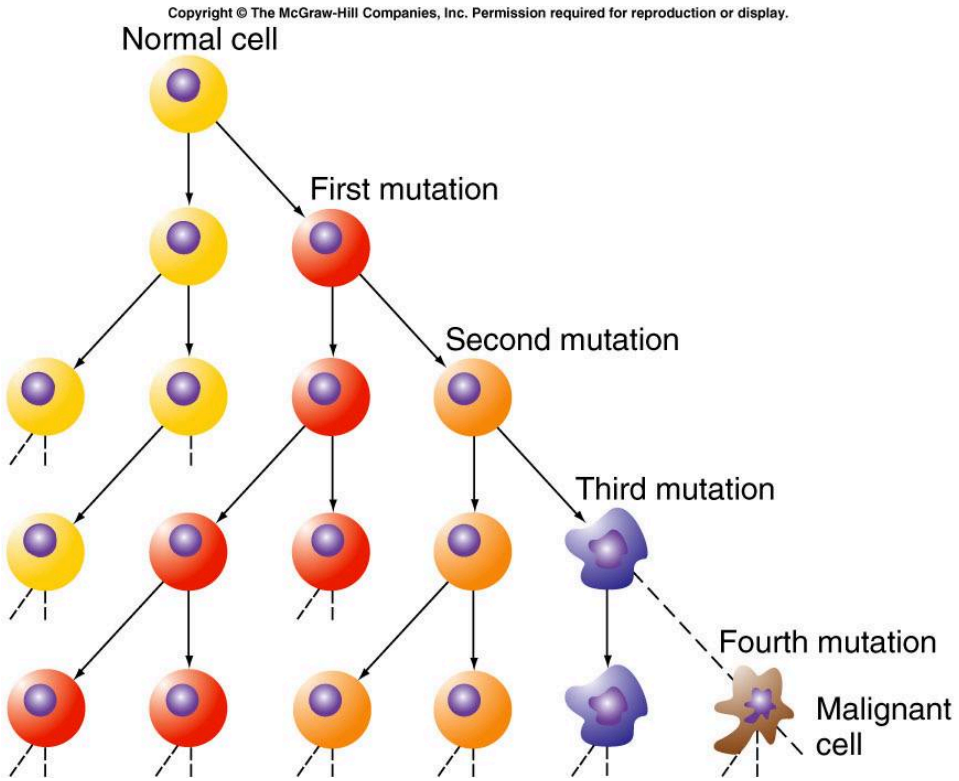


Multiple mutation events are required. Some of these increase the overall mutation rate by interfering with DNA repair or by creating aneuploidy





Alterations in multiple processes are needed



Wild mice under laboratory conditions: 40% have cancer at death (1-3 years).

Humans are 3000 times larger and live 20-30 times longer. ~40% of us will have cancer. ~ 16-17% of us will die of it.

It cannot be the case that the probability of of a cell becoming cancerous/per unit time is the same for us as for a mouse. Otherwise, we would all be dead in utero.

Anti-cancer adaptations

1. **Reduce the mutation rate**
2. **Reduce the selective advantage of each intermediate step towards tumor formation.**
3. **Increase the number of mutations required to turn a cell cancerous.**

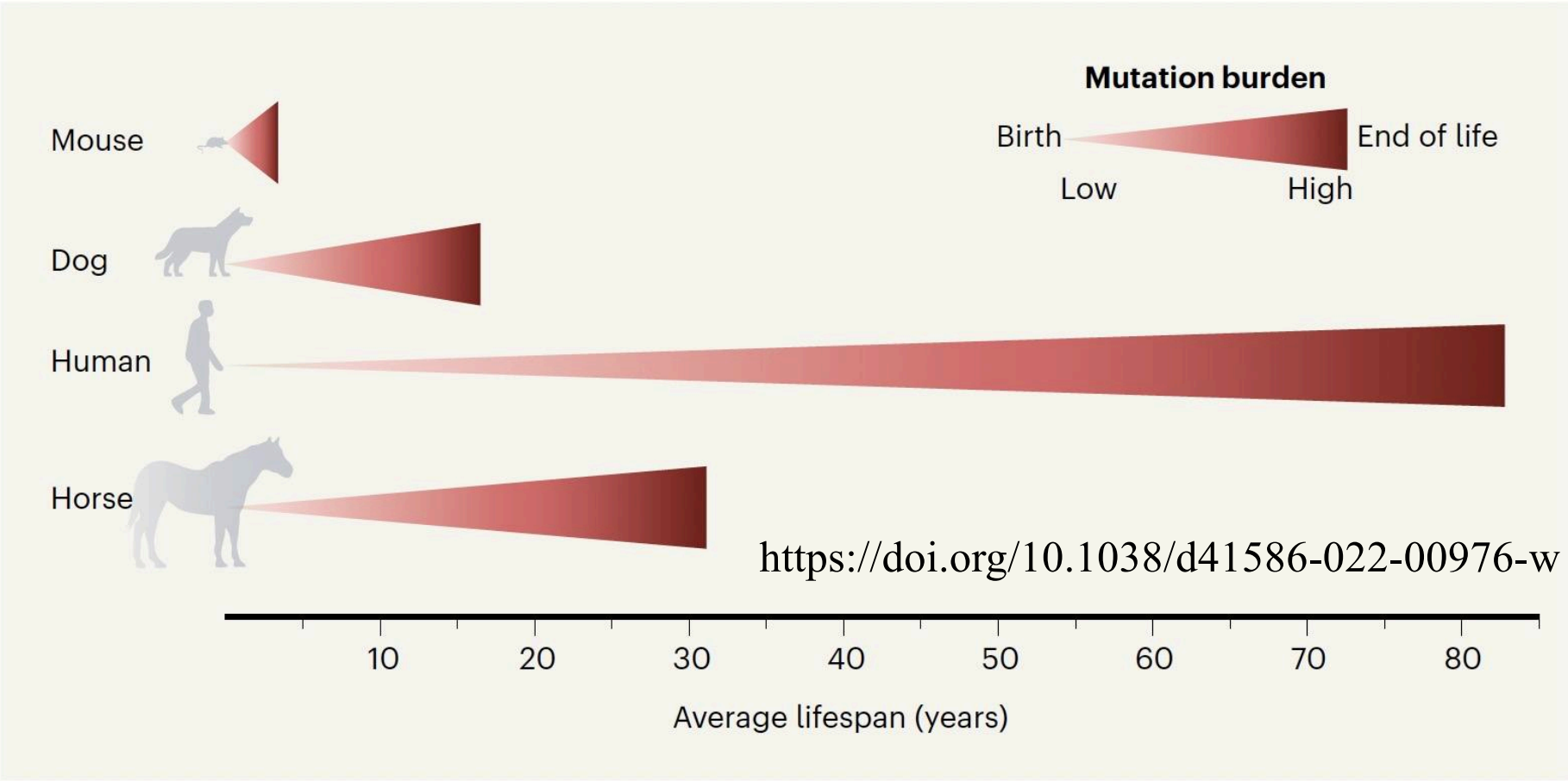


Figure 1 | Lifespan and the accumulation of mutations across species. If the number of mutations in a cell (the mutation burden) drives the risk of developing cancer, then animals that live longest and have the most cells should be the most likely to die of cancer. However, as confirmed by Vincze *et al.*[2], this is not the case, and this puzzle is known as Peto's paradox[3]. Cagan *et al.*[1] gathered data that enabled them to estimate the mutation rate (the number of mutations per cell per year) for 16 animal species, 4 of which are shown here. The authors found that species with shorter lifespans accrue mutations at higher rates compared with long-lived species, resulting in similar end-of-life mutation burdens per cell for different species. This finding partially explains Peto's paradox. Long-lived species also tend to be larger, and therefore might have evolved further mechanisms for combating cancer, such as extra copies of genes that function to prevent tumour formation.

Peto's paradox: Modeled probability of cancer based on divisions and mutation rate does not fit the data: elephants get cancer less frequently than humans

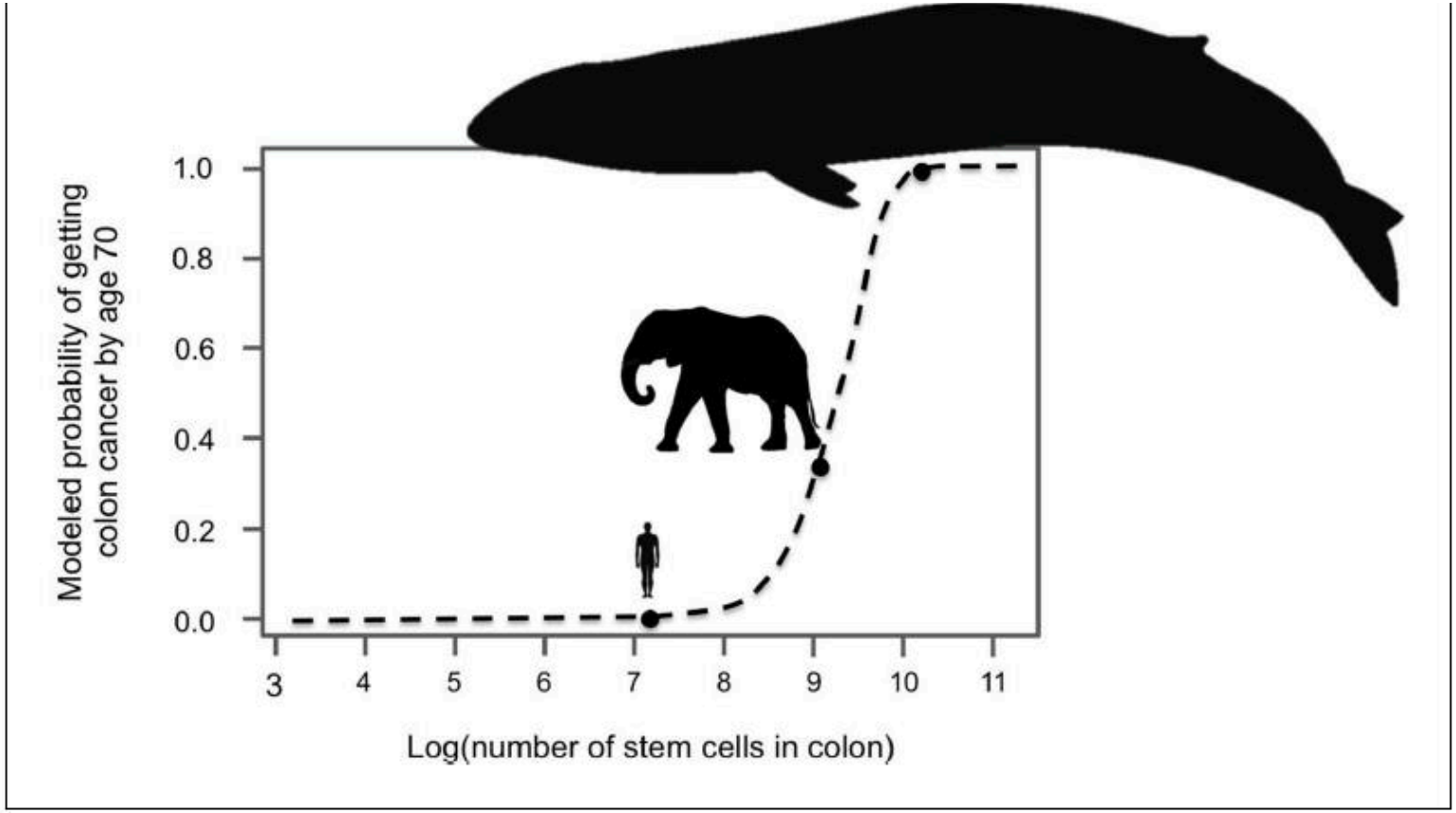
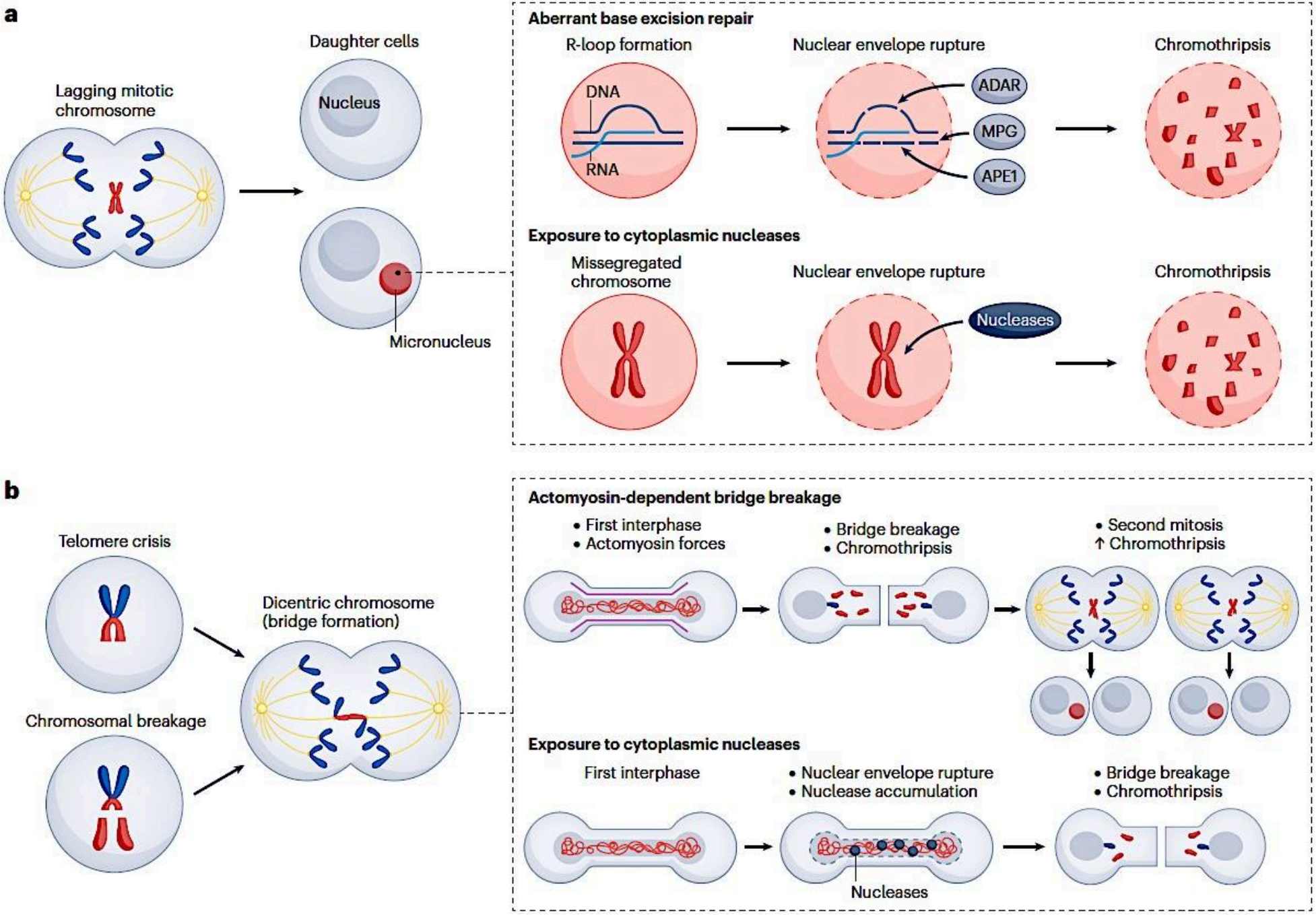


Figure 1. Large-bodied animals have much lower rates of cancer than models predict. Based on data on number of cell divisions and mutation rate, a model estimates that larger animals with larger colons should have a much higher risk developing colon cancer by age 70 (dashed line). This predicts a probability of less than 1% for humans, which matches reported incidence statistics in the UK (***Cancer Research UK***). However, although the model estimates much higher probabilities for large-bodied animals such African elephants and blue whales, cancer risk is actually much lower in elephants than in humans. Sulak et al. suggest that elephants have evolved to have this significantly reduced risk of cancer by replicating the tumor suppressor gene *TP53*. Whales appear to have evolved other solutions, which remain unknown. This model and figure are adapted from ***Caulin and Maley (2011)***


a
Daughter cells
Lagging mitotic chromosome
Nucleus
Micronucleus
Aberrant base excision repair
R-loop formation
Nuclear envelope rupture
Chromothripsis
DNA
RNA
ADAR
MPG
APE1
Exposure to cytoplasmic nucleases
Missegregated chromosome
Nuclear envelope rupture
Chromothripsis
Nucleases
b
Telomere crisis
Chromosomal breakage
Dicentric chromosome (bridge formation)
Actomyosin-dependent bridge breakage
• First interphase
• Actomyosin forces
• Bridge breakage
• Chromothripsis
• Second mitosis
↑ Chromothripsis
Exposure to cytoplasmic nucleases
First interphase
• Nuclear envelope rupture
• Nuclease accumulation
• Bridge breakage
• Chromothripsis
Nucleases

Suppose that the mutation rate for the average cancer promoting gene is 10^{-7}/gene/cell division. The body contains roughly 10^{13} cells. Therefore, we should all have cancer. Why is this not the case?

Multiple mutations are necessary for tumor formation and progression to metastasis (about 6). But then the frequency of cancer should be quite low = $(10^{-7})^6 \times 10^{13} = 1$ in 10^{29}. This is not true either.

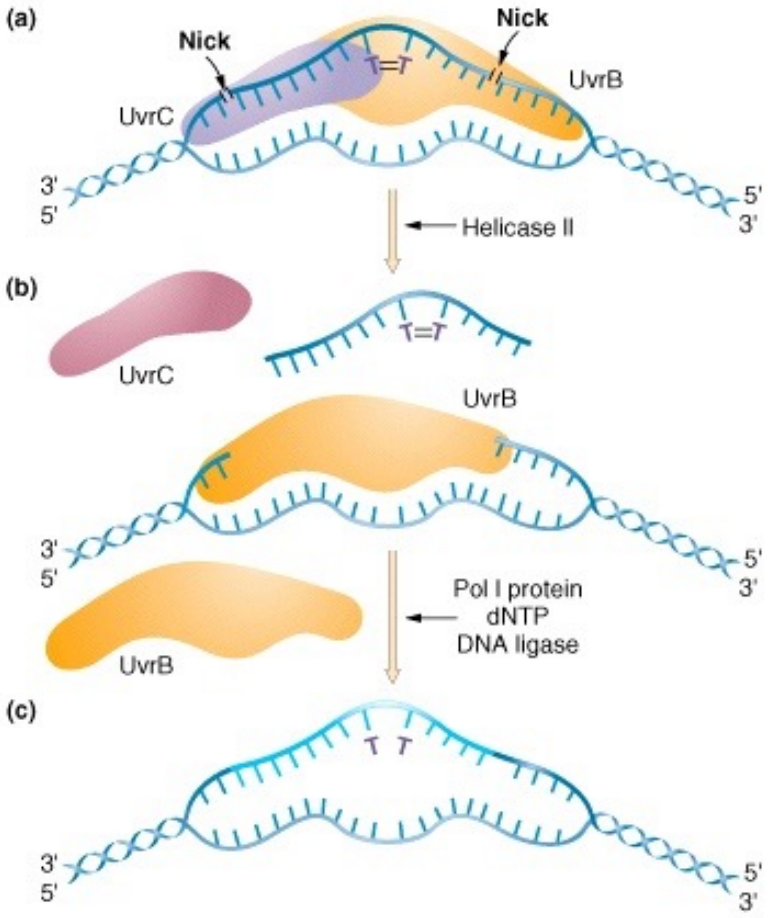
1. Some mutations enhance cell proliferation or prevent cell death, creating an expanded target population of cells for the second mutation.

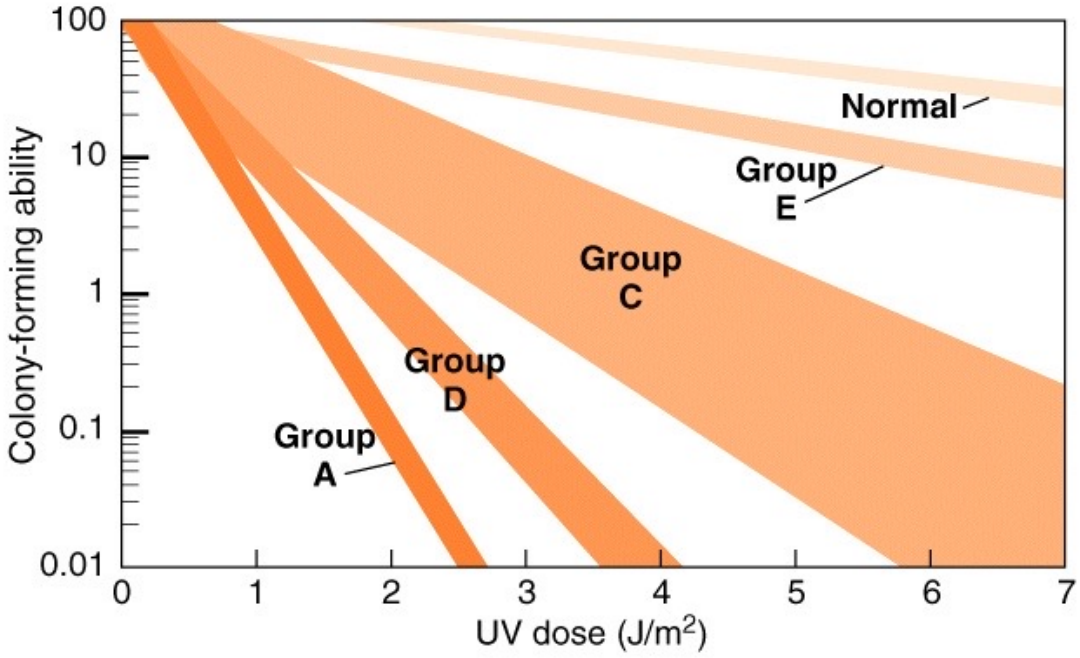
2. Some mutations affect the stability of the entire genome, at either the DNA or the chromosome level, thereby increasing the overall mutation rate.

Excision-repair pathways

Nucleotide excision repair involves the removal of a single stranded region surrounding a damaged group of bases, in this case a thymidine dimer. Repair occurs using the opposite strand as a template. Xeroderma pigmentosum is a group of human diseases due to defects in NER. Individuals homozygous mutant for components of this pathway are very susecptable to skin UV irradiation, as well as other chemical mutagens. They develop many tumors early in life.

Mutations on distinct chromosomes give rise to the XP phenotype. These phenotypes can be shown to be due to recessive loss of function mutations, and to map to distinct loci through the use of a complementation test in which cells from different individuals with the disease are fused and their sensitivity to UV irradiation measured. Fusion of cells in different complementation groups will result in heterozygosity at both loci, resulting in cells with wildtype resistance to UV.

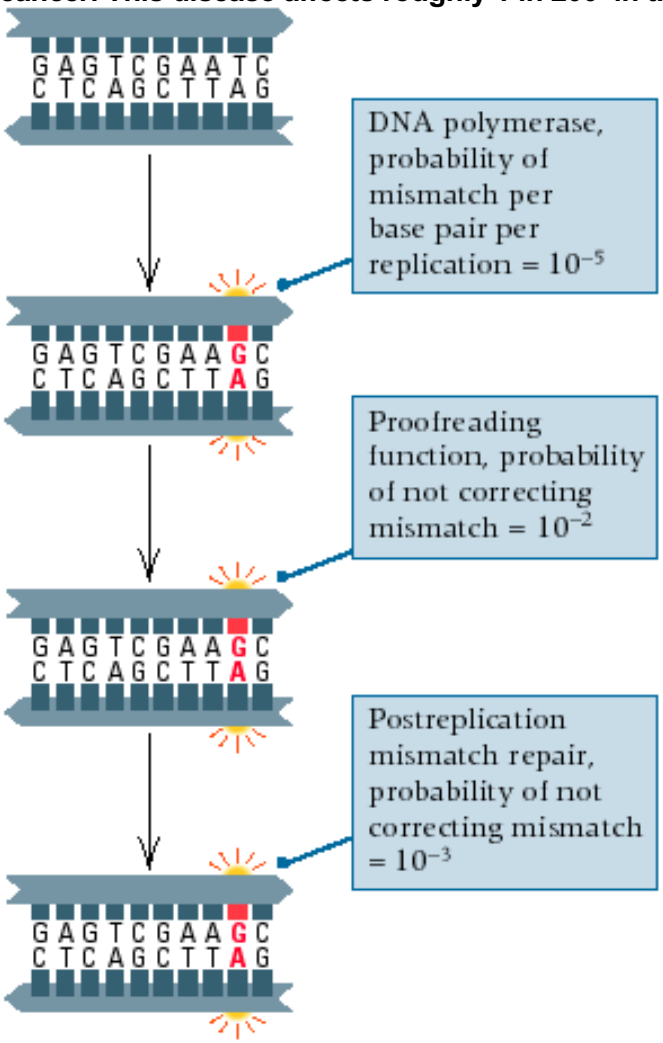




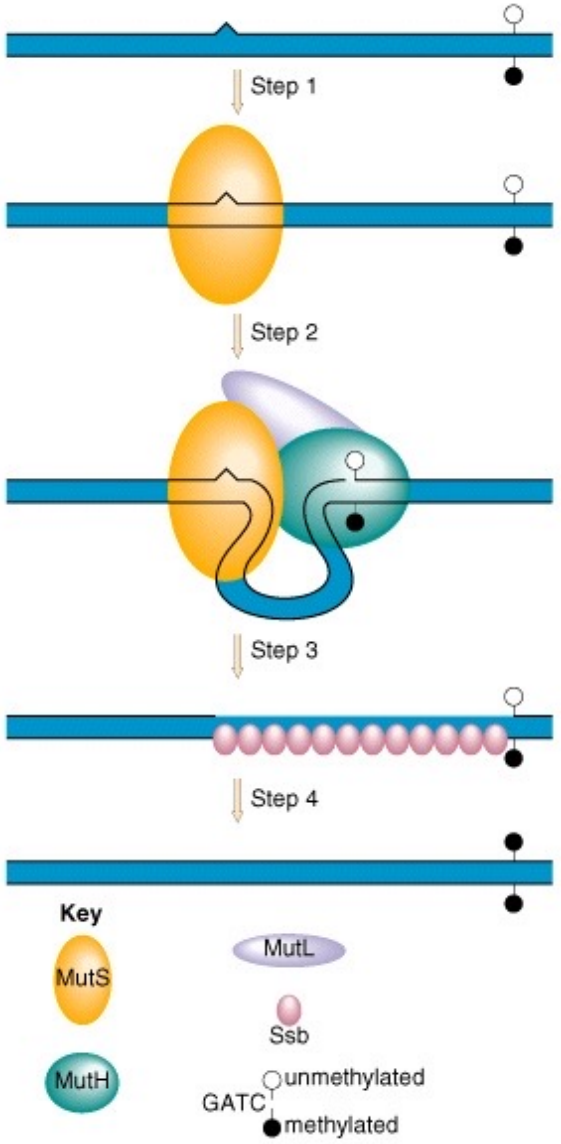
Methyl-directed, mismatch repair

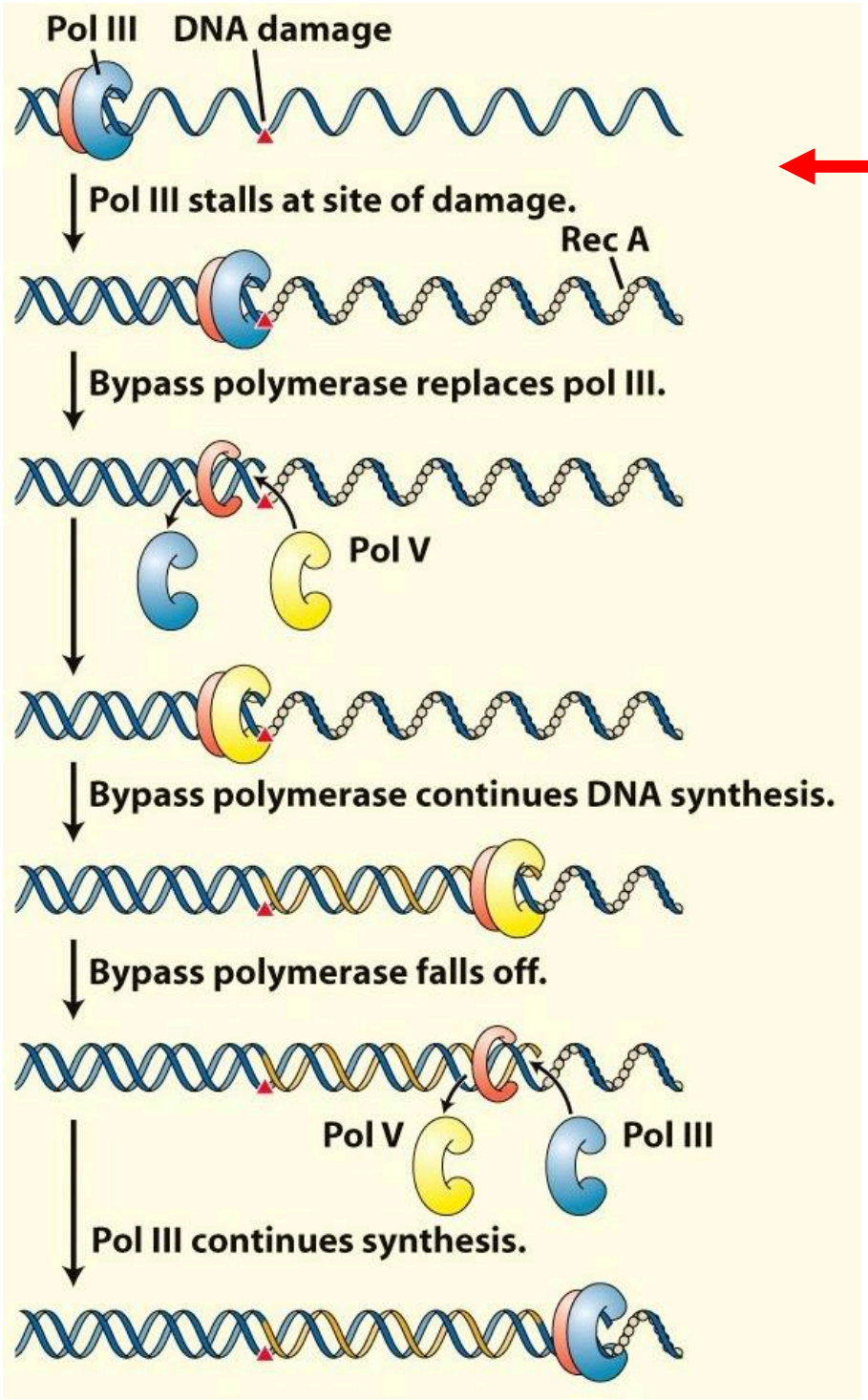
Methyl-directed mismatch repair uses the fact that the newly replicated strand of DNA lacks methylation for a period of time: until the methylases have time to do their thing. The template strand is methylated. Thus, a repair machinery that recognizes two bases as mismatched has an idea as to which one is the correct template strand and which is the daughter with the newly introduced mismatch.

mutations in the methyl-directed mismatch repair system are associated with a high frequency of cancers, including HNPCC, a form of colon cancer. This disease affects roughly 1 in 200 in the Western world. That means the allele frequency in the population must be very high.



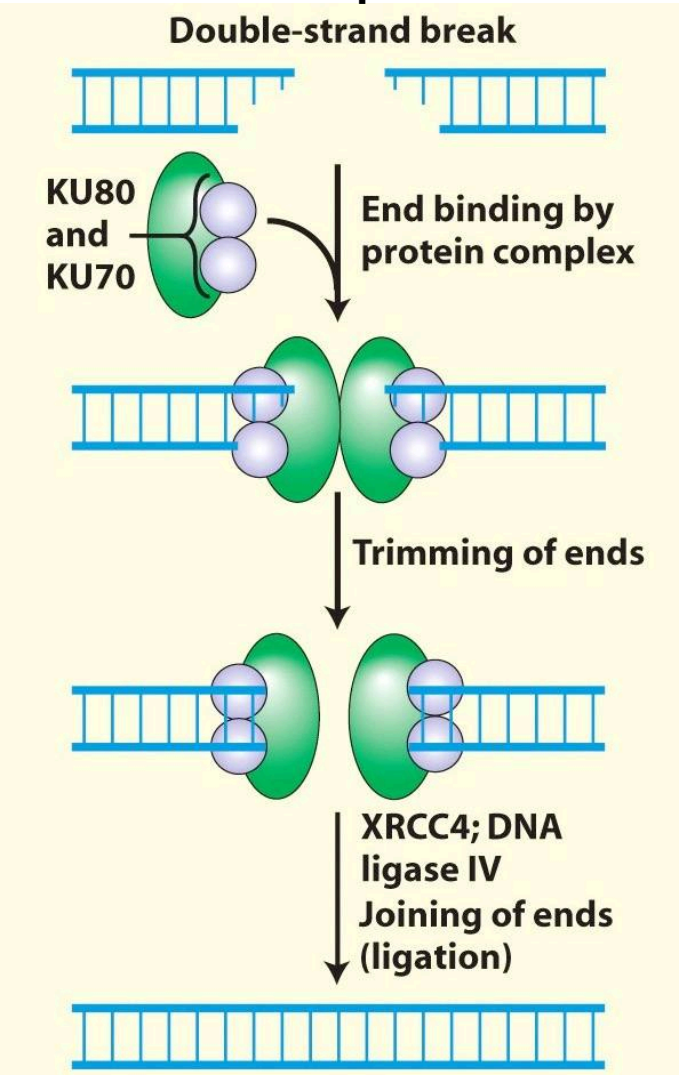
Overall probability of incorporating a mismatched base that remains uncorrected = $10^{-5} \times 10^{-2} \times 10^{-3} = 10^{-10}$ per base pair per replication





Translesion synthesis at a stalled replication fork allows synthesis beyond a lesion, but it is error-prone.

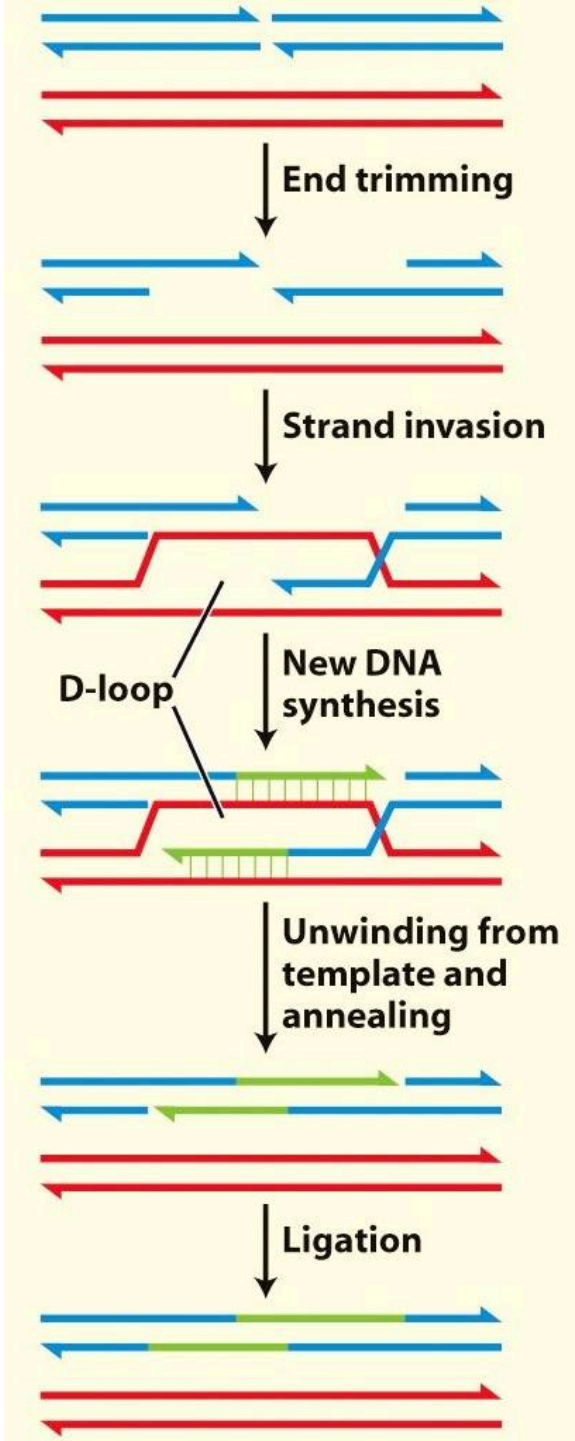
Nonhomologous end joining repairs, but is also error-prone



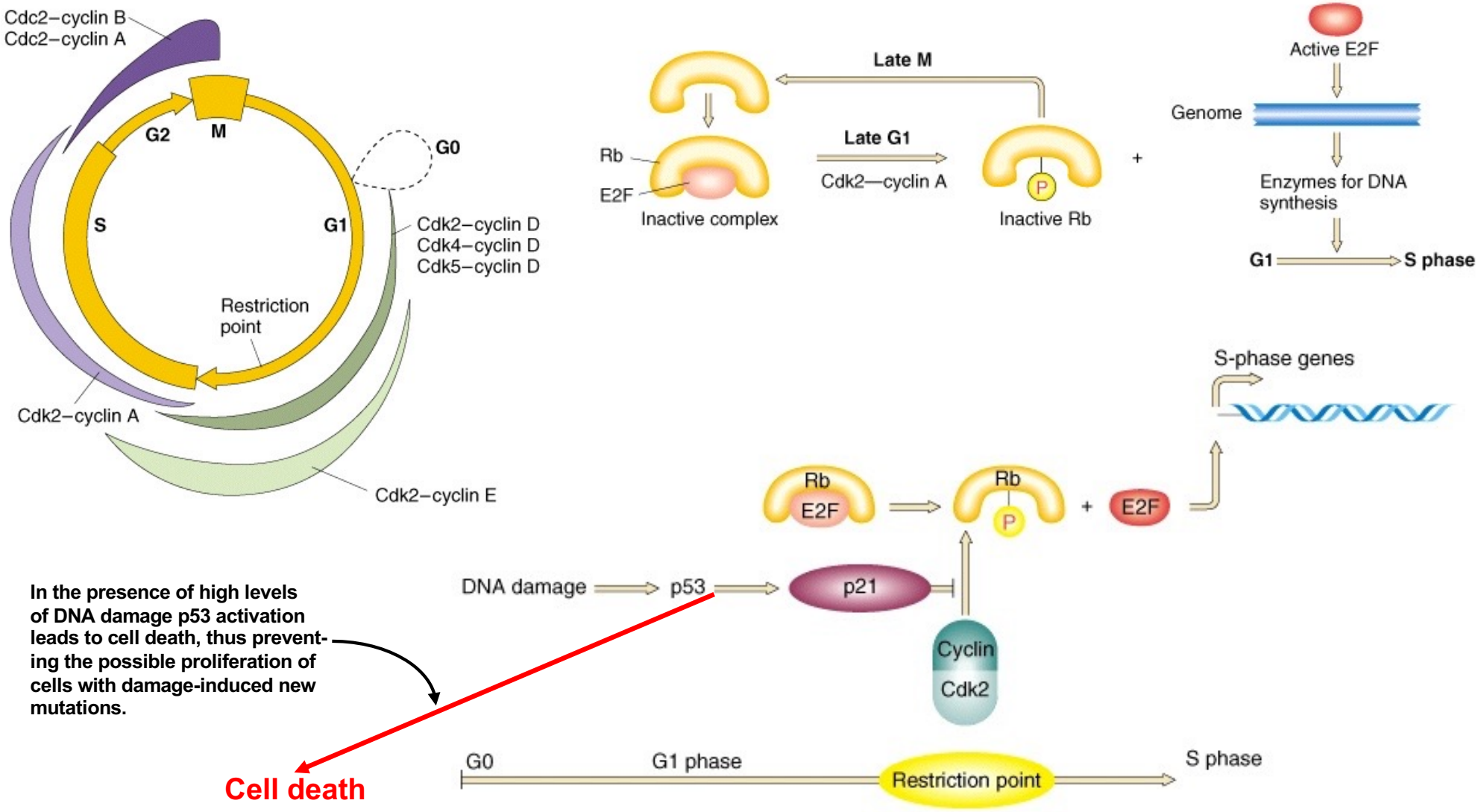
Error-free repair of double-strand breaks by SDSA

(synthesis-dependent strand annealing)

But, if the repair template is a homologous chromosome with a different allele repair can result in homozygosity



When DNA synthesis occurs mistakes sometimes happen. In addition, DNA damage from environmental or internal sources can lead to chromosome breaks. As an example, consider DNA damage occurring during G1, just before DNA synthesis. If this DNA went unrepaired and DNA synthesis was allowed to continue, the mutational consequences of the damage would be transmitted into daughter cells. Cell cycle checkpoints act to stop cell cycle progression when such damage is detected in order to give the DNA machinery time to repair it. One important part of this pathway involves the p53 protein. DNA damage activates p53, leading to p53-dependent cell cycle arrest. In the presence of high, unrepairable levels of DNA damage, p53 signals cell death, effectively removing the cell from the organism's pool of genomes. Homozygous loss of p53 or other components of the p53 pathway leads to the accumulation of mutations, including large chromosomal rearrangements, because these checkpoints are no longer functional.



HUMAN PAPILOMA VIRUS AND CERVICAL CARCINOMA IN WOMEN
IMMUNIZATION WITH A CANCER VACCINE

Know the link:
Cervical cancer and HPV

WHAT IS CERVICAL CANCER?

Cervical cancer is cancer of the cervix (the lower part of the uterus that connects to the vagina). Cervical cancer is caused by certain types of HPV. When a female becomes infected with certain types of HPV and the virus doesn't go away on its own, abnormal cells can develop in the lining of the cervix. If not discovered early and treated, these abnormal cells can become cervical precancers and then cancer.

THERE'S GOOD NEWS

GARDASIL is the only vaccine that may help guard against diseases caused by HPV Types 16 and 18, which cause 70% of cervical cancer cases, and HPV Types 6 and 11, which cause 90% of genital warts cases.

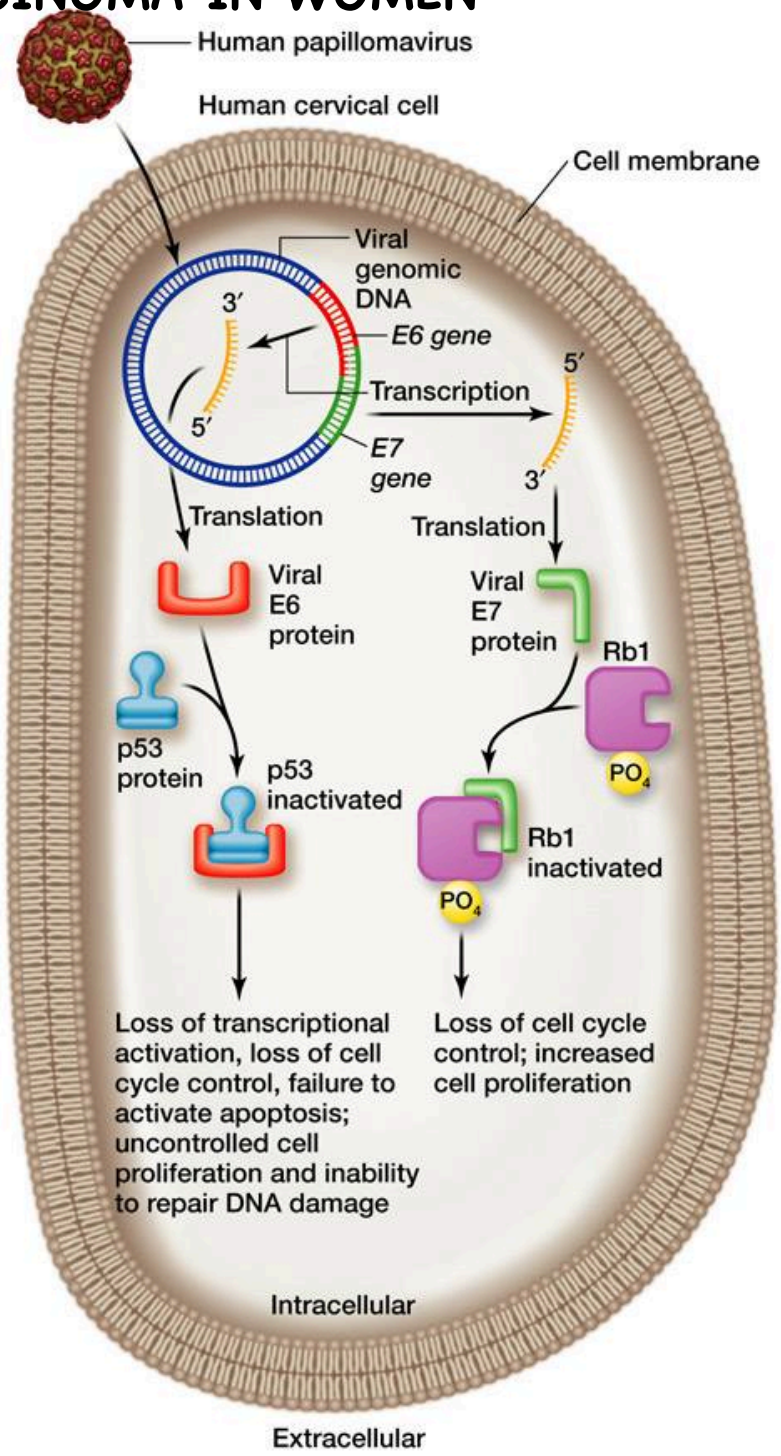
IMPORTANT INFORMATION ABOUT GARDASIL

HPV Types 16 and 18 cause 70% of cervical cancer cases, and HPV Types 6 and 11 cause 90% of genital warts cases.

GARDASIL may not fully protect everyone and does not prevent all types of cervical cancer, so it is important to continue regular cervical cancer screenings.

Anyone who is allergic to the ingredients of GARDASIL should not receive the vaccine. GARDASIL is not for women who are pregnant.

GARDASIL will not treat cervical cancer and genital warts and will not protect against diseases caused by other HPV types.



Queens live up to 28 years. Cancer has never been observed.

The Life Span of a Rodent May Aid Human Health

Frans Lanting/Corbis

PROTECTED EXISTENCE Naked mole rats like this one in South Africa rarely leave the safety of their underground tunnels. The queens never come to the surface. Even the workers are exposed only when they need to shovel out dirt.
More Photos >

Hypersensitivity to contact inhibition provides a clue to cancer resistance of naked mole-rat

Andrei Seluanov[a], Christopher Hine[a,b], Jorge Azpurua[a], Marina Feigenson[a,b], Michael Bozzella[a], Zhiyong Mao[a], Kenneth C. Catania[c], and Vera Gorbunova[a,1]

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Edited by Eviatar Nevo, University of Haifa, Haifa, Israel, and approved September 16, 2009 (received for review May 12, 2009)

The naked mole-rat is the longest living rodent with a maximum lifespan exceeding 28 years. In addition to its longevity, naked mole-rats have an extraordinary resistance to cancer as tumors have never been observed in these rodents. Furthermore, we show that a combination of activated Ras and SV40 LT fails to induce robust anchorage-independent growth in naked mole-rat cells, while it readily transforms mouse fibroblasts. The mechanisms responsible for the cancer resistance of naked mole-rats were unknown. Here we show that naked mole-rat fibroblasts display hypersensitivity to contact inhibition, a phenomenon we termed "early contact inhibition." Contact inhibition is a key anticancer mechanism that arrests cell division when cells reach a high density. In cell culture, naked mole-rat fibroblasts arrest at a much lower density than those from a mouse. We demonstrate that early contact inhibition requires the activity of p53 and pRb tumor suppressor pathways. Inactivation of both p53 and pRb attenuates early contact inhibition. Contact inhibition in human and mouse is triggered by the induction of $p27^{Kip1}$. In contrast, early contact inhibition in naked mole-rat is associated with the induction of $p16^{Ink4a}$. Furthermore, we show that the roles of $p16^{Ink4a}$ and $p27^{Kip1}$ in the control of contact inhibition became temporally separated in this species: the early contact inhibition is controlled by $p16^{Ink4a}$, and regular contact inhibition is controlled by $p27^{Kip1}$. We propose that the additional layer of protection conferred by two-tiered contact inhibition contributes to the remarkable tumor resistance of the naked mole-rat.

Mammals have evolved complicated anti-cancer defenses consisting of cell cycle checkpoints, apoptosis, and replicative senescence controlled by a network of tumor-suppressor genes such as p53 and Rb. Anticancer mechanisms have been studied extensively in humans and mice. These studies revealed important differences between human and mouse anti-cancer defenses, which may explain the differences in cancer susceptibility between these species (10). Human cells use replicative senescence as an anticancer mechanism (11), while mouse somatic cells express telomerase (12) and are immortal in culture (13). Another difference is that in humans both the Rb and p53 tumor suppressors play important roles in controlling cell proliferation, creating backup barriers for cancer progression, while in the mouse Rb plays a relatively minor role (14, 15).

Contact inhibition is a process of arresting cell growth when cells come in contact with each other. As a result, normal cells stop proliferating when they form a monolayer in a culture dish. Contact inhibition is a powerful anticancer mechanism that is lost in cancer cells (16). Cancer cells do not arrest their growth when they fill a culture dish, but continue to proliferate, piling up on top of each other and forming multilayered foci. The growth arrest in contact inhibition is signaled by membrane proteins, and is mediated by elevated levels of $p27^{Kip1}$ (p27) cyclin-dependent kinase inhibitor. p27 binds cyclin-CDK complexes and arrests the cells in the G1 phase of the cell cycle (17–20). The importance of contact inhibition

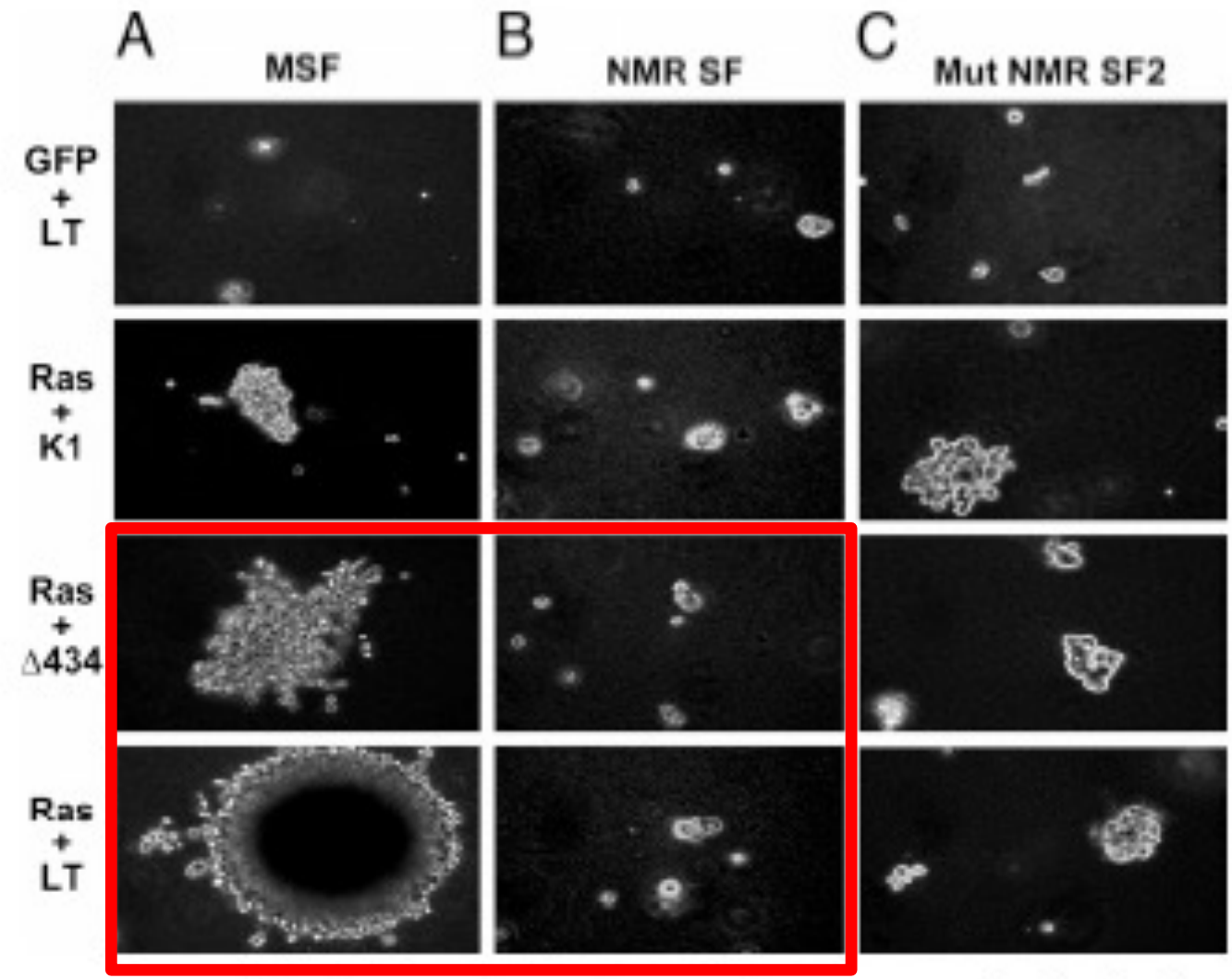
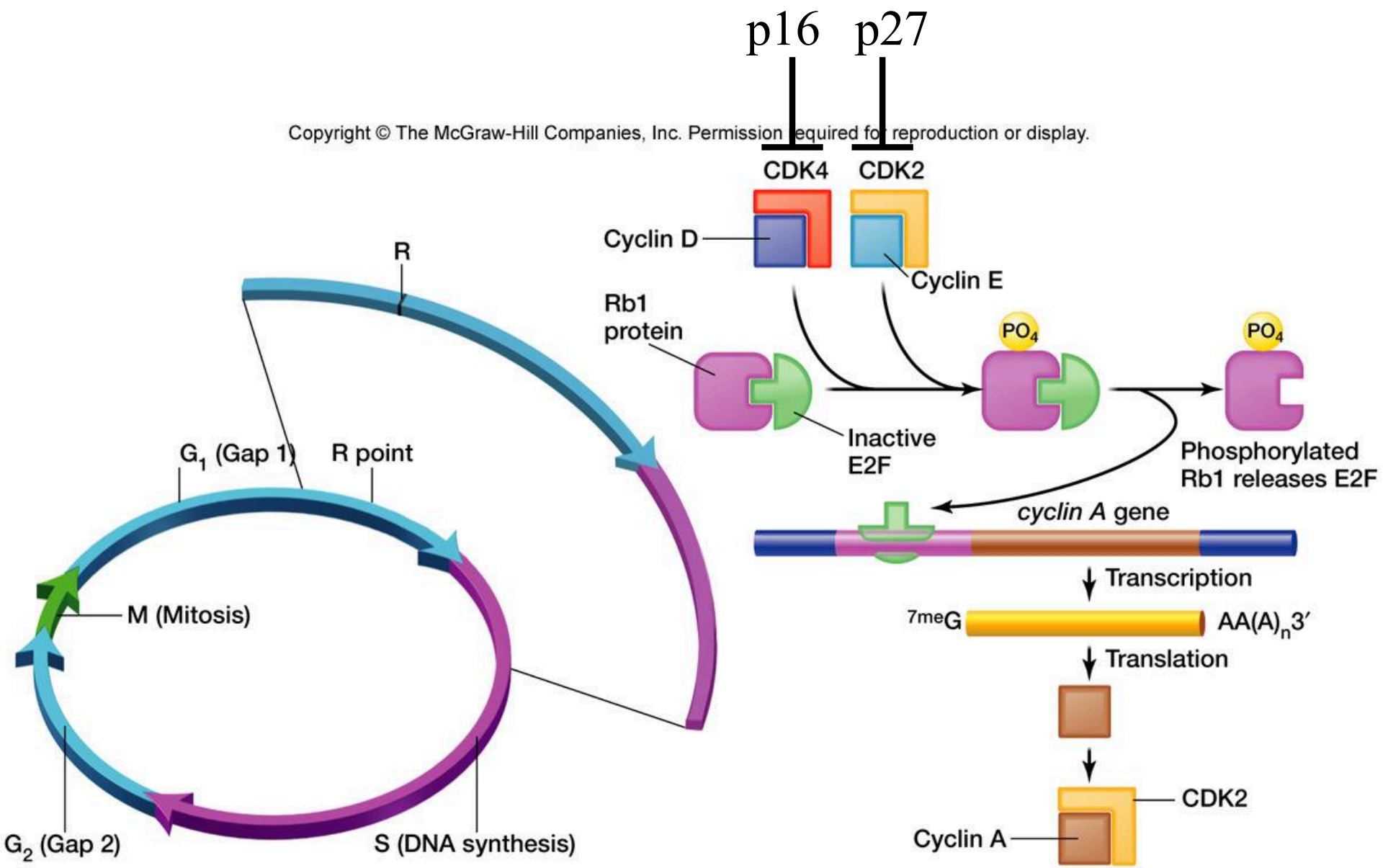


Fig. 1. Assay of anchorage-independent growth in mouse and naked mole-rat skin fibroblasts. Cells were transfected with the vectors encoding different forms of LT antigen (LT, LTK1, and LTΔ434–44) and oncogenic Ras, and plated in soft agar. Figure shows representative microphotographs of colonies generated after 3 weeks at magnification ×20. (*A*) Mouse skin fibroblasts. (*B*) Naked mole-rat skin fibroblasts. (*C*) NMRSF2, a mutated line of naked mole-rat skin fibroblasts that lost early contact inhibition.



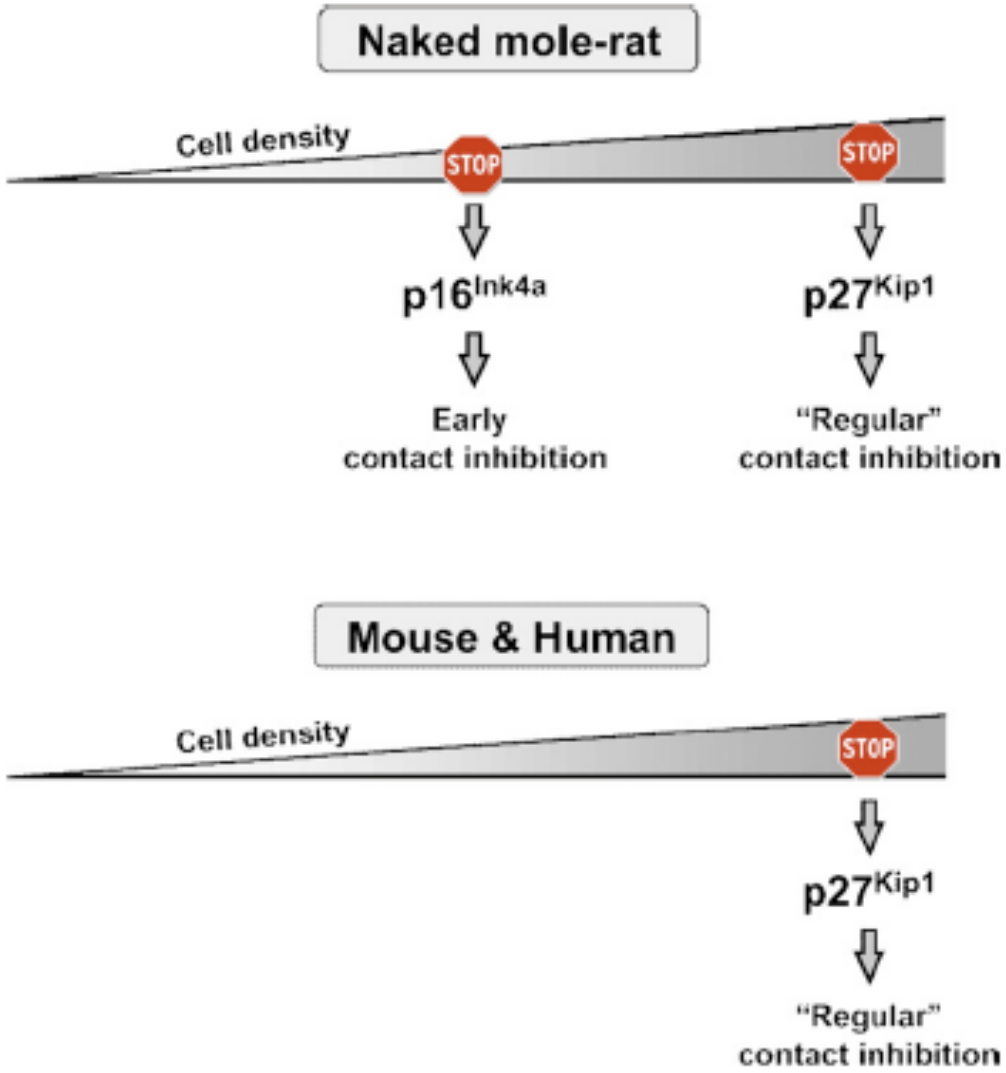
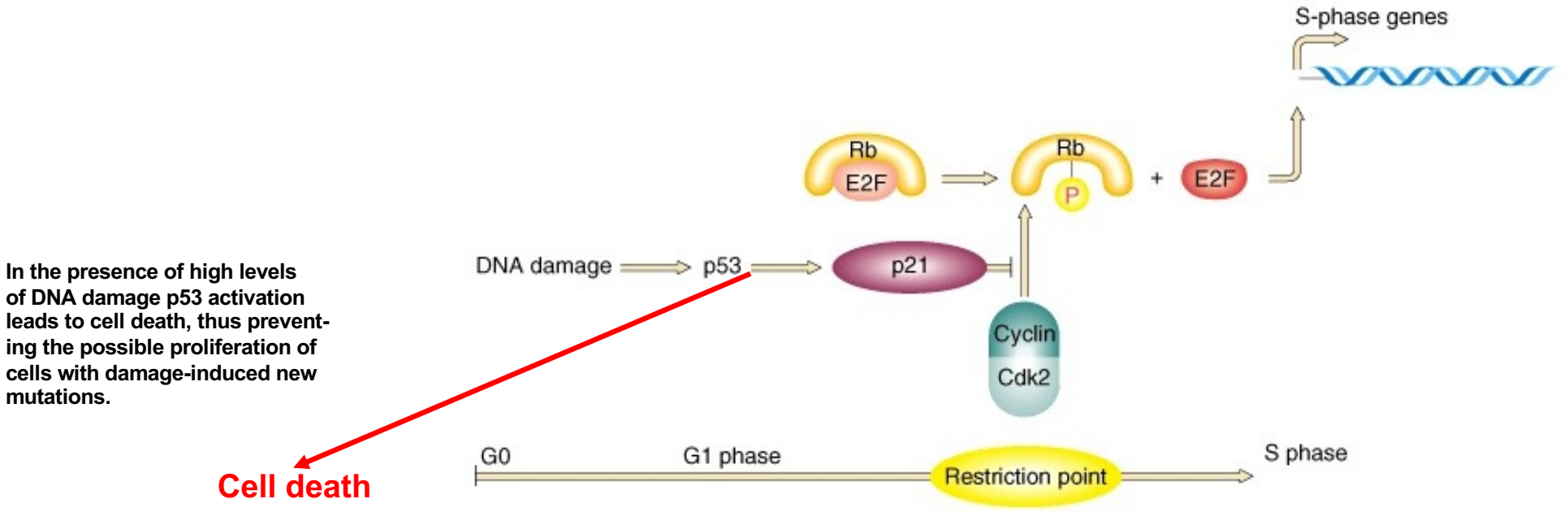


Fig. 7. A model comparing contact inhibition in naked mole-rat to mouse and human. Naked mole-rat cells have two tiers of contact inhibition: early contact inhibition mediated by p16 and regular contact inhibition mediated by p27. In contrast, human and mouse only have regular contact inhibition. The presence of two-tiered contact inhibition may provide naked mole-rats an increased protection against tumor development.

Preliminary Communication

Potential Mechanisms for Cancer Resistance in Elephants and Comparative Cellular Response to DNA Damage in Humans

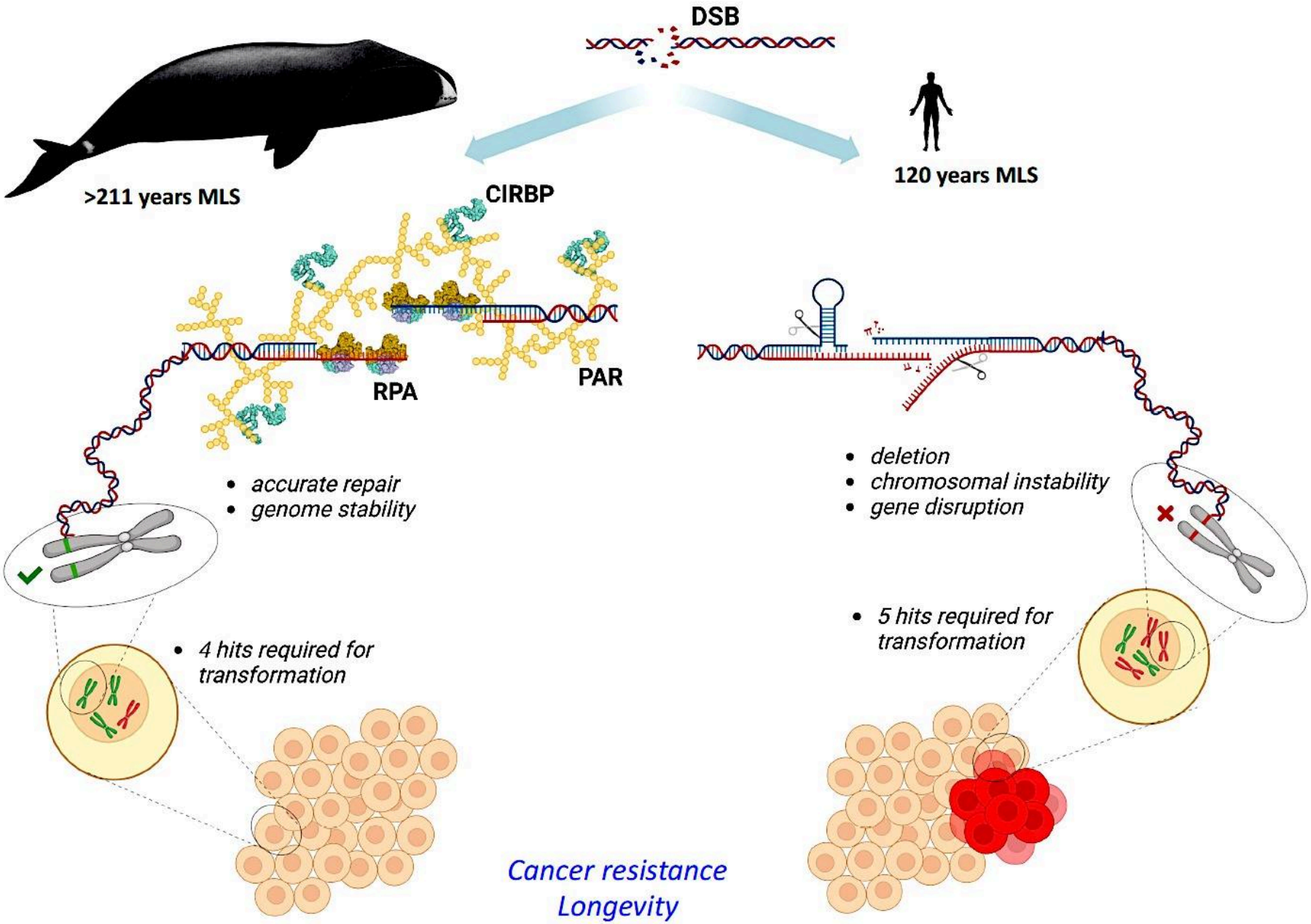
Lisa M. Abegglen, PhD; Aleah F. Caulin, PhD; Ashley Chan, BS; Kristy Lee, PhD; Rosann Robinson, BS; Michael S. Campbell, PhD; Wendy K. Kiso, PhD; Dennis L. Schmitt, DVM, PhD; Peter J. Waddell, PhD; Srividya Bhaskara, PhD; Shane T. Jensen, PhD; Carlo C. Maley, PhD; Joshua D. Schiffman, MD



In the presence of high levels of DNA damage p53 activation leads to cell death, thus preventing the possible proliferation of cells with damage-induced new mutations.

Humans have 2 copies of p53 (one on each homolog). Elephants Have 40 copies!!!!!!!!!

More accurate DNA repair

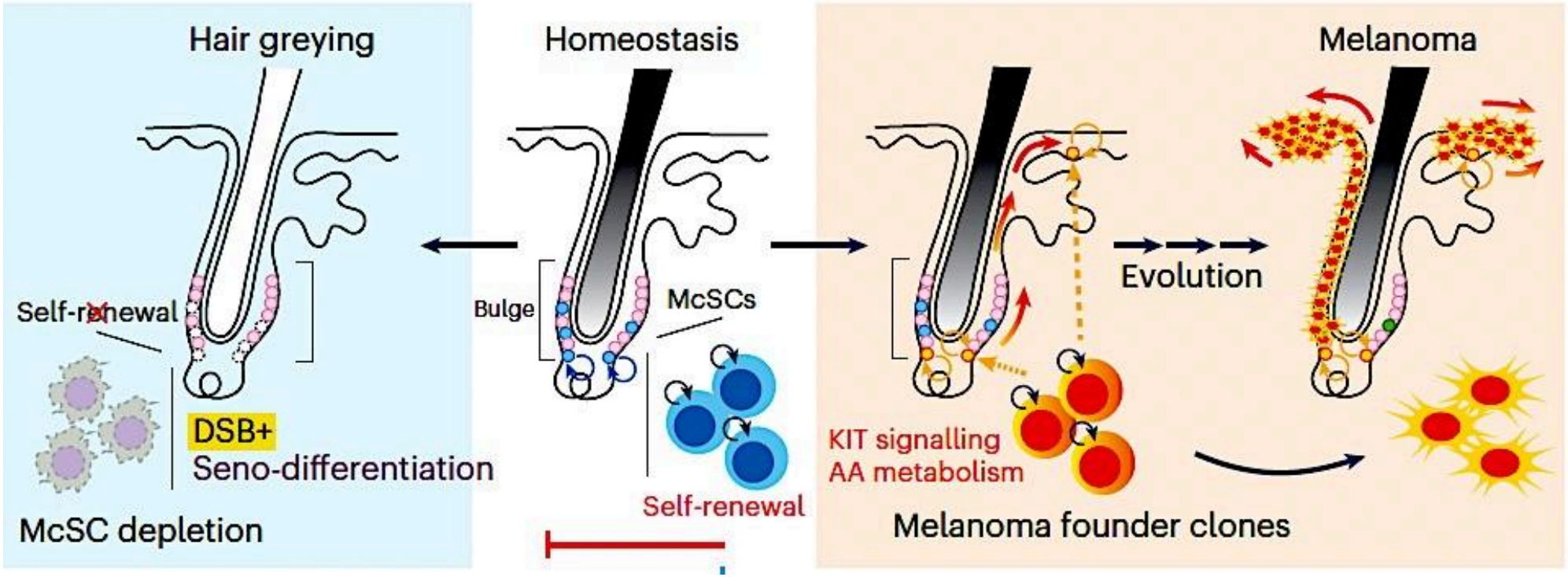


https://doi.org/10.1038/s41586-025-09694-5

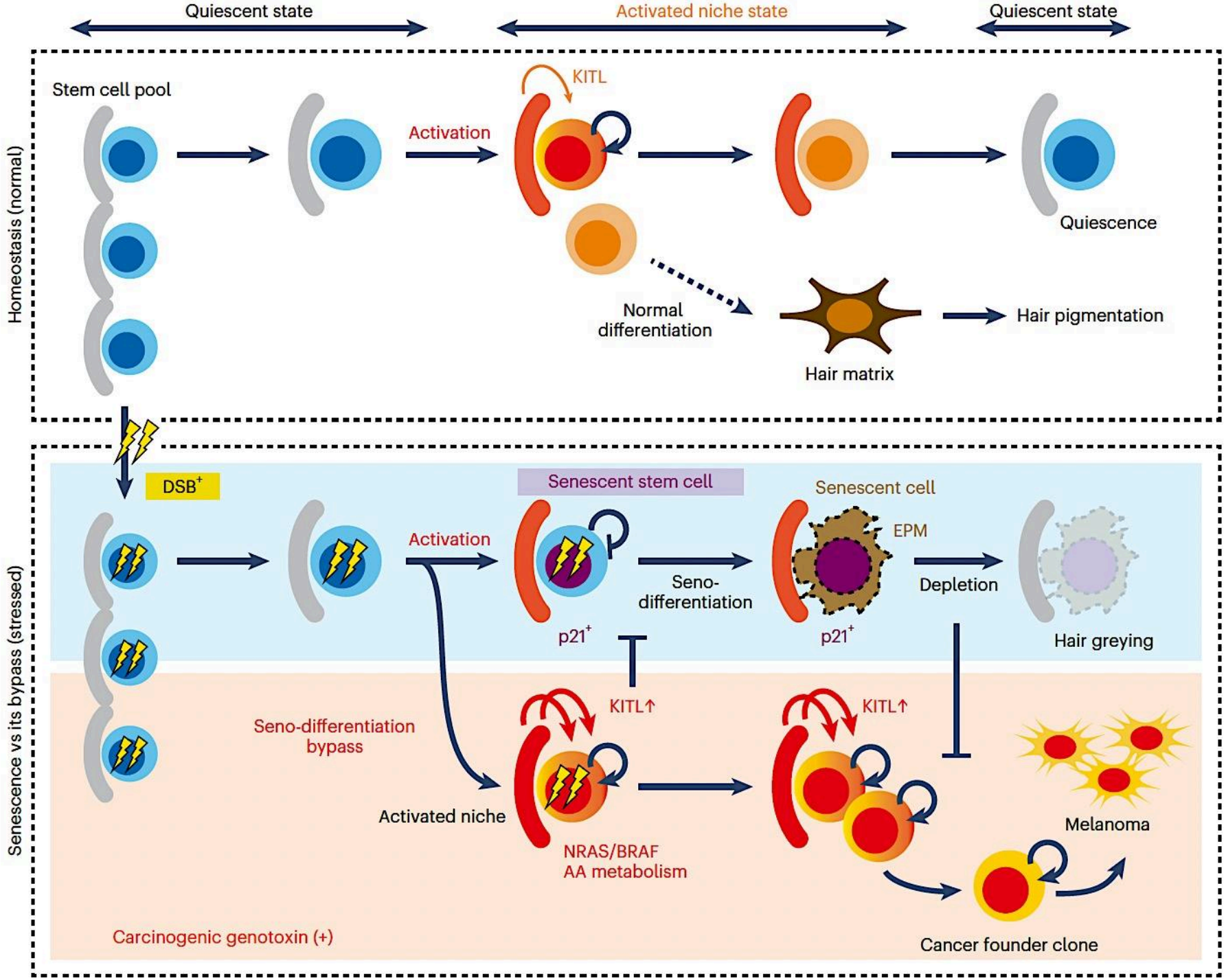
Hair graying as protection against melanoma

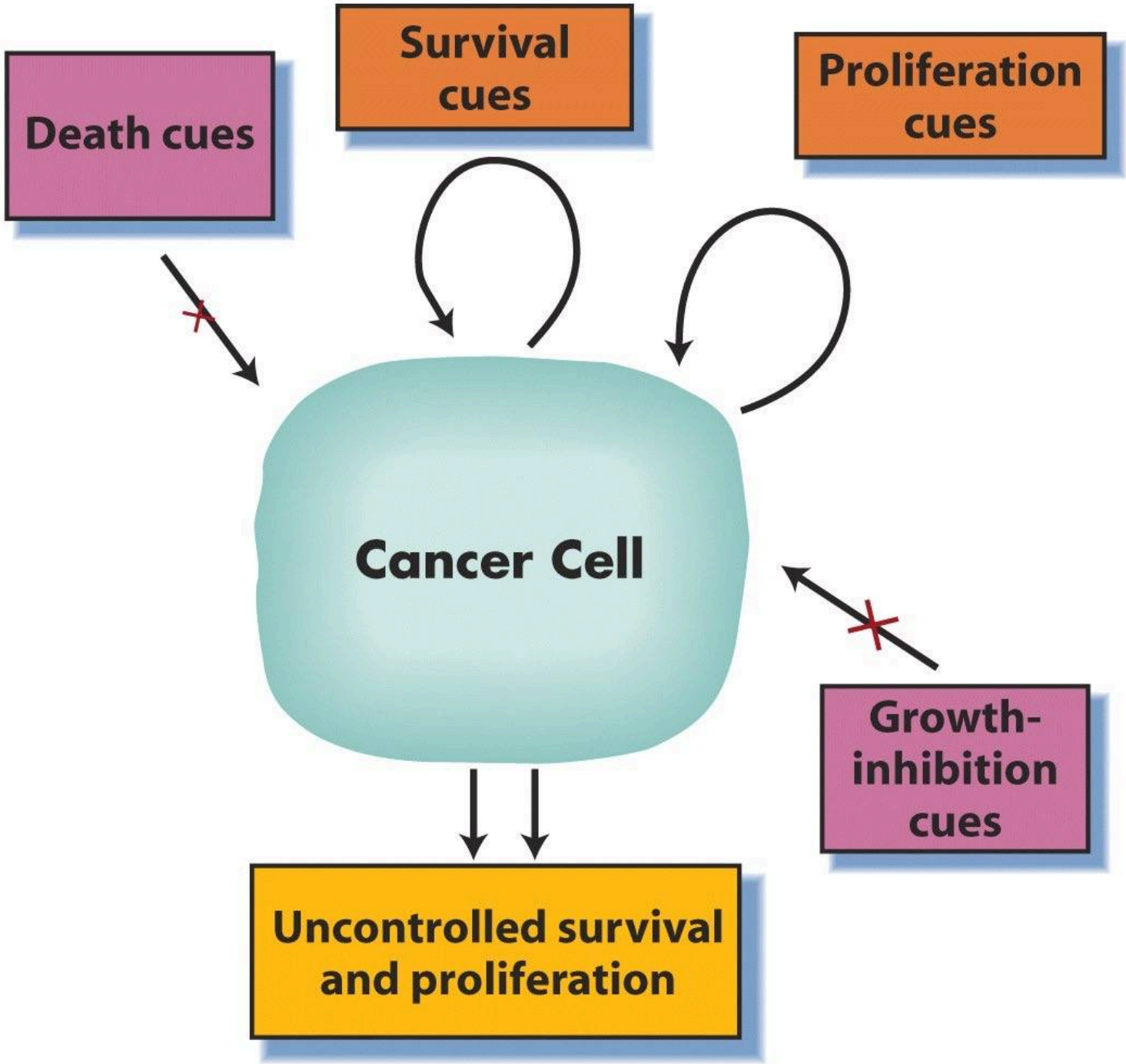
Article | Published: 06 October 2025

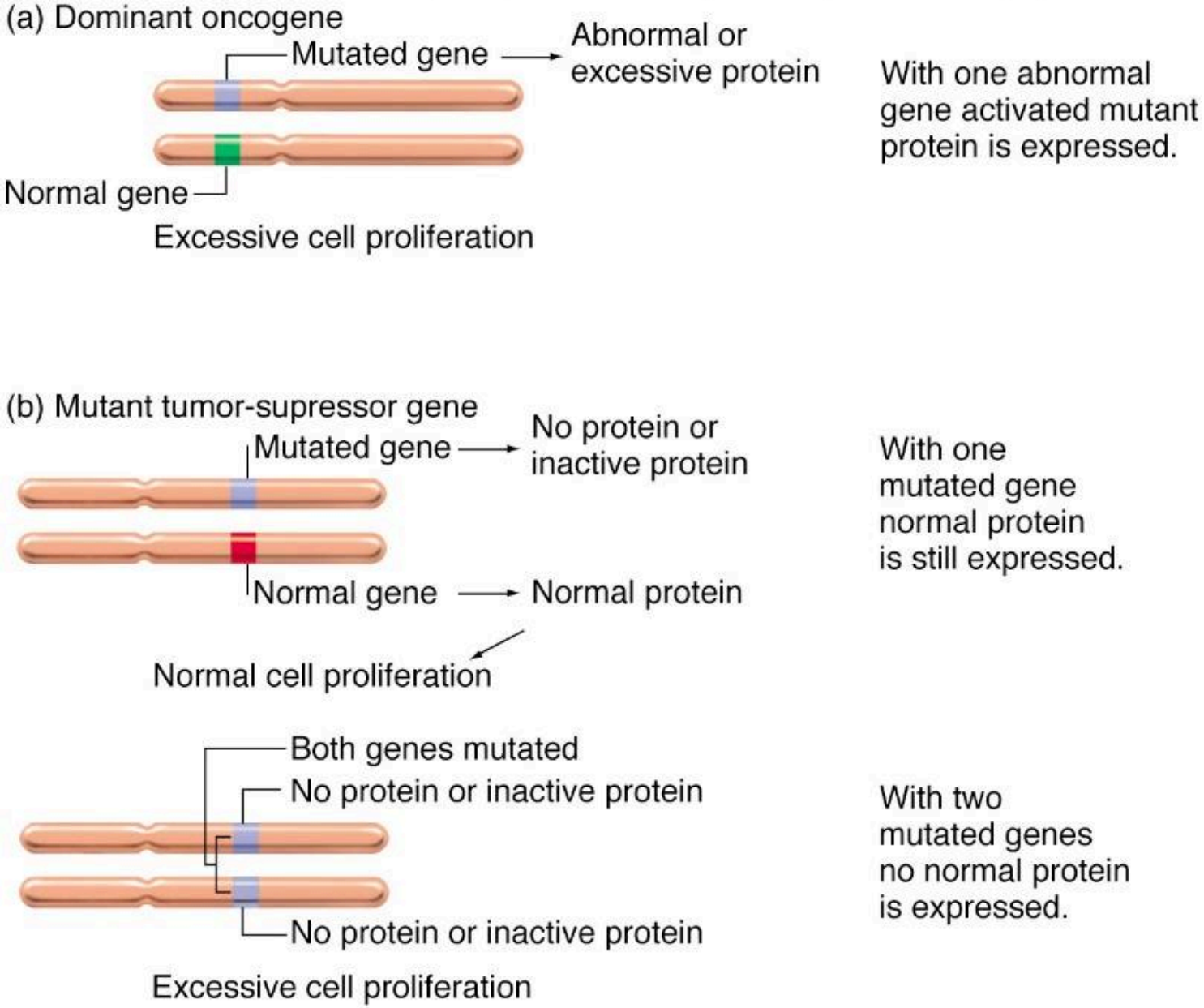
Antagonistic stem cell fates under stress govern decisions between hair greying and melanoma



Hair graying as protection against melanoma




Death cues
Survival cues
Proliferation cues
Cancer Cell
Growth-inhibition cues
Uncontrolled survival and proliferation



Oncogenes vs Tumor suppressor genes

Oncogenes	Tumor suppressor gene Positive regulator of DNA repair
Positive regulator of cell growth	Negative regulator of cell growth
Activated forms promote malignancy	Inactivated forms promote malignancy
The mutated form is dominant	The mutated form is recessive

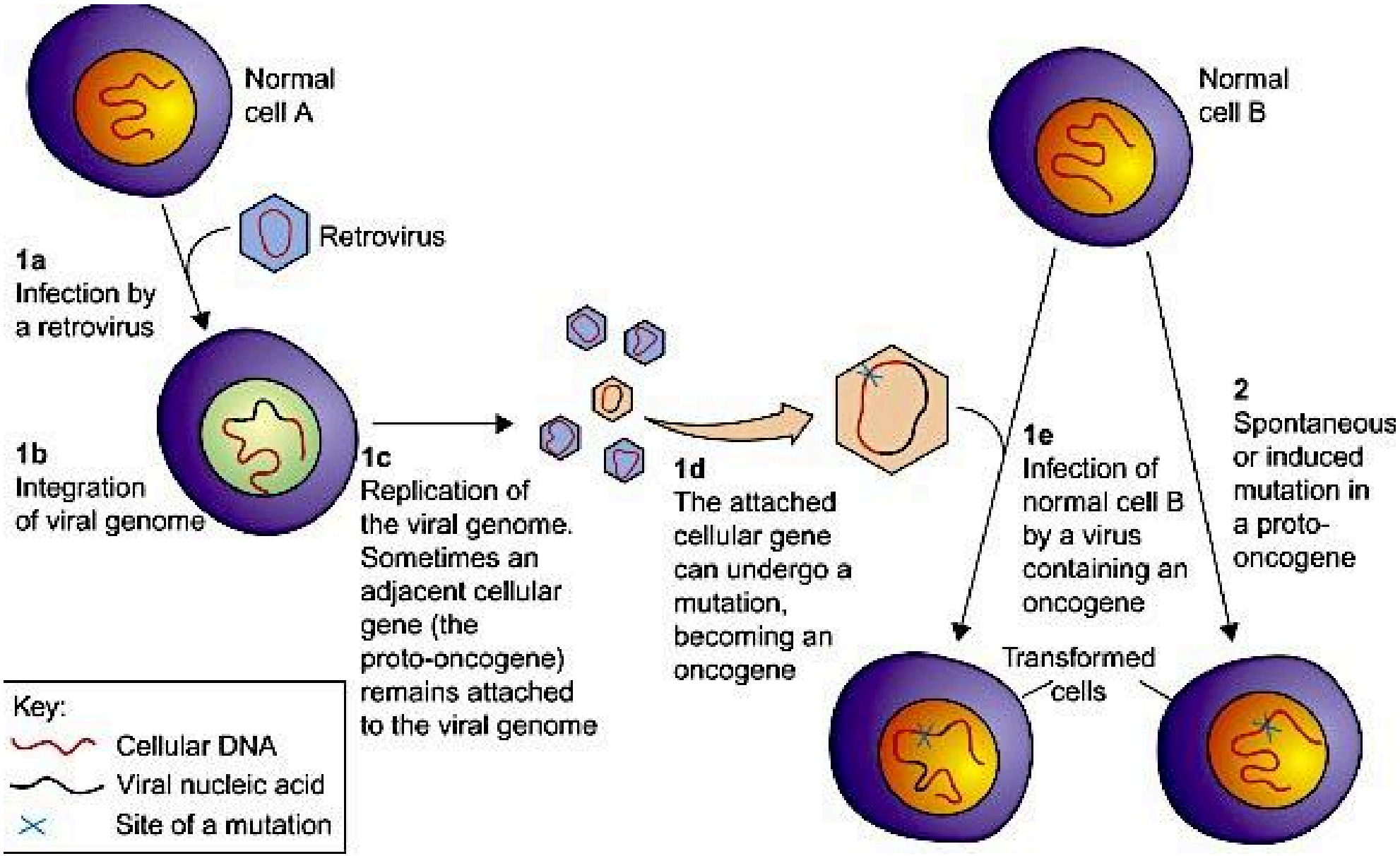
Oncogenes :

the positive regulators of cell growth

The first oncogene (v-src) was identified from a retrovirus in 1910 (Rous Sarcoma virus).

v-onc can cause cellular transformation.

v-onc are related to normal cellular genes (proto-oncogenes) which are involved in growth control or signal transduction mechanisms.


Normal cell A
Retrovirus
1a Infection by a retrovirus
1b Integration of viral genome
1c Replication of the viral genome. Sometimes an adjacent cellular gene (the proto-oncogene) remains attached to the viral genome
1d The attached cellular gene can undergo a mutation, becoming an oncogene
Normal cell B
1e Infection of normal cell B by a virus containing an oncogene
2 Spontaneous or induced mutation in a proto-oncogene
Transformed cells
Key:
Cellular DNA
Viral nucleic acid
Site of a mutation

Viral Oncogenes (*v-onc*)

As compared to their cellular counterpart (c-onc), *v-onc* contains crucial changes :

- c-onc have introns, v-onc don't. Removed during transcription of neighboring retrovirus and then reverse transcribed with virus

- c-onc encode proteins that can be in a active or inactive state, v-onc are always in an active (or overactive) conformation.

- v-onc have escaped the control the c-onc are subjected to.

Retroviral oncogenes : a “inhuman” thing?

TABLE 28.1
Retroviral Oncogenes

Oncogene	*Virus*	*Host Species*	*Function of Gene Product*
abl ←	Abelson murine leukemia virus	Mouse	Tyrosine-specific protein kinase
erbA	Avian erythroblastosis virus	Chicken	Analog of thyroid hormone receptor
erbB	Avian erythroblastosis virus	Chicken	Truncated version of epidermal growth factor (EGF) receptor
fes	ST feline sarcoma virus	Cat	Tyrosine-specific protein kinase
fgr	Gardner-Rasheed feline sarcoma virus	Cat	Tyrosine-specific protein kinase
fms	McDonough feline sarcoma virus	Cat	Analog of colony stimulating growth factor (CSF-1) receptor
fos	FJB osteosarcoma virus	Mouse	Transcriptional activator protein
fps	Fuginami sarcoma virus	Chicken	Tyrosine-specific protein kinase
jun	Avian sarcoma virus 17	Chicken	Transcriptional activator protein
mil (mht)	MH2 virus	Chicken	Serine/threonine protein kinase
mos	Moloney sarcoma virus	Mouse	Serine/threonine protein kinase
myb	Avian myeloblastosis virus	Chicken	Transcription factor
myc	MC29 myelocytomatosis virus	Chicken	Transcription factor
raf	3611 murine sarcoma virus	Mouse	Serine/threonine protein kinase
H-ras ←	Harvey murine sarcoma virus	Rat	GTP-binding protein
K-ras	Kirsten murine sarcoma virus	Rat	GTP-binding protein
rel	Reticuloendotheliosis virus	Turkey	Transcription factor
ros	URII avian sarcoma virus	Chicken	Tyrosine-specific protein kinase
sis	Simian sarcoma virus	Monkey	Analog of platelet-derived growth factor (PDGF)
src ←	Rous sarcoma virus	Chicken	Tyrosine-specific protein kinase
yes	Y73 sarcoma virus	Chicken	Tyrosine-specific protein kinase

receptors

kinases

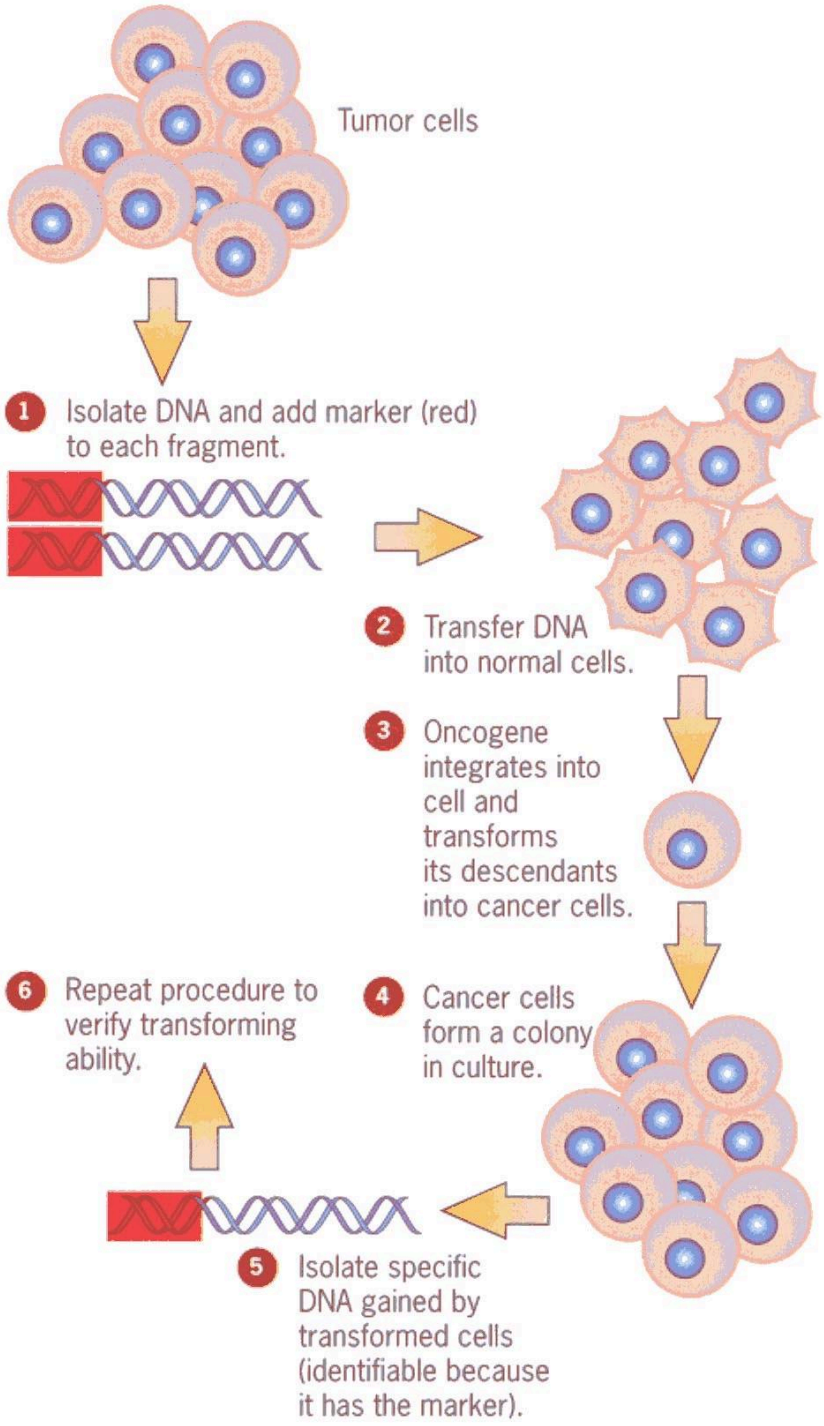
Transcription factors

GTP-binding proteins

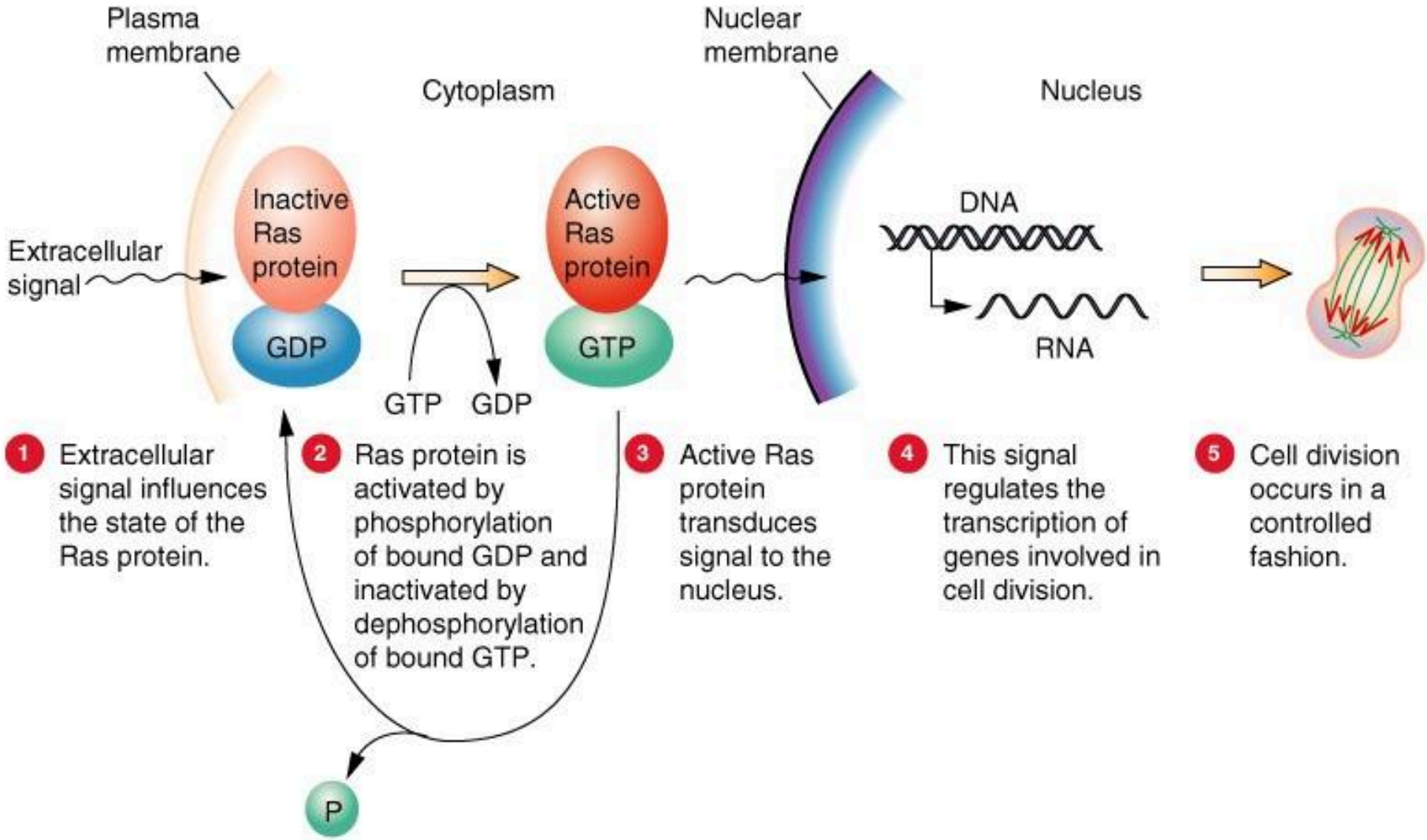
Something is … out there!!

Isolation of oncogenes from human cells

The c-H-ras oncogene is implicated in human bladder cancer.

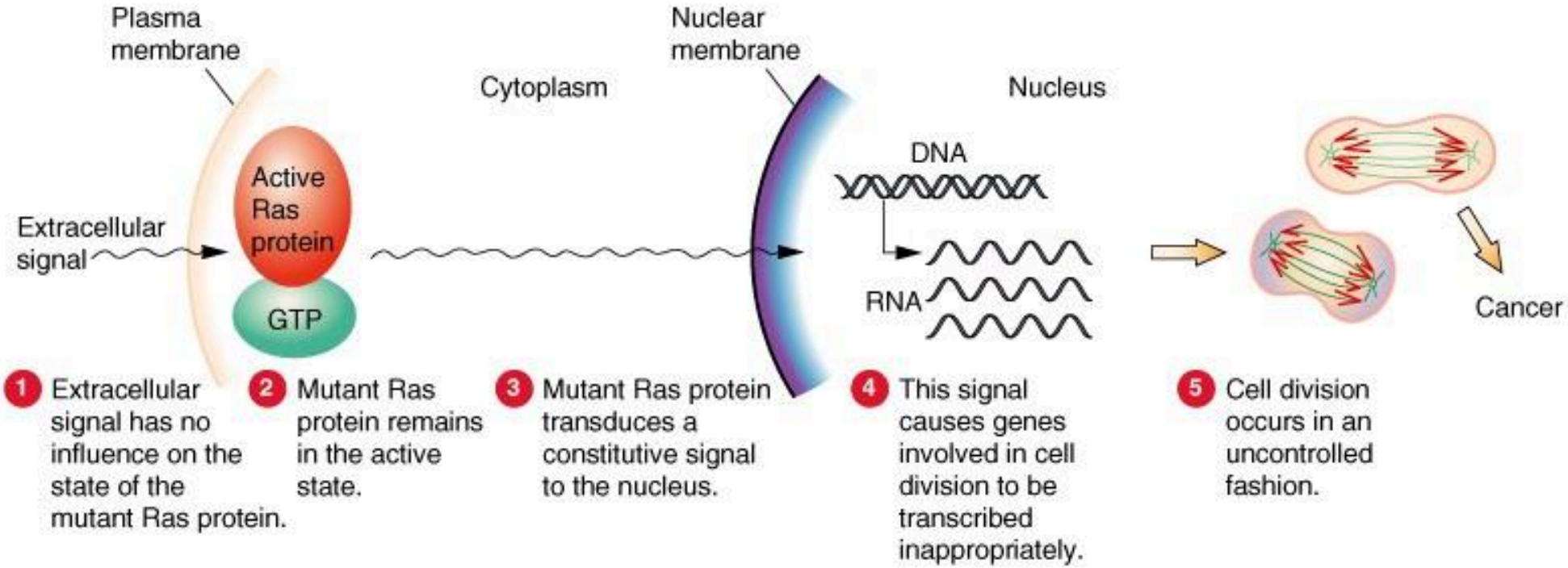


Ras activity is carefully controlled in normal cells

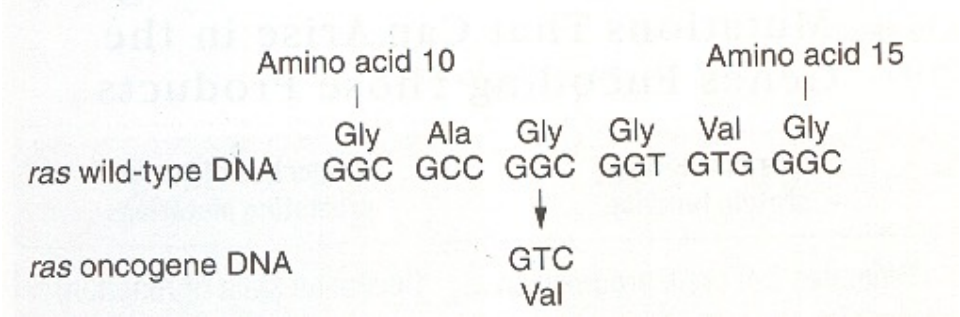


(a) Normal Ras protein signaling.

Ras activity is no longer regulated in cancer cells

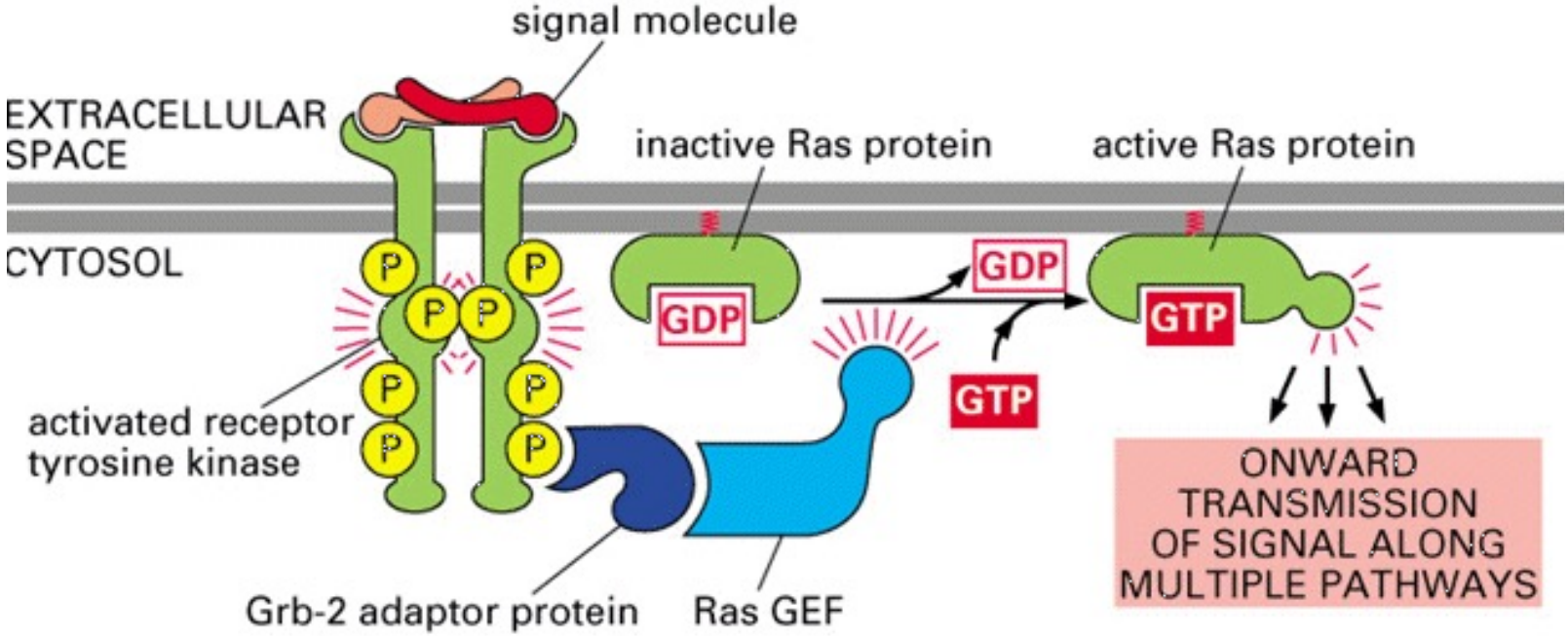


(b) Oncogenic Ras protein signaling.



A single point mutation (Gly ⟶Val) locks the ras protein in an active, GTP-binding position.

Activated versions of the EGFR are oncogenic



- Iressa (Gefitinib) is a small molecule inhibitor of EGFR.
- Only a small proportion of non-small cell lung cancer (NSCLC) patients respond to gefitinib.

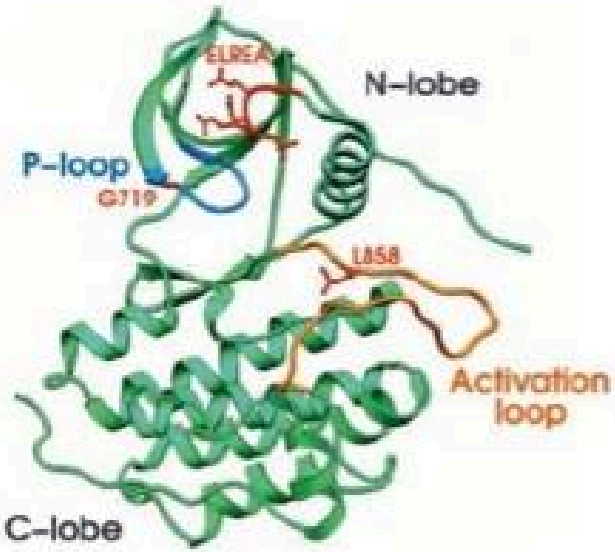
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 20, 2004 VOL. 350 NO. 21

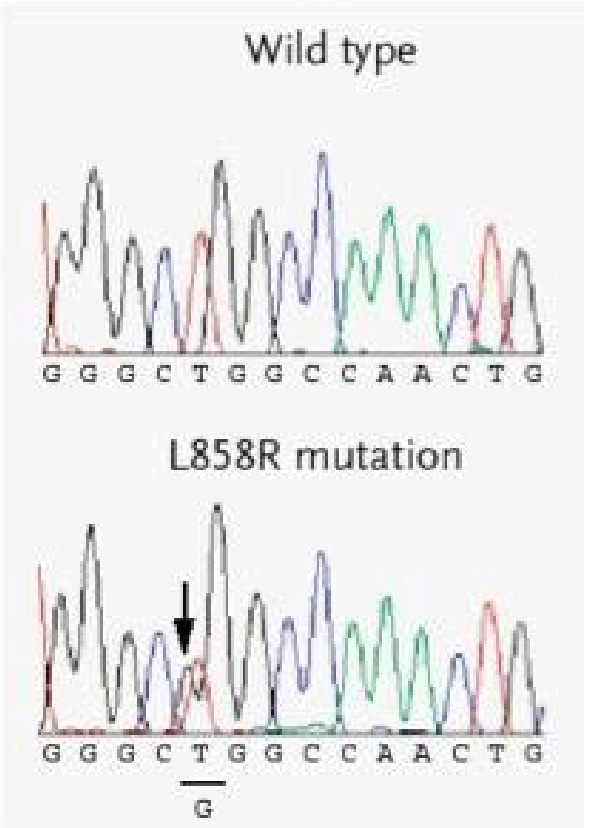
Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non–Small-Cell Lung Cancer to Gefitinib

- Sequence mutations in the tumor EGFR gene confer *sensitivity* to gefitinib.

- Mutations occur in *functionally* important domains of the protein.

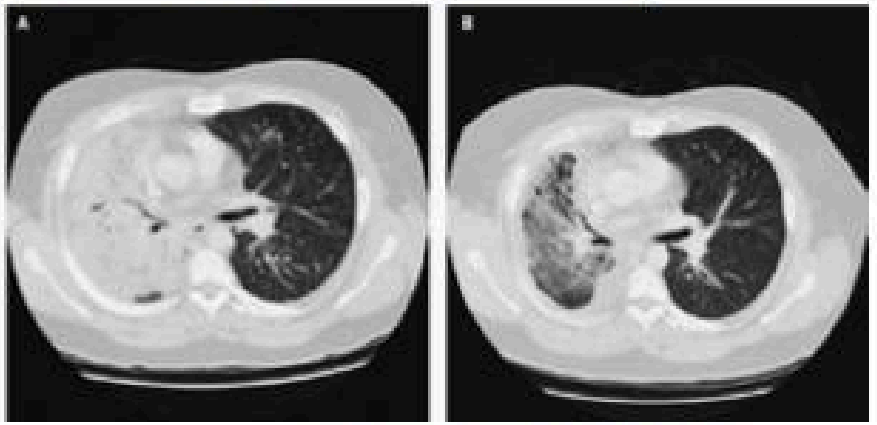


Paez, et. al. Science, 2004



Lynch, et. al. NEJM, 2004

- Patients with mutations show dramatic response to gefitinib treatment.



Lynch, et. al. NEJM, 2004

- Testing tumors for EGFR mutations could help to select cancer therapy.

- Perhaps not:

Somatic Mutations of *EGFR* in Colorectal Cancers and Glioblastomas

N ENGL J MED 351;27 WWW.NEJM.ORG DECEMBER 30, 2004

sponses to gefitinib.[1,2] Are similar *EGFR* mutations present in a significant fraction of other tumor types for which gefitinib might be suitable therapy? To answer this question, we screened DNA from 293 colorectal tumors and 59 glioblastomas for alterations in the EGFR kinase domain (exons 17 to 24). These tumors were chosen for analysis because they have been linked to EGFR signaling: EGFR-targeted antibodies (cetuximab) have been approved for use in patients with colorectal cancer, and structural alterations of the *EGFR* gene (amplifications and rearrangements) have been described in glioblastomas.[3] However, our analysis showed that only one of the colorectal cancers and none of the glioblastomas harbored a mutation. The single mutation

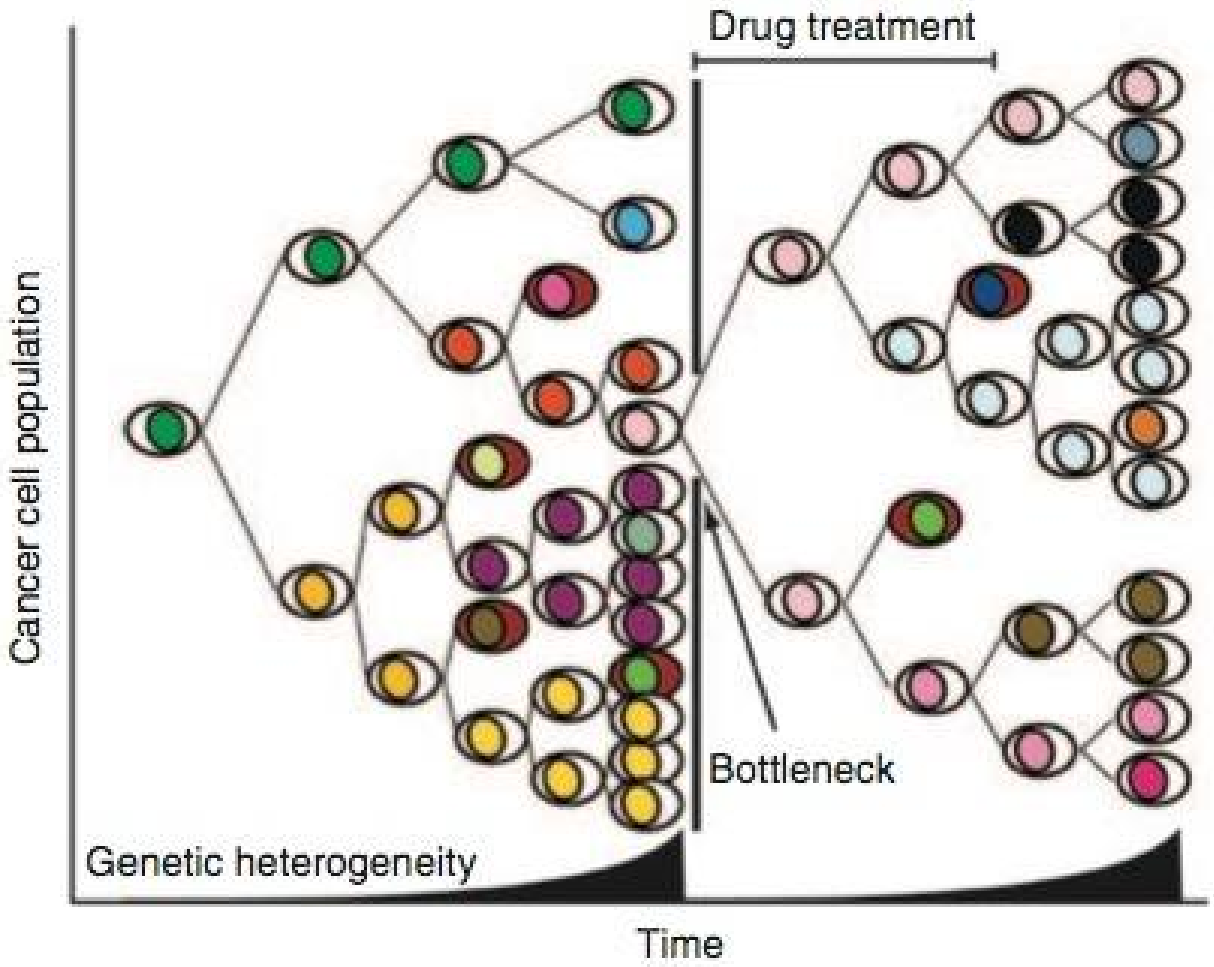
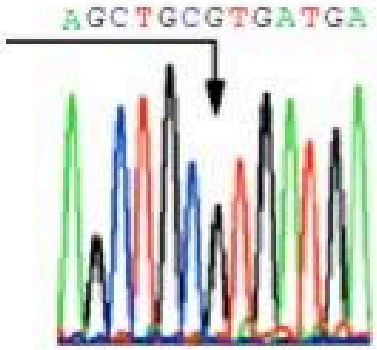
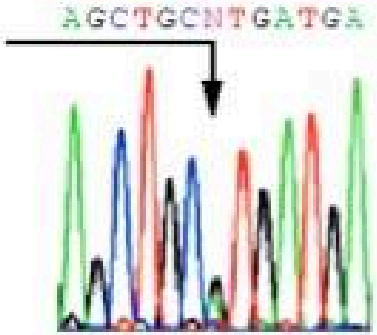


Figure 1 Schematic view of tumour heterogeneity during tumour progression and treatment. Acquired mutations in daughter cells of a single founder cell (left) promote diversion into subclones (different colours reflect different clones). Some new mutations lead to accelerated growth (for example yellow 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.

- Treatment resistance can also occur by acquisition of a second EGFR mutation.



Before Therapy



At Relapse

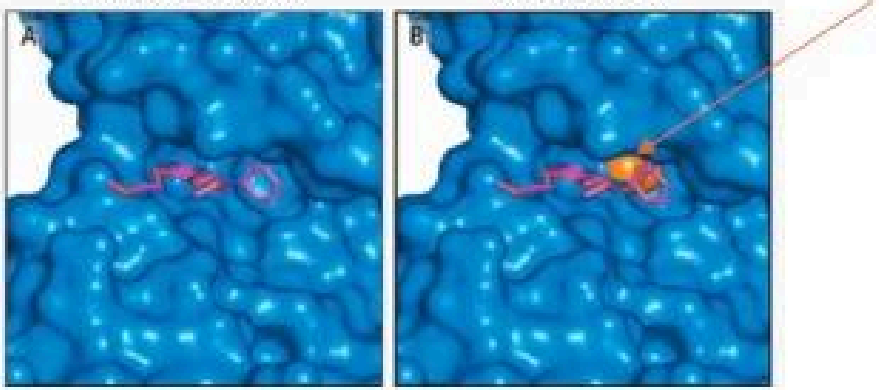
The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

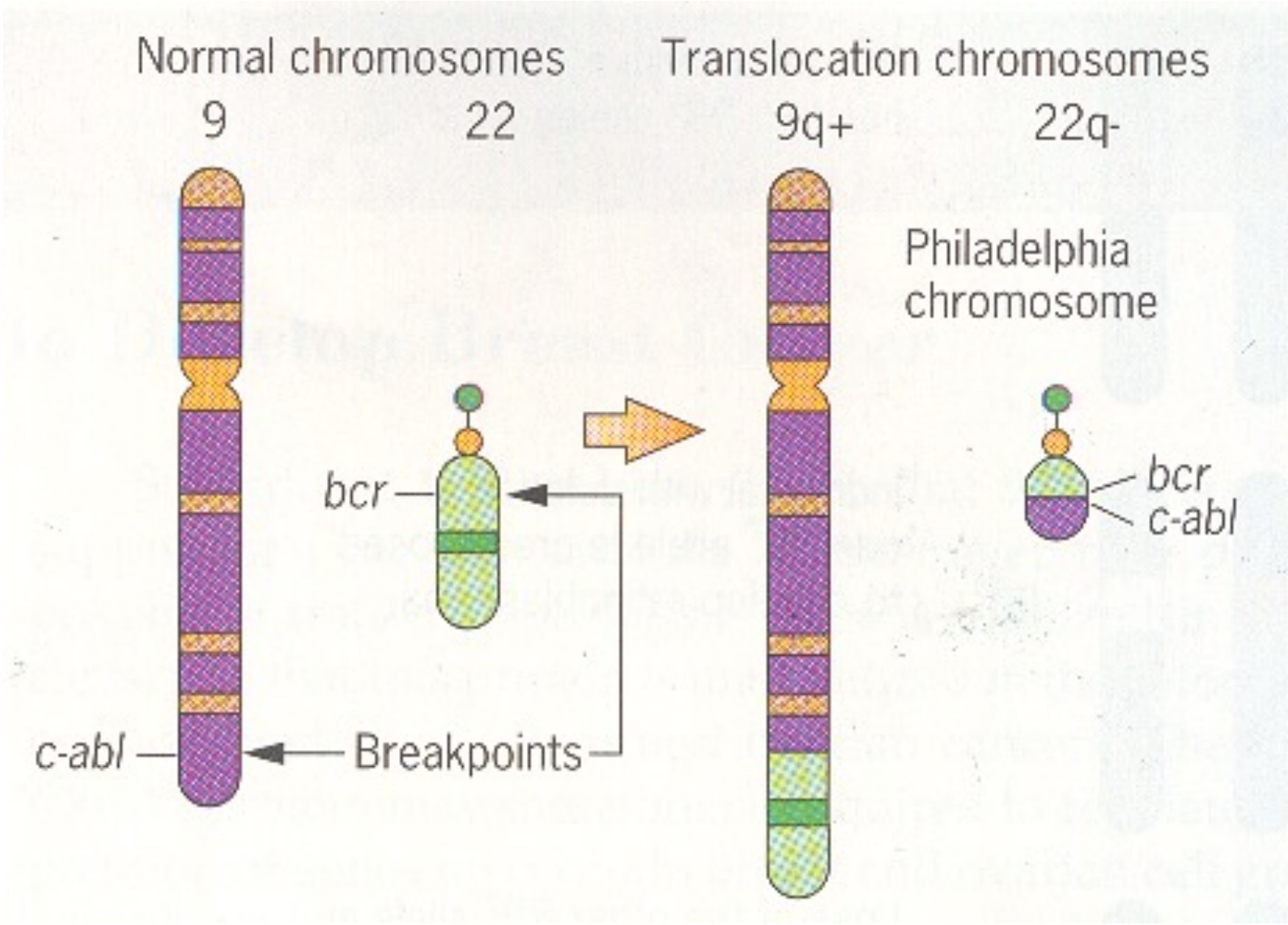
EGFR Mutation and Resistance of Non–Small-Cell Lung Cancer to Gefitinib

N ENGL J MED 352;8 WWW.NEJM.ORG FEBRUARY 24, 2005

Before Therapy *At Relapse*



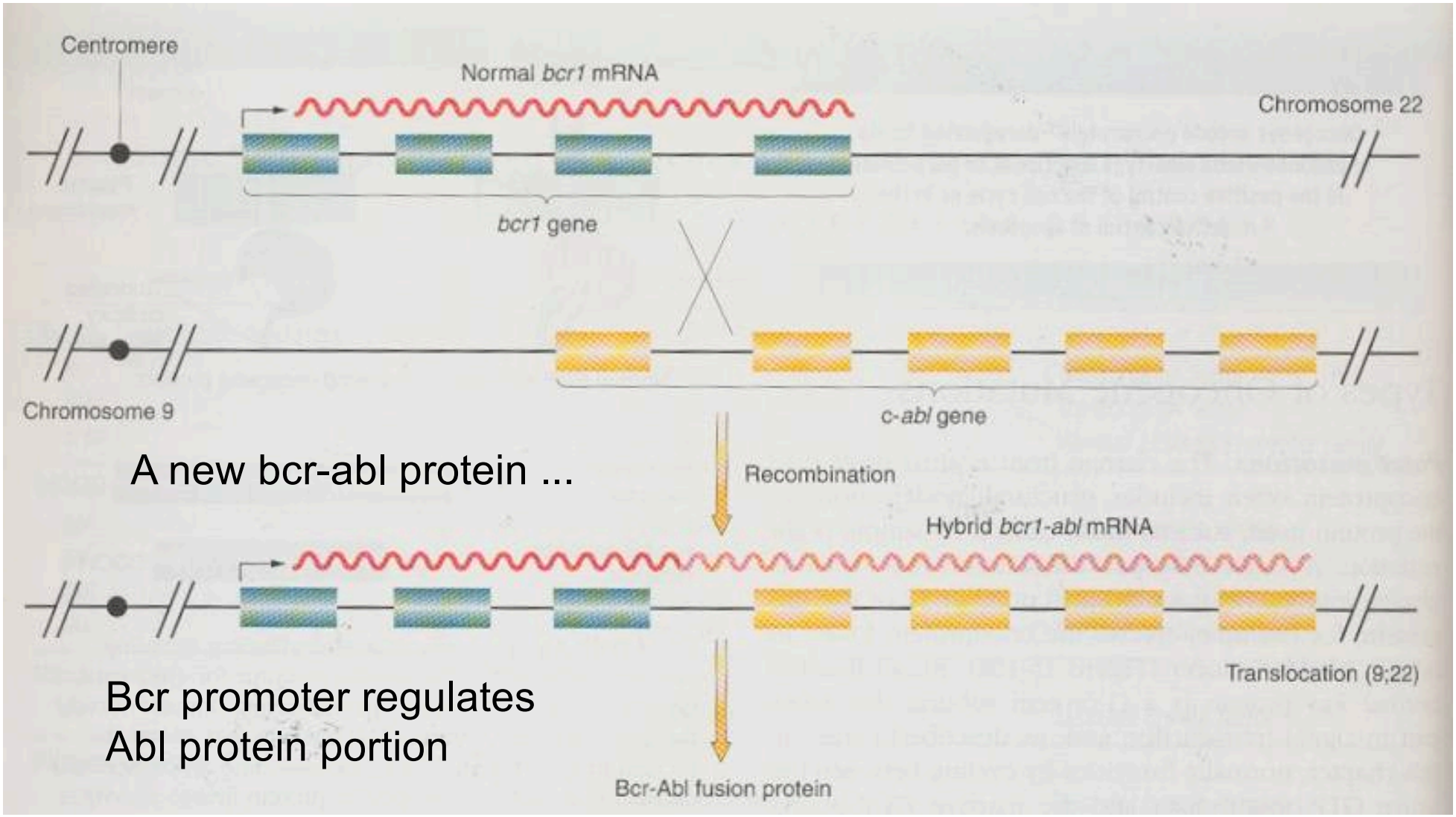
Chimeric oncogenes … the Philadelphia chromosome in Chronic myelogenous leukemia (CML)



bcr-abl fusion

… at the molecular level

A new protein is born ...



Oncogenes: promoting proliferation or cell survival

Depending on the nature of the gene, oncogenes can become activated in a Variety of ways.

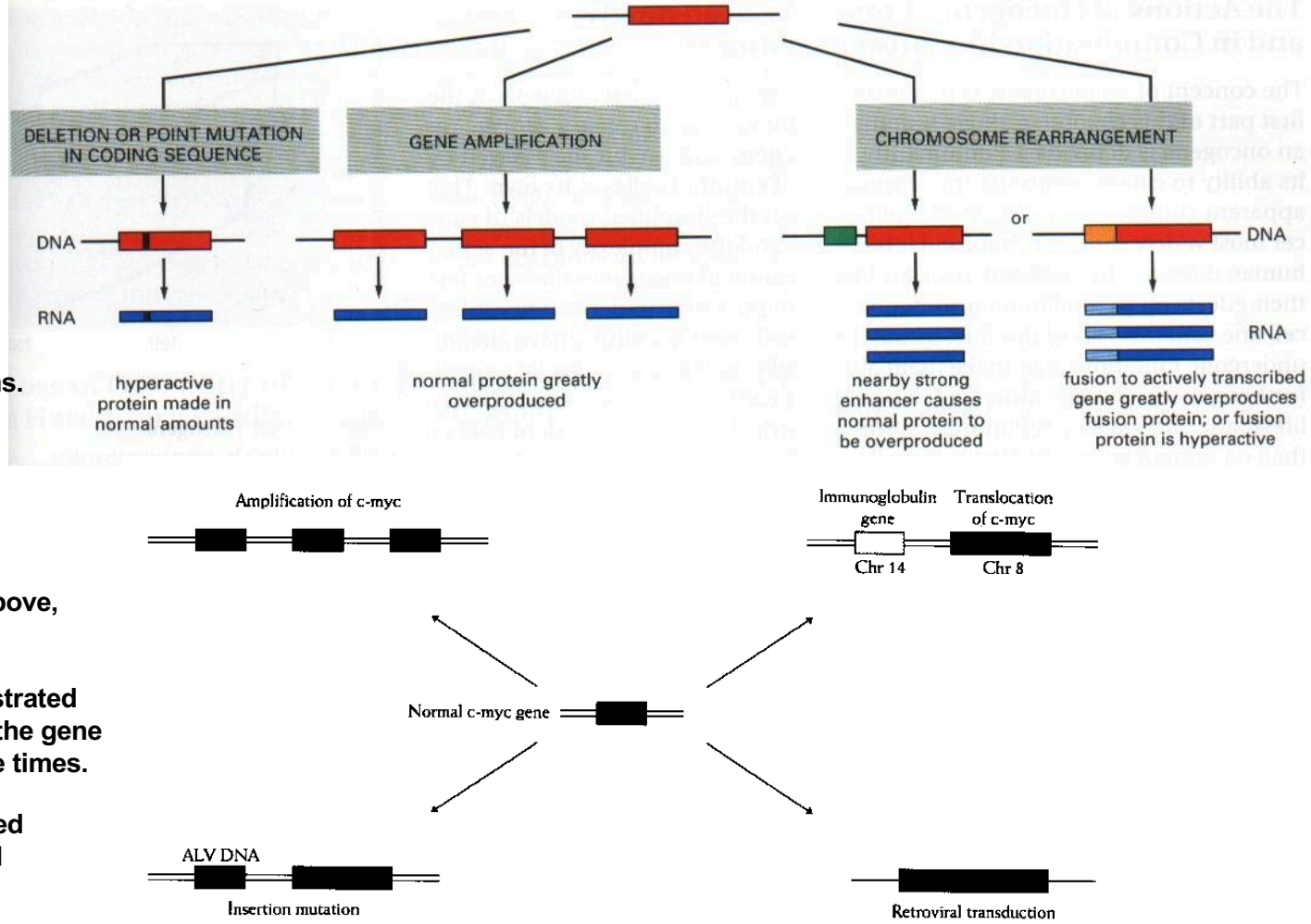
1. Activating point mutation that creates a constitutively active protein.

2. Gene amplification leads to overexpression of a normal protein.

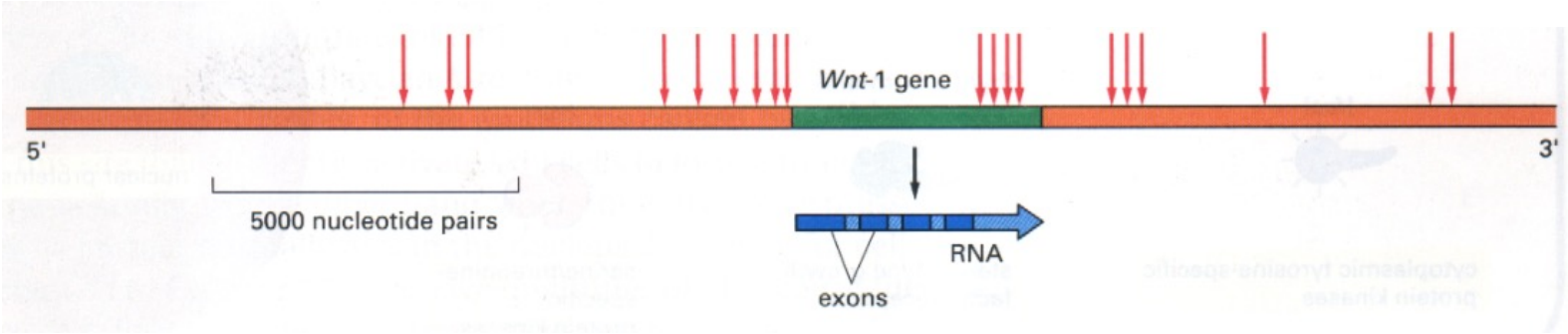
3. Chromosome rearrangement can lead to gene activation through several mechanisms. Rearangment can bring the gene under the transcriptional control of a promoter that drives expression inappropriately, either in time or tissue type. Rearrangements may also directly fuse two different protein coding regions, creating chimeric proteins that have novel properties, or that are, as above, simply overexpressed.

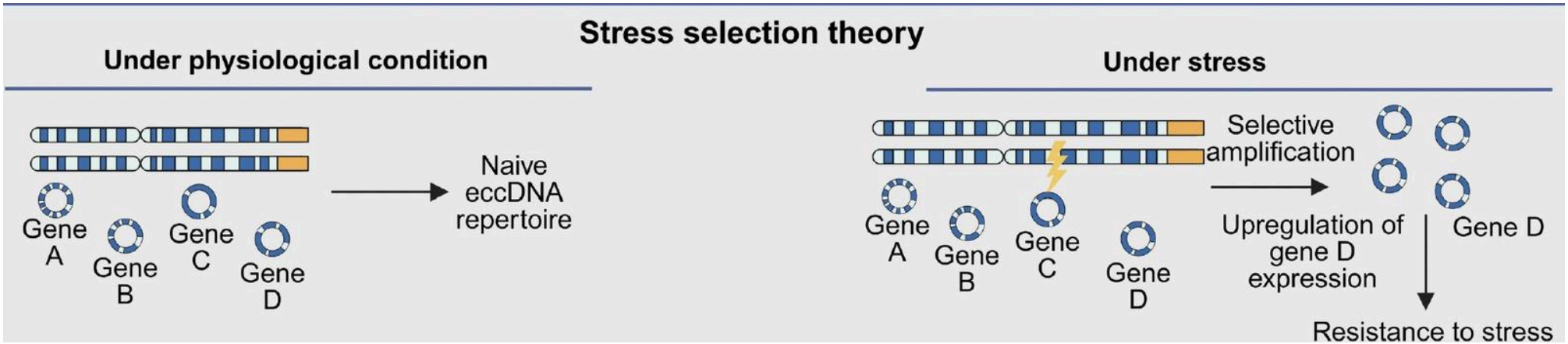
3. Retrovirus insertions near a gene, as illustrated below, can lead to high level expression of the gene in inappropriate tissues, or at inappropriate times.

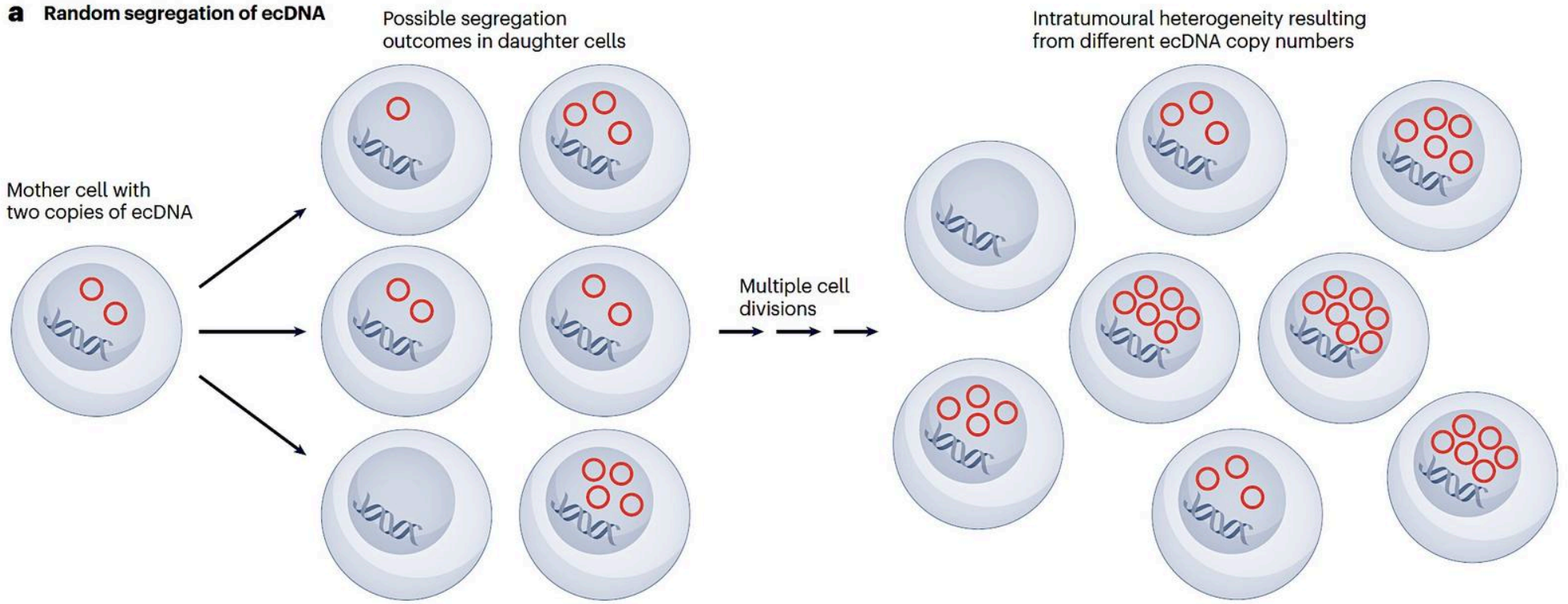
4. Finally, the gene may become incorporated into the retroviral genome under the control of a strong retroviral promoter.



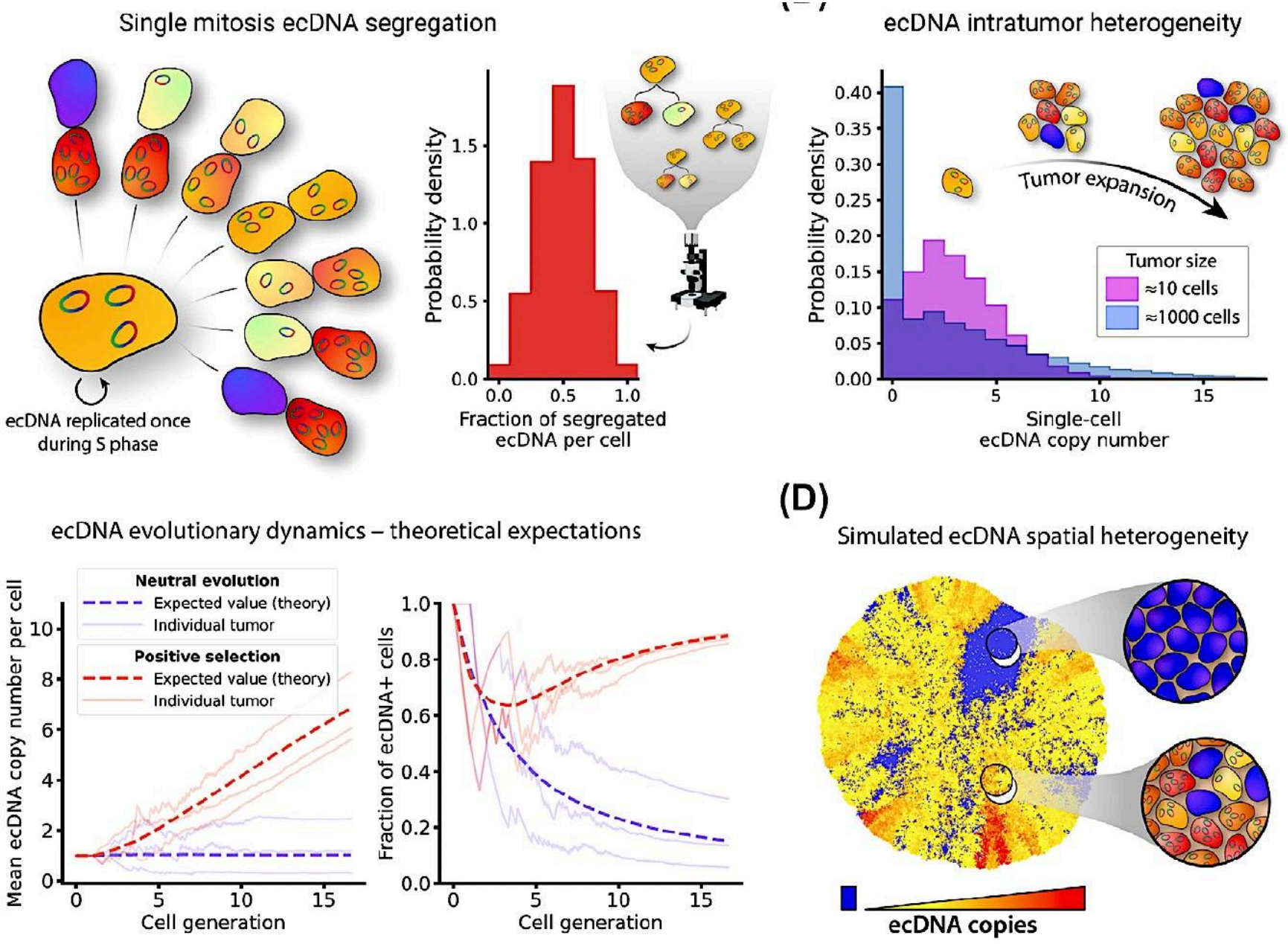
Most of the ways in which a proto-oncogene can be converted to an oncogene are illustrated with the c-myc gene, which has been found to be activated by gene amplification, chromosomal translocation, retroviral transduction (forming a viral oncogene), and proviral insertion mutations.

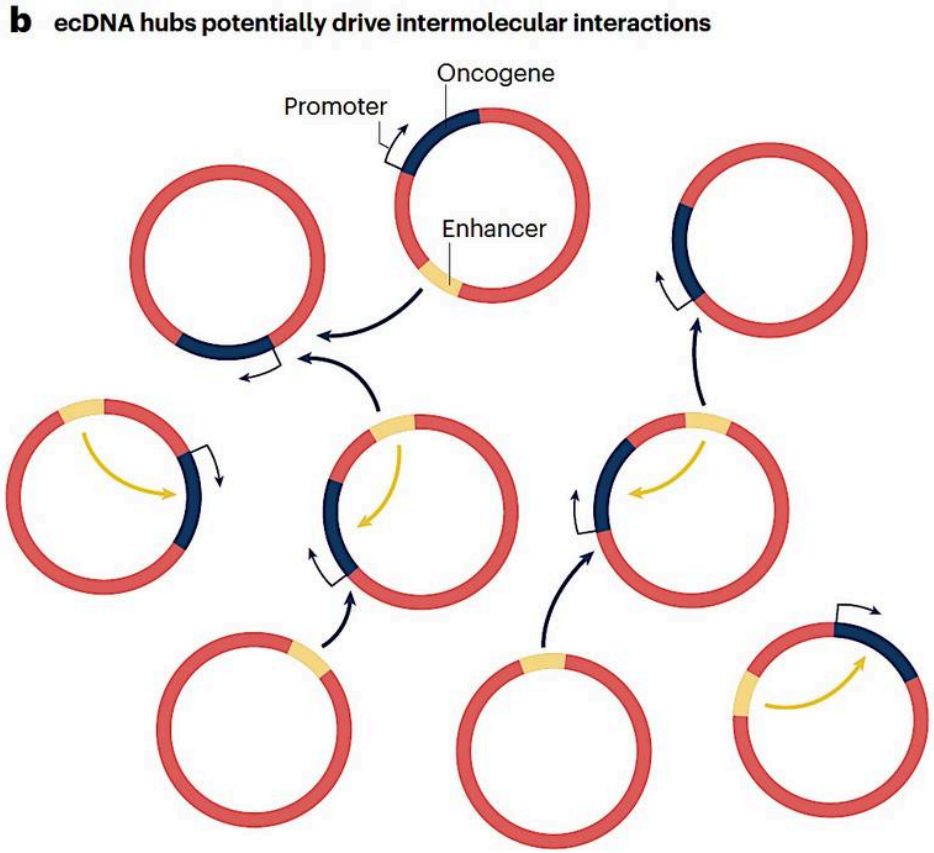


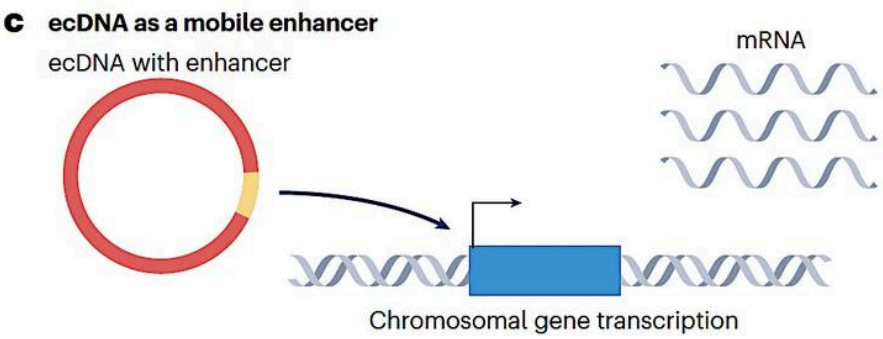

Stress selection theory
Under physiological condition
Under stress
Gene A
Gene B
Gene C
Gene D
Naive eccDNA repertoire
Selective amplification
Upregulation of gene D expression
Gene D
Resistance to stress


a Random segregation of ecDNA
Possible segregation outcomes in daughter cells
Mother cell with two copies of ecDNA
Multiple cell divisions
Intratumoural heterogeneity resulting from different ecDNA copy numbers

The unique inheritance pattern of ecDNA makes ecDNA-driven tumors more evolvable in three main ways. First, it enables tumors to hedge their bets by maintaining both high-and low-ecDNA cell subpopulations which, together, can withstand the fluctuating tumor microenvironment. Second, by accelerating the rate of copy number evolution, ecDNA-driven tumors are far more agile in response to new external pressures. Last, if the previous environmental conditions are restored (e.g., treatment is ceased), tumors can rapidly restore the optimal ecDNA copy numbers and resume growth.







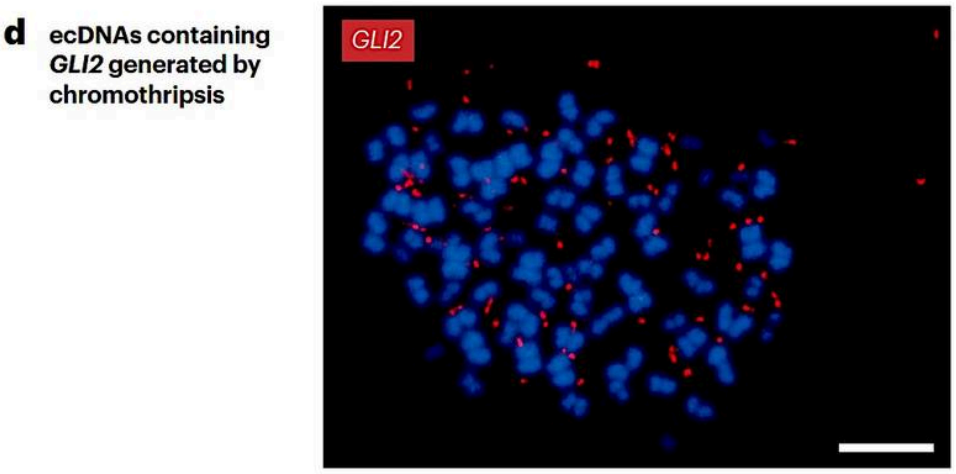


Fig. 4 | The links between extrachromosomal DNA and chromothripsis in cancer. **a**, Random segregation of extrachromosomal DNAs (ecDNAs; red circles) in daughter cells leads to increased intratumoural genetic heterogeneity[71]. **b**, Formation of ecDNA hubs results in spatial proximity between ecDNA molecules and enables the intermolecular sharing of regulatory elements as well as potentially enhanced oncogene transcription through combinatorial promoter–enhancer interactions[68]. Enhancers can interact with promoters located either on a different ecDNA molecule (black arrows) or within the same ecDNA molecule (yellow arrows). **c**, ecDNAs can act as mobile enhancers and potentially promote genome-wide chromosomal gene transcription[74]. **d**, Fluorescence in situ hybridization (FISH) image of medulloblastoma cells derived from patient-derived xenografts, showing chromosome spread in metaphase. Multiple copies of the *GLI2* oncogene (red) are present on ecDNAs. Chromosomes were stained with 4′,6-diamidino-2-phenylindole (DAPI; blue)[132]. Scale bar, 5 µm.

But in human, oncogene activation is not enough ...

1. Cell hybrid fusion:

Normal and cancer cells :

Hybrids are non-tumorigenic

Malignant A and Malignant B:

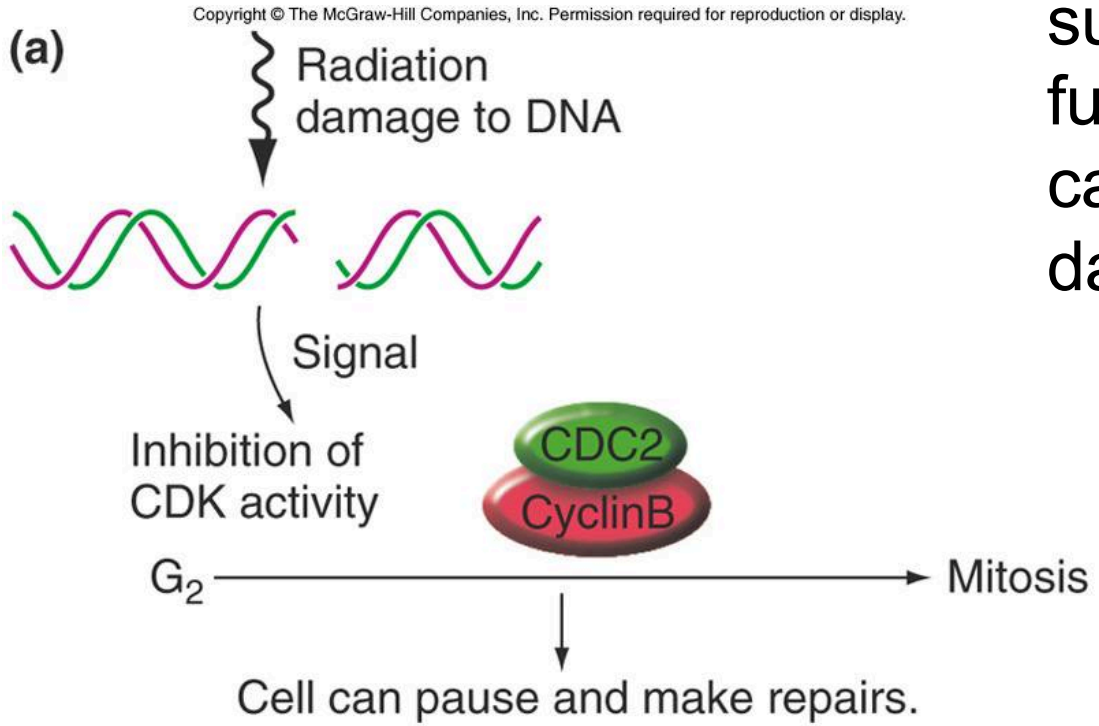
Hybrids are non-tumorigenic

2. Karyotype of human tumor:

Loss of specific chromosomal regions

Checkpoint genes arrest division

In higher organisms, called tumor suppressors; if lose function, cell division can proceed after DNA damage



Or die: apoptosis

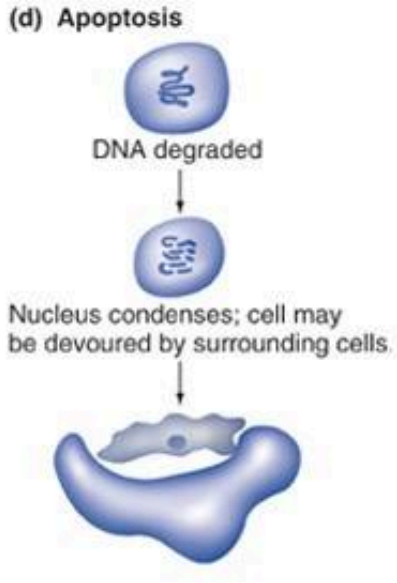
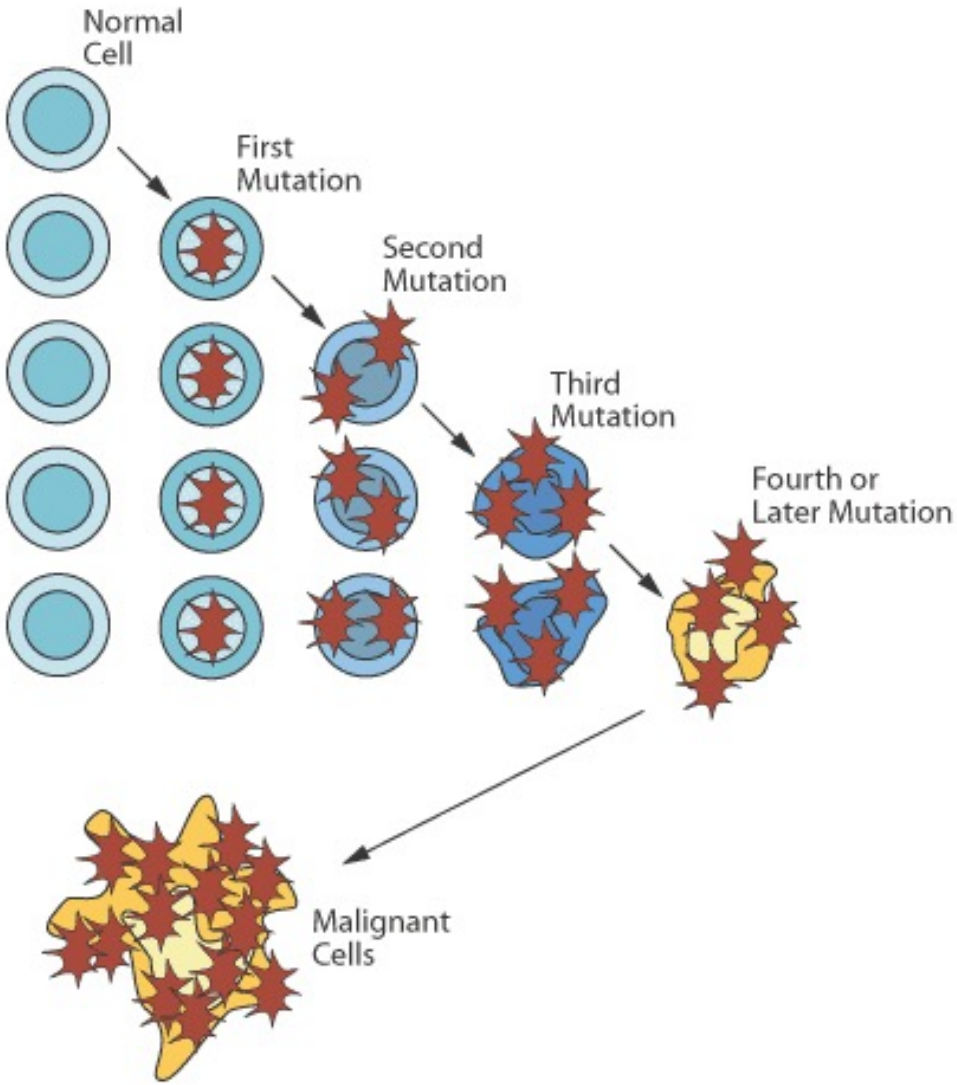


Fig. 19.12

Individuals carrying mutations that result in defects in DNA synthesis/repair have a high frequency of cancer.

TABLE 5–1 The Three Steps That Give Rise to High-Fidelity DNA Synthesis	
Replication step	Errors per nucleotide added
5′ → 3′ polymerization	1 in 10^5
3′ → 5′ exonucleolytic proofreading	1 in 10^2
Strand-directed mismatch repair	1 in 10^3
Combined	1 in 10^{10}

For example:
1. proofreading-defective polymerase
2. Mutations in Brca1 or Brca2 (DNA break repair)
3. Defects in mismatch repair



Checkpoint genes arrest division

TABLE 19.5 Mutant Alleles of These Tumor-Suppressor Genes Decrease the Accuracy of Cell Reproduction*

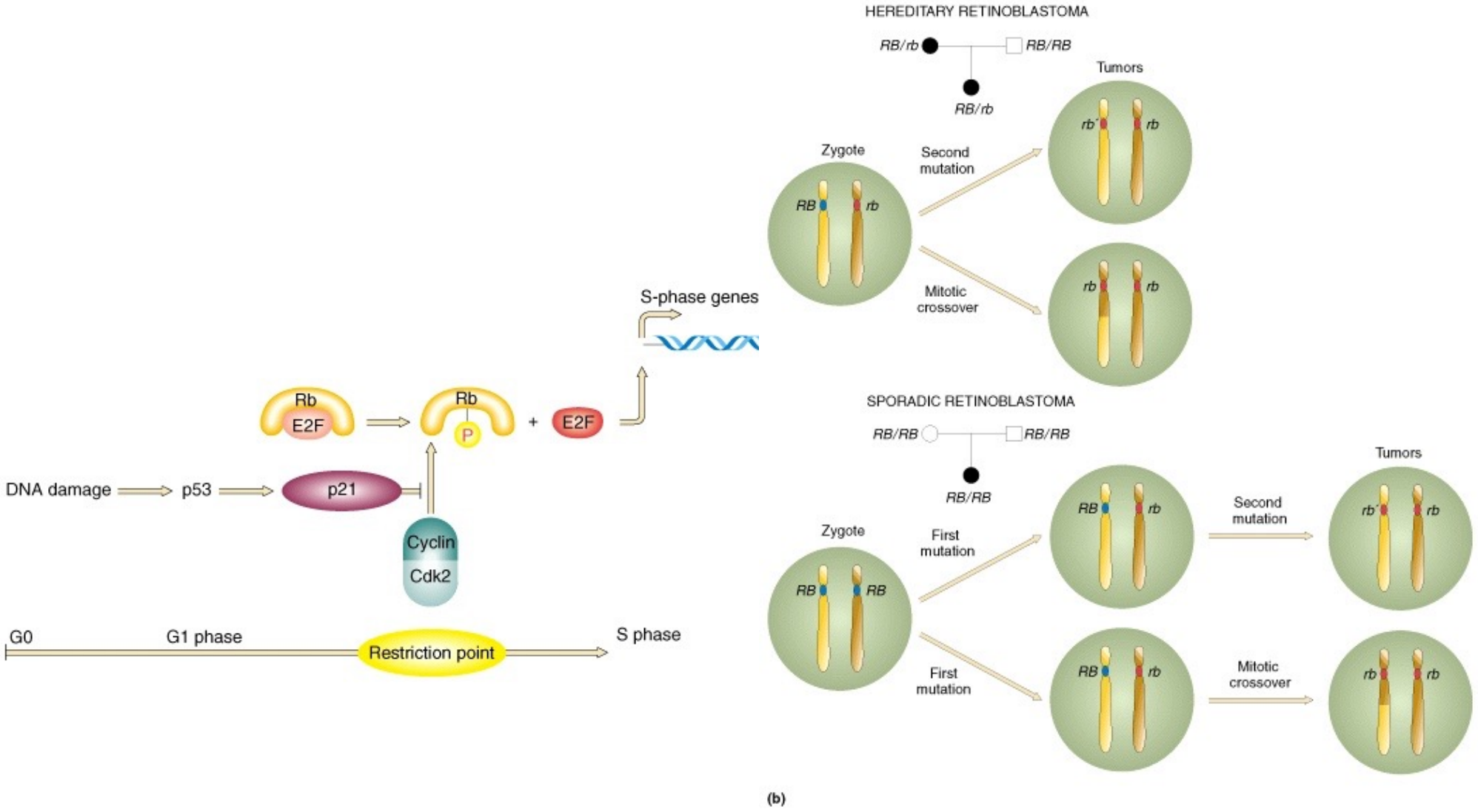
Gene	Normal Function of Gene (if known), or Disease Syndrome Resulting from Mutation	Function of Normal Protein Product
p53	Controls G_1-to-S checkpoint	Transcription factor
RB	Controls G_1-to-S transition	Inhibits a transcription factor
ATM	Controls G_1-to-S phase, and G_2-to-M checkpoint	DNA-dependent protein kinase
BS	Recombinational repair of DNA damage	DNA/RNA ligase
XP	Excision of DNA damage	Several enzymes
hMSH2, hmLH1	Correction of base-pair matches	Several enzymes
FA	Fanconi anemia	Unknown
BRCA1	Repair of DNA breaks	Unknown
BRCA2	Repair of DNA breaks	Unknown

*Many tumor-suppressor genes have been associated with a specific function in the cell cycle necessary for accuracy of cell division.

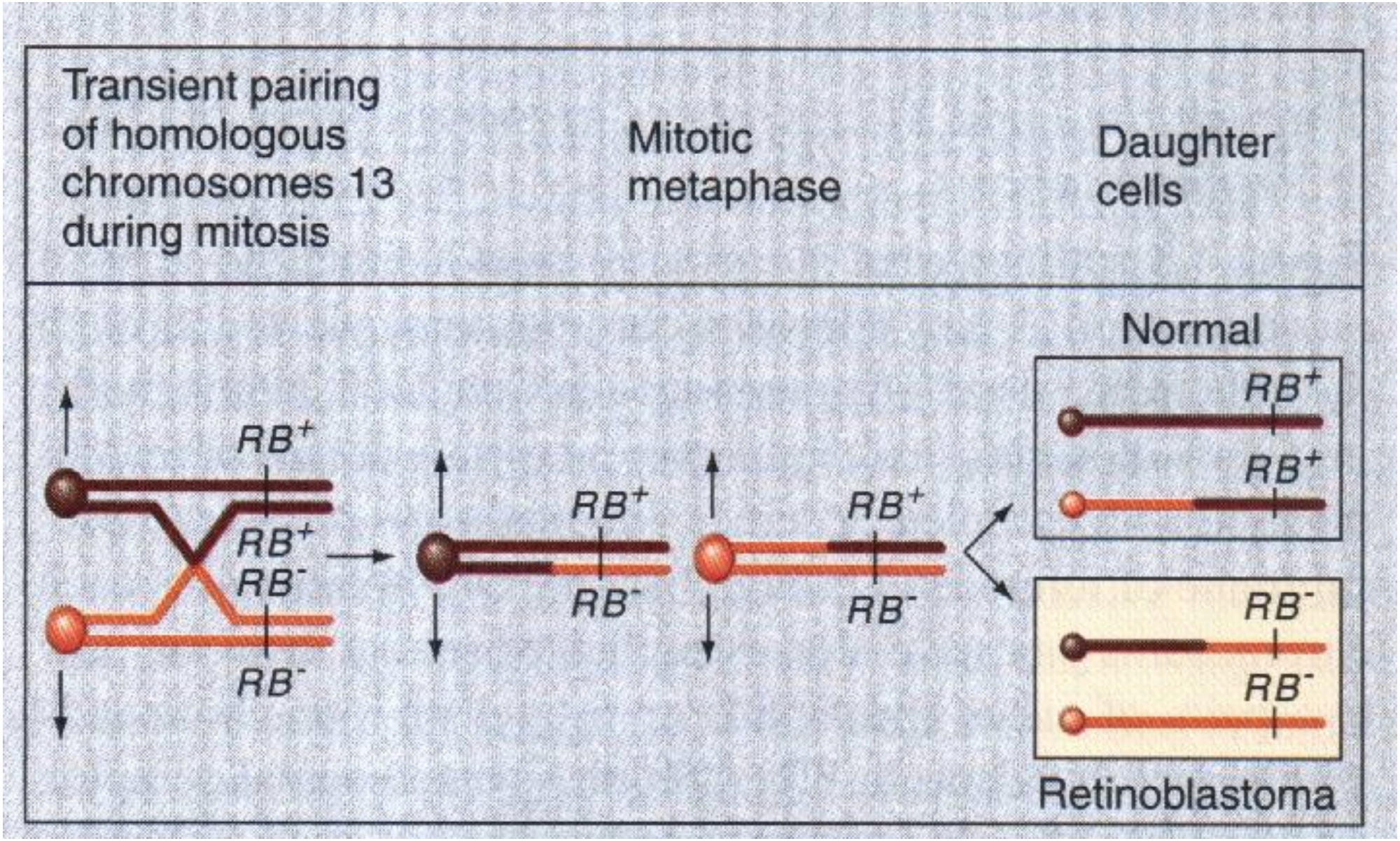
Table 19.5

Tumor suppressors: the two hit model

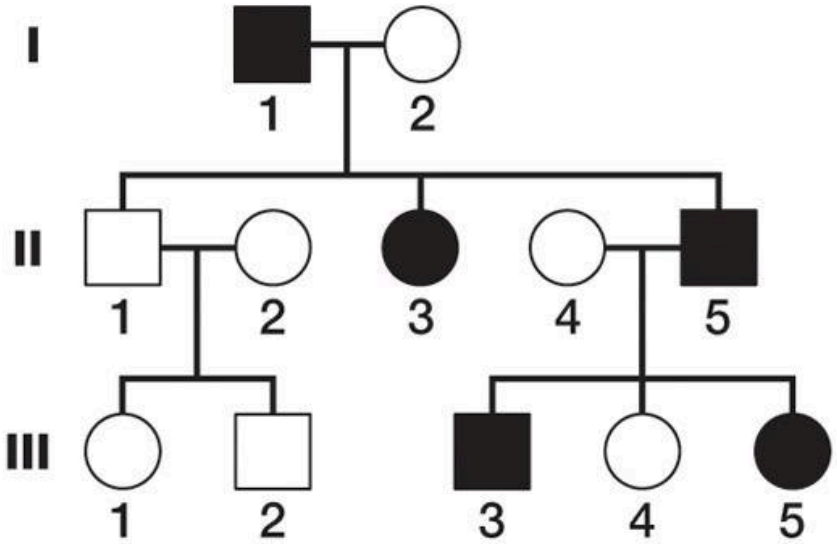
Retinoblastoma and the two hit model. Suppose the target cell population is 10^6 and the probability of mutation is 10^{-5}. Sporadic retinoblastoma requires two hits and will affect 1 in 10^4 (10^6 x 10^{-5} x 10^{-5}), primarily in one eye. In contrast the familial form requires one hit and will be quite highly penetrant 10^6 x 10^{-5} = 10. Essentially all germline heterozygotes will get the disease. There will be a much higher frequency of bilateral tumors.



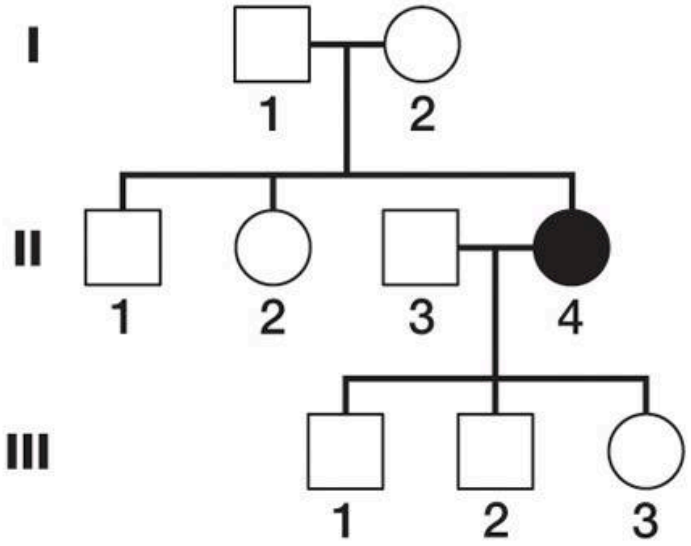
Loss of heterozygosity for a tumor suppressor through mitotic recombination



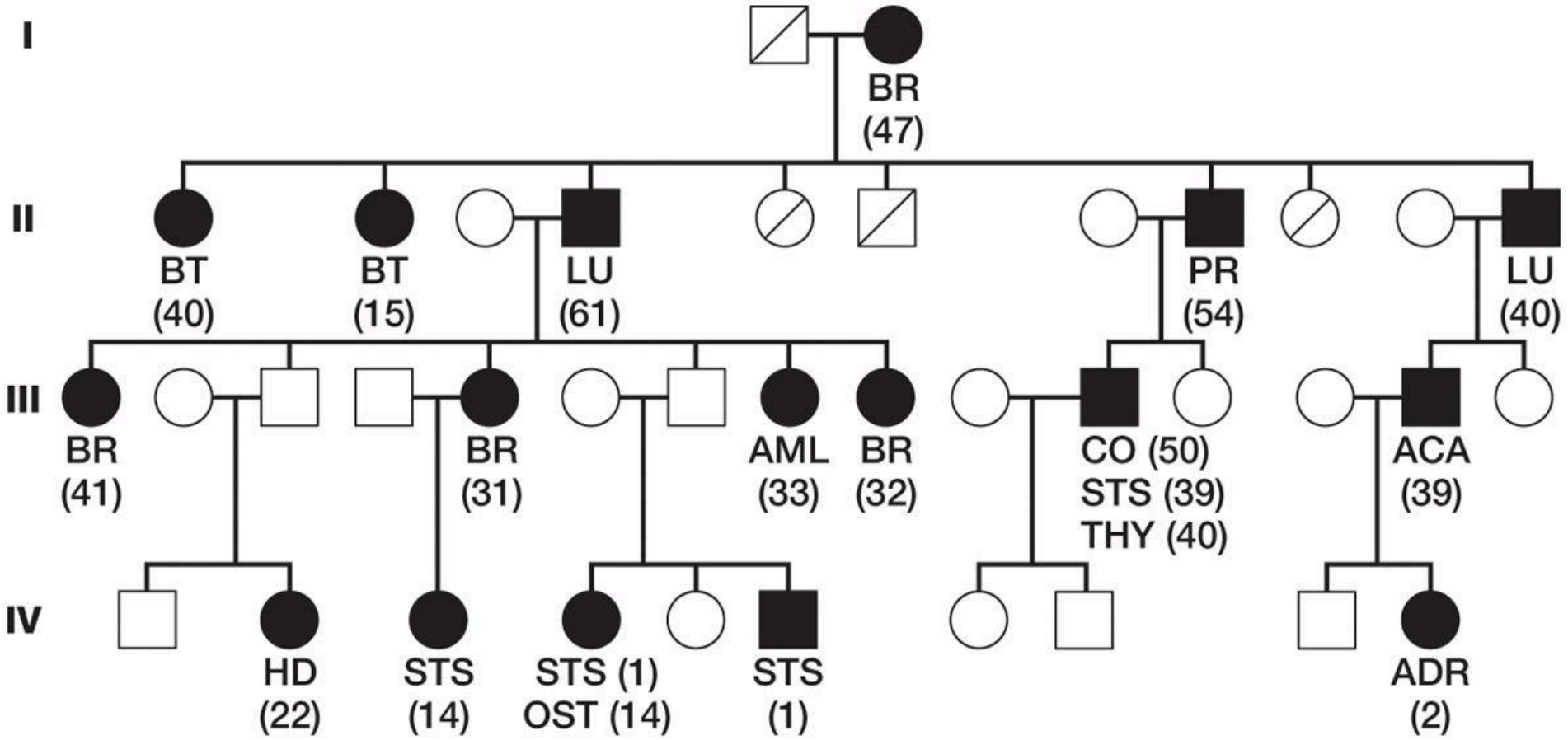
Familial retinoblastoma



Sporadic retinoblastoma

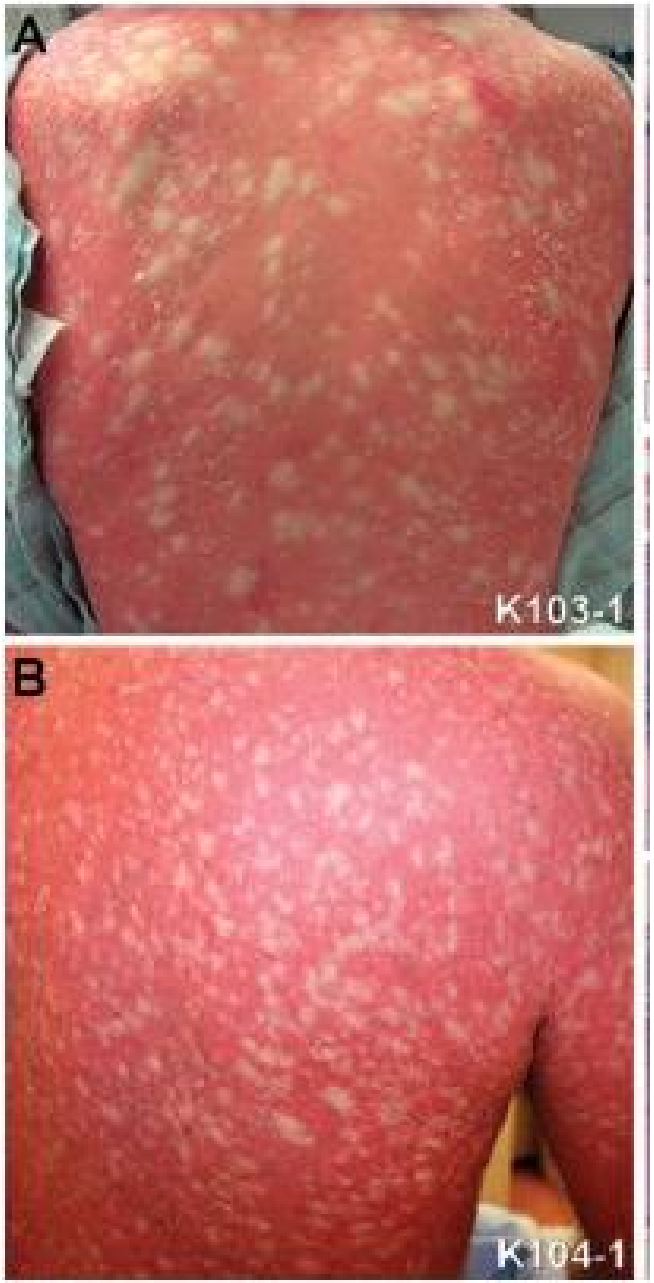


Familial retinoblastoma behaves as a genetic dominant, even though at the cellular level it only shows a phenotype as a recessive loss of function mutation.



A dominant condition reverting back to wildtype through mitotic recombination and loss of heterozygosity

Fig. 1. Frequent revertants in ichthyosis with confetti. (**A** and **B**) The backs of an 18-year-old female subject (103-1) and 42-year-old male (104-1) show background redness and scaling with hundreds of white, normal-appearing "confetti" spots. (**C**) Histology of normal human skin showing basal layer (labeled B), stratum spinosum (S), granular layer (G), and stratum corneum (SC). (**D**) Affected skin shows loss of differentiation of all layers above the basal layer and hypercellularity with increased epidermal thickness. There is no granular layer, and



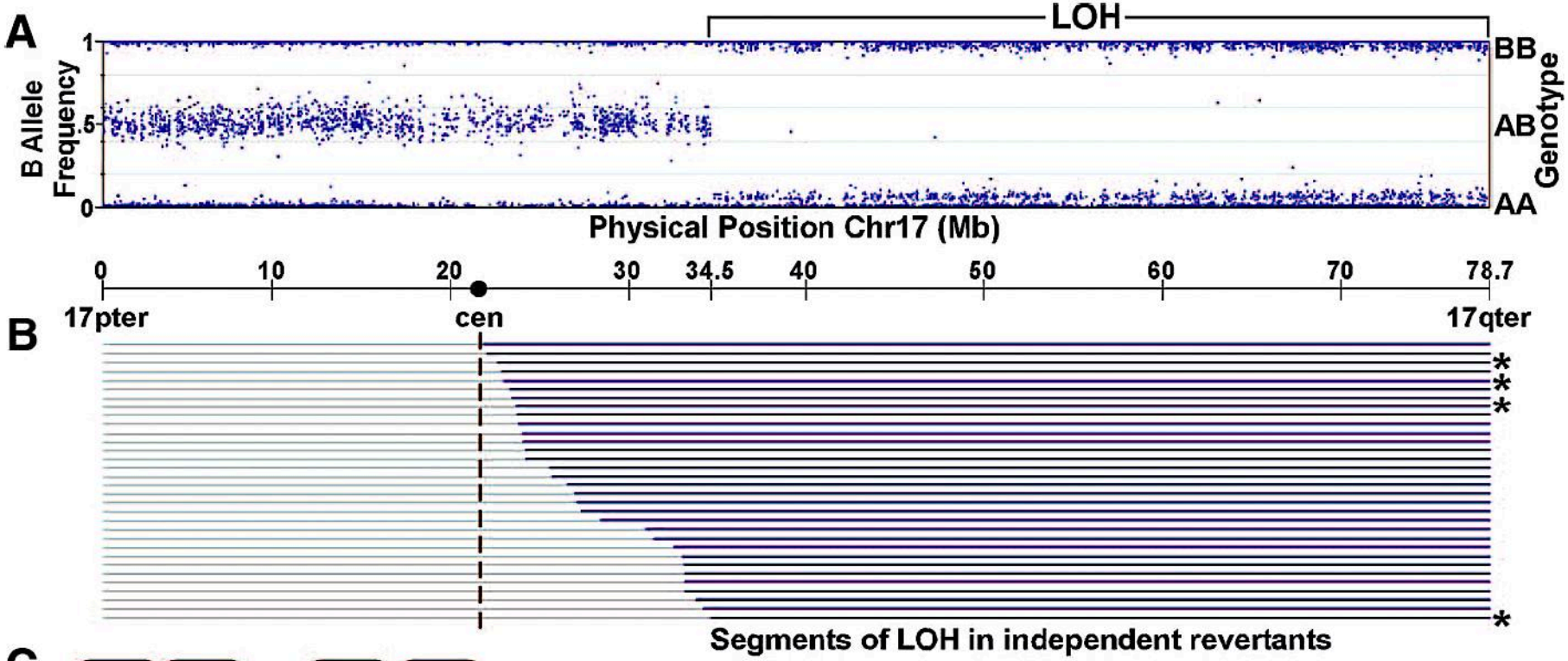
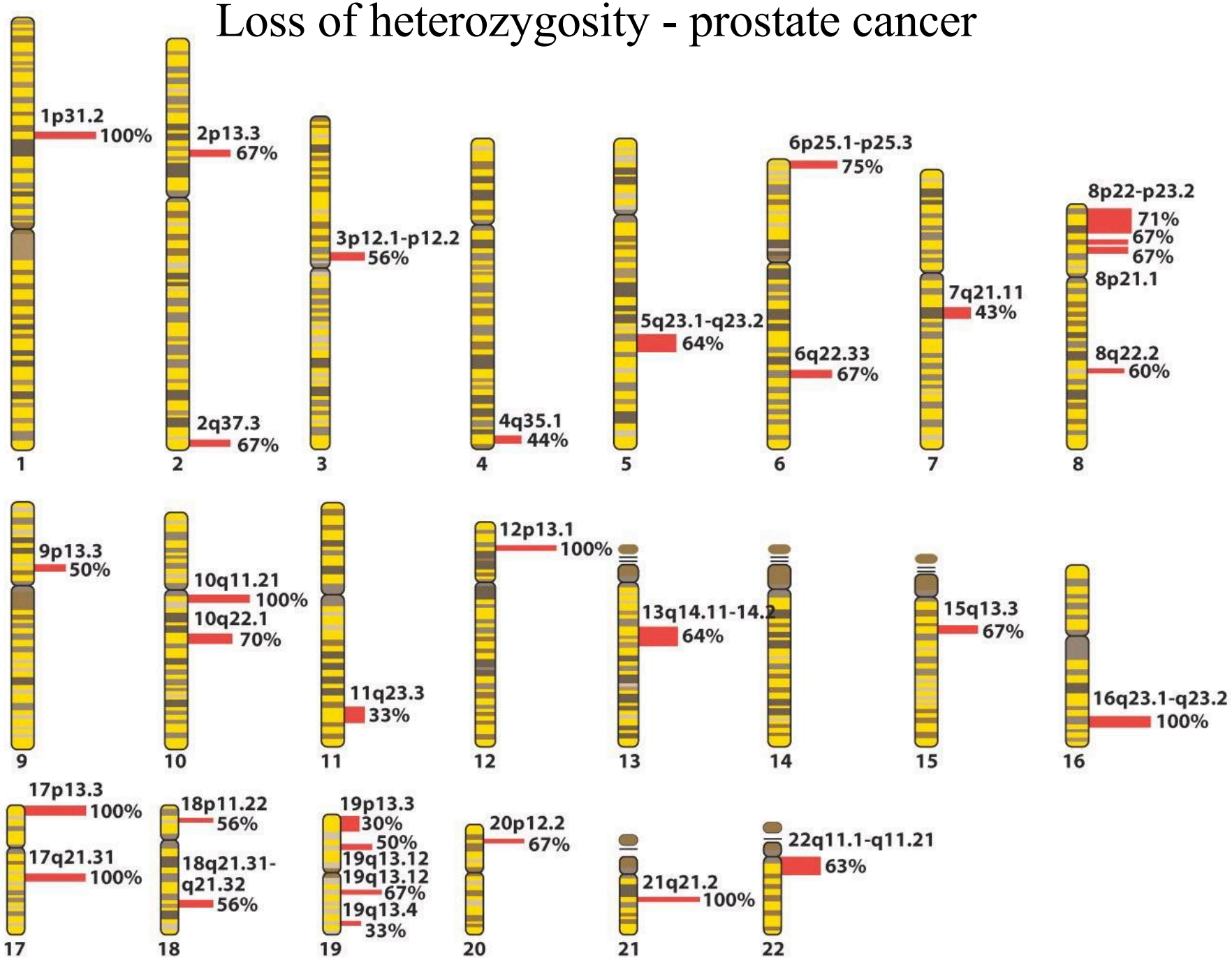


Fig. 2. Revertant spots show loss of heterozygosity on 17q. (**A**) Genotypes on chromosome 17 from revertant keratinocytes of IWC subject 106-1 are shown. From 17pter to 34.5 Mb, genotypes show the expected heterozygosity with genotypes identical to blood and disease keratinocyte DNA (fig. S2), whereas from 34.5 Mb to 17qter, genotypes are homozygous with no change in diploid copy number (fig. S2). (**B**) Results of genotyping keratinocytes of 32 revertant spots from seven unrelated IWC subjects (106-1 revertants denoted with an asterisk). Gray lines, genomic segments with heterozygous genotypes matching blood DNA; blue lines, segments showing copy-neutral LOH. These results are consistent with the hypothesis that IWCs are caused by a dominant allele distal to 34.5 Mb that is lost by mitotic recombination, as depicted in (**C**).

Loss of heterozygosity - prostate cancer



Tumor suppressors can be identified by screening paired blood and tumor samples with markers spaced across the genome for multiple individuals with a particular form of cancer.

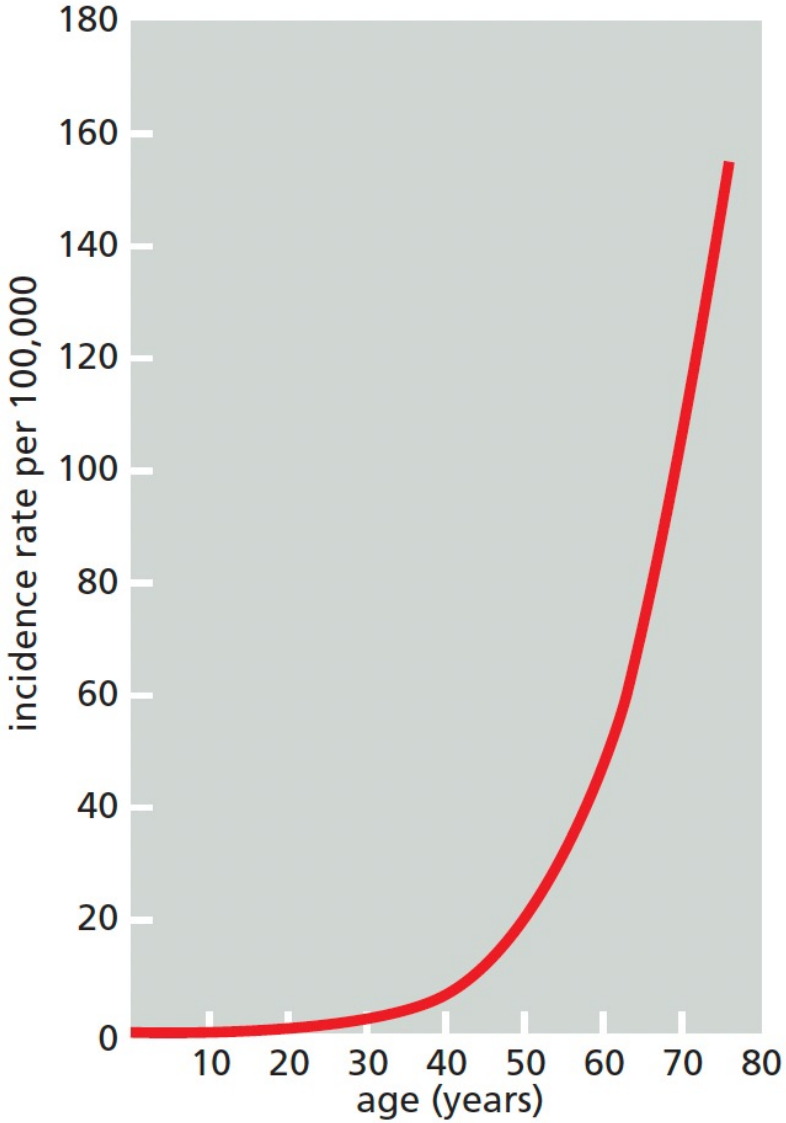
The idea is to identify regions of the genome that lack heterozygosity in the tumor sample, but not in the blood sample. These regions are good candidates to tumor suppressors.

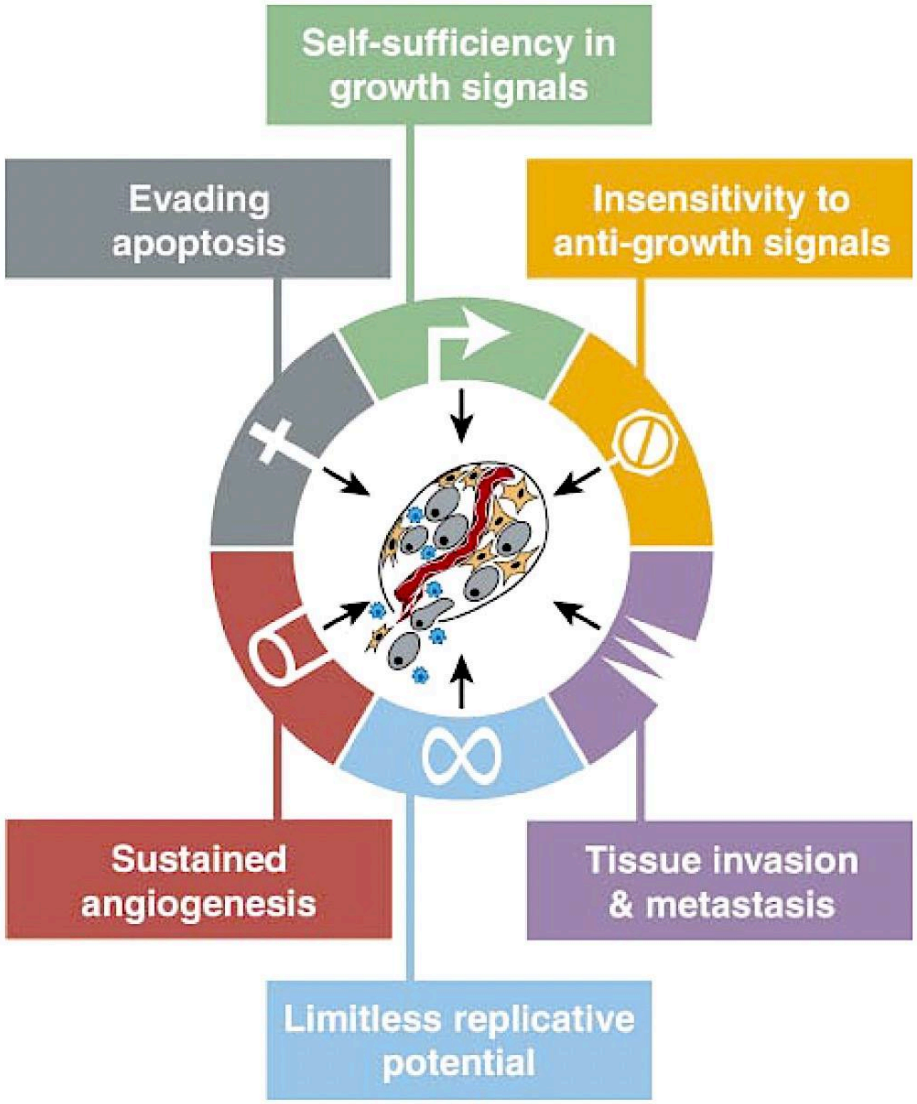
The heterozygosity may have been lost as a result of
1. mitotic recombination.

2. deletions of the same region on both homologs.

3. methylation of a wildtype allele in a heterozygote for a mutant allele. Cannot be detected through sequencing

If cancer generation only required one mutation, which occurred with a fixed probability per unit time during your life, then the chance of developing any given cancer should be independent of age. In fact this is not the case. For most cancers the probability goes up very steeply with age, typically as the third, fourth or fifth power. These epidemiological observations suggest that from 4-6 independent events are required.

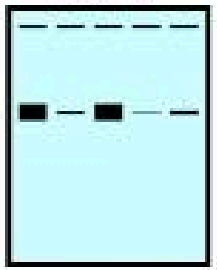




How do cancer cells differ at the transcriptional level from normal cells

- DNA microarrays provide a method for simultaneously assessing thousands of genetic loci in a single sample:
  - DNA ⇨ "SNP Arrays" ⇨ Genotype / Copy Number
  - DNA ⇨ "Sequence Arrays" ⇨ DNA Sequence
  - **RNA ⇨ "Expression Arrays" ⇨ Gene Expression**

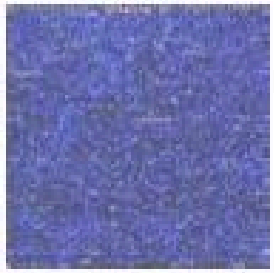
1990



Northern Blot

One Transcript / Several Samples

2005



GeneChip® Microarray

One Sample / > 50,000 transcripts

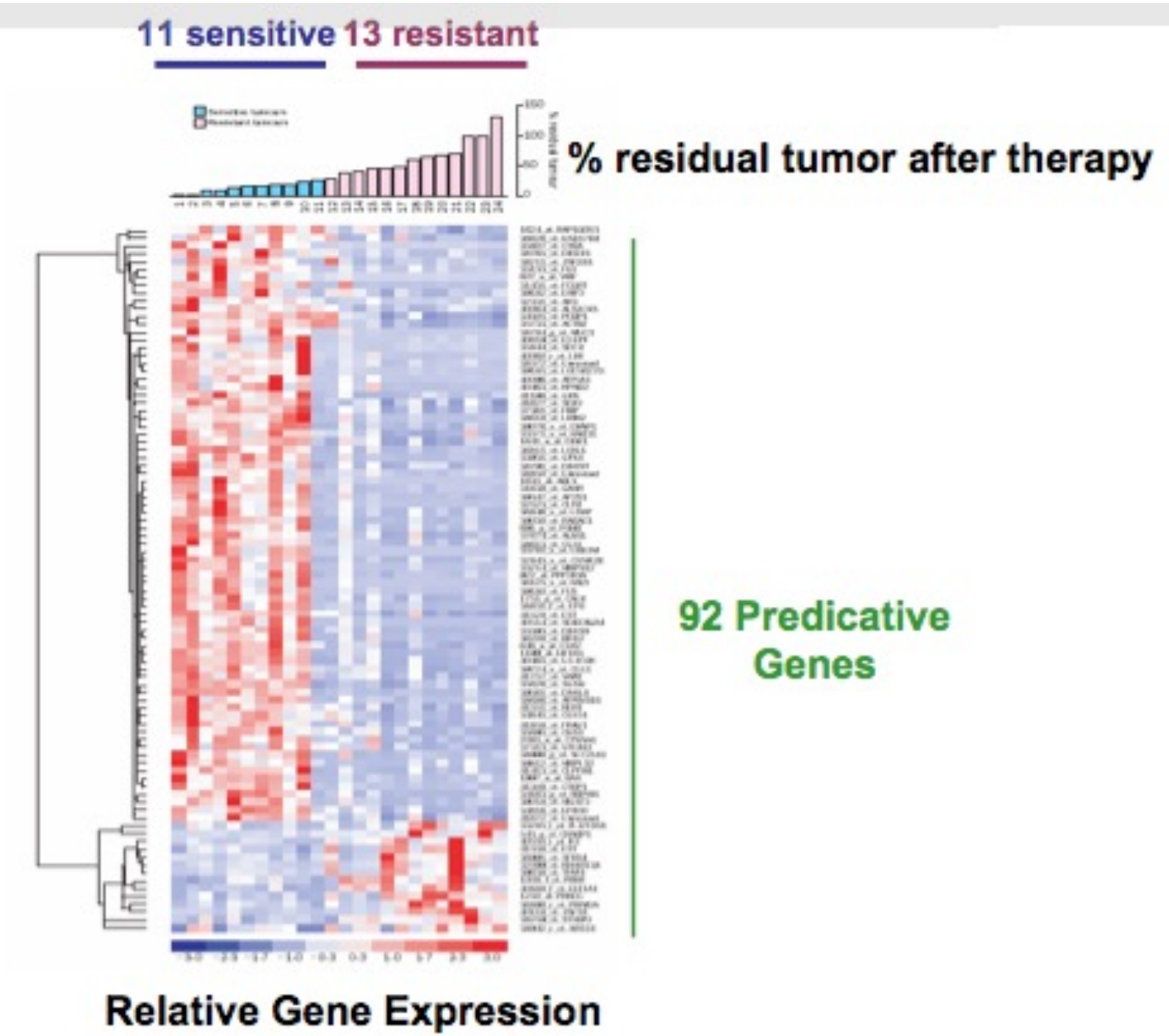
- Docetaxel is frequently given as chemotherapy for breast cancer, but many tumors are resistant.
- Can patterns of gene expression predict patient response to therapy?

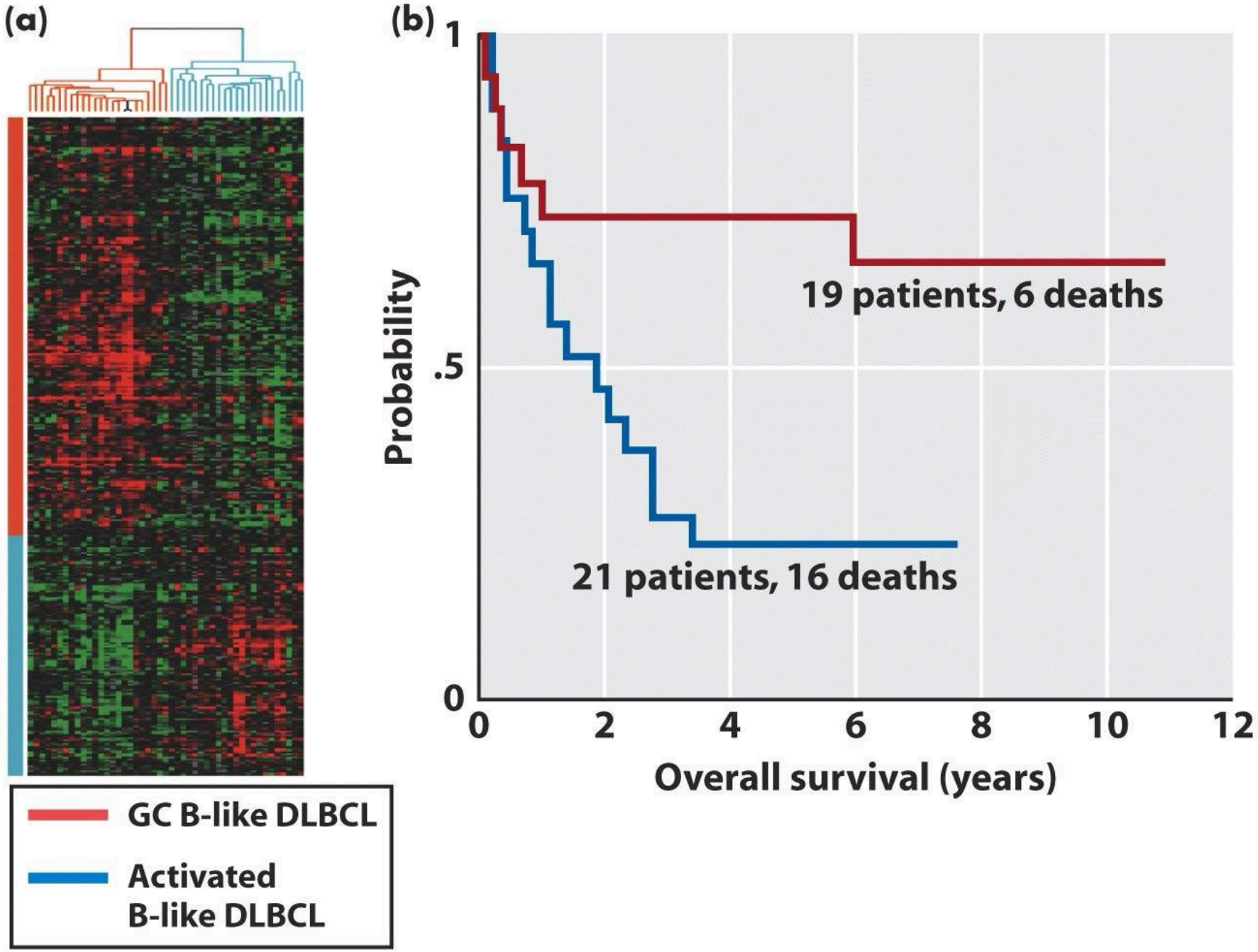
Gene expression profiling for the prediction of therapeutic response to docetaxel in patients with breast cancer

Jenny C Chang, Eric C Wooten, Anna Tsimelzon, Susan G Hilsenbeck, M Caroline Gutierrez, Richard Elledge, Syed Mohsin, C Kent Osborne, Gary C Chamness, D Craig Allred, and Peter O'Connell

THE LANCET • Vol 362 • August 2, 2003 • www.thelancet.com

- 24 tumors (13 resistant / 11 sensitive) and ~1,600 genes.
- Results: 92 predictive genes with 88% accuracy


11 sensitive
13 resistant
% residual tumor after therapy
92 Predicative Genes
Relative Gene Expression


(a)
GC B-like DLBCL
Activated
B-like DLBCL
(b)
Probability
1
.5
0
0
2
4
6
8
10
12
Overall survival (years)
19 patients, 6 deaths
21 patients, 16 deaths

Synthetic lethal screening.

Looking for gene knockdown or drugs that kill cancer cells carrying a specific mutation but not normal cells

An example using shRNAs and the K-Ras mutant.

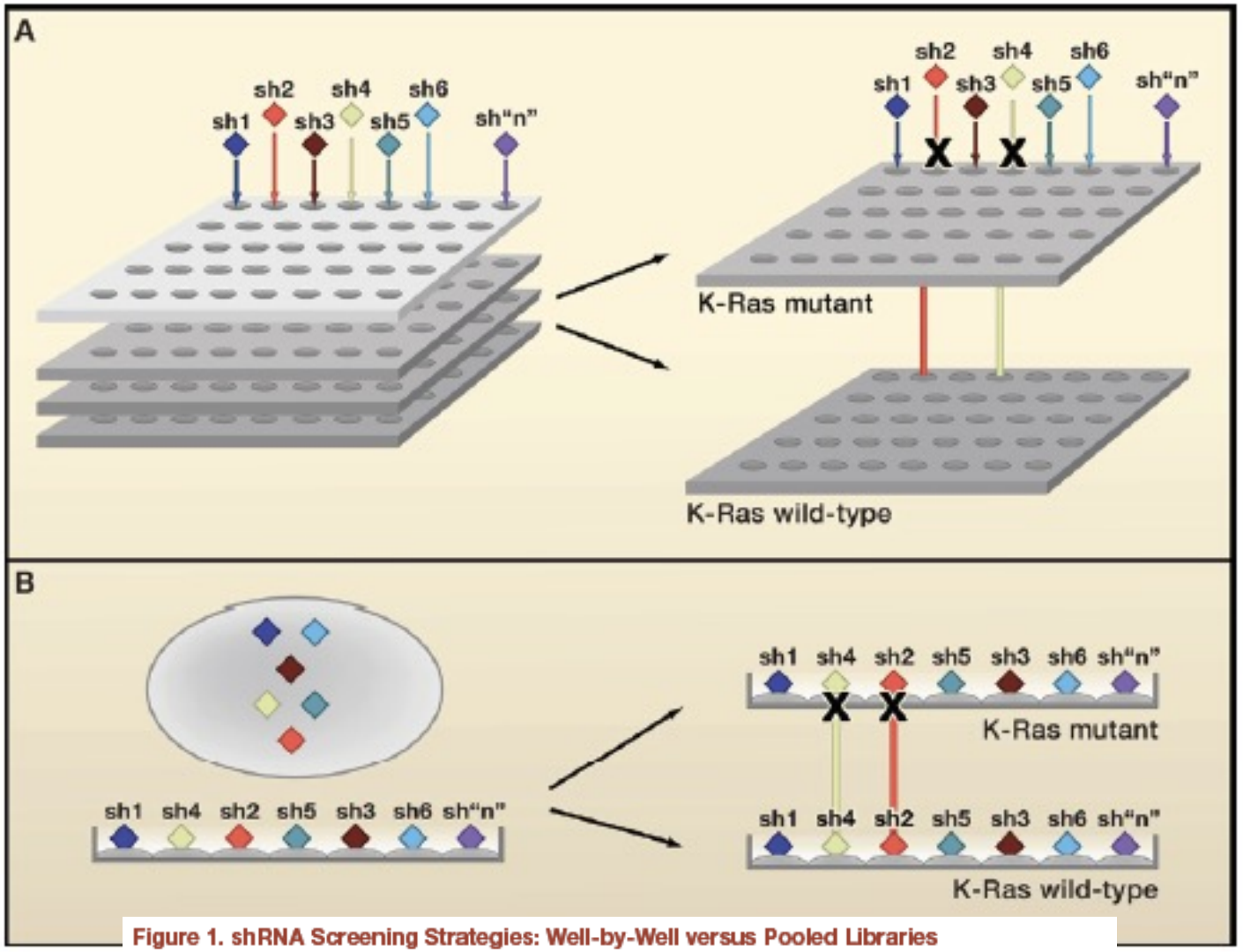


Figure 1. shRNA Screening Strategies: Well-by-Well versus Pooled Libraries

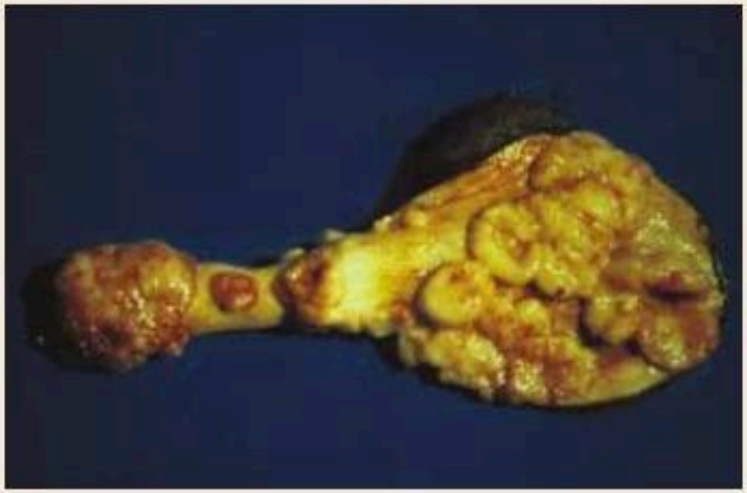
(A) In the well-by-well approach, the impact of each individual short hairpin RNA (shRNA) on growth or survival is scored after a predefined incubation period. shRNAs that selectively kill cells bearing the mutant oncogene versus wild-type cells (designated by "X") are deemed "hits." Genes targeted across a panel of mutant cell lines and by independent hairpins rank highest on the hit list. The well-by-well approach requires a high-throughput screening infrastructure due to the number of shRNAs in a reasonably comprehensive library and the number of cell lines screened to generate confidence in hits.

(B) With the pooled screening approach, cells are infected with the entire pooled shRNA library at a low multiplicity of infection (to assure one shRNA per cell. The cells are then passaged for multiple population doublings to deplete those cells whose growth is adversely impacted by a specific shRNA. The identity of shRNAs that drop out during serial passage (designated by "X") is determined by barcode array hybridization. As with the well-by-well approach, genes targeted by more than one independent shRNAs in multiple cell lines are ranked most highly. Both strategies are limited by an unknown but presumably high "false negative" rate, given that few of the shRNAs in current libraries are validated to confer substantial knockdown.

A cancer as a new, parasitic, species of animal

Box 1 | **Dog venereal cancer: a highly degenerate mammal**

Mammals are continually sloughing off cells, but these cells usually die once they are separated from the organism. Even the most aggressive and invasive cancer cells usually die when their host dies. However, there is a fascinating exception: canine transmissible venereal sarcoma (CTVS) is an infectious disease of dogs that is caused by a pathogenic lineage of cancerous cells[70]. This cell lineage is transmitted from one dog to another, usually during coitus. Once on a new host, the cells reproduce to form a tumour-like growth, usually around the genitals, but occasionally on the skin and in and around the mouth. The figure shows a primary venereal cancer in the dog, involving the penis and surrounding tissue. The cell lineage can then be transmitted to another host. There are no obvious differences in susceptibility between breeds of dogs, and the cells can even be transmitted to foxes. It is this continuity of the cell lineage (as opposed to merely continuity of an infectious virus) that distinguishes CTVS from other transmissible cancers (for example, human cervical cancer). Even without treatment, tumours usually regress after 1–3 months, and if regression is complete, then the host is immune to subsequent re-infection. CTVS can be found in many parts of the world, and in some regions is the most common dog tumour. It is thought to have originated only once and spread worldwide, and a LINE retrotransposable element insertion upstream of the c-*MYC* oncogene[71] was presumably important in its genesis. This 'naturally occurring allograft' has become a true pathogen, even a highly degenerate mammal. Image courtesy of Wilfried T. Weber, Pennsylvania, USA.



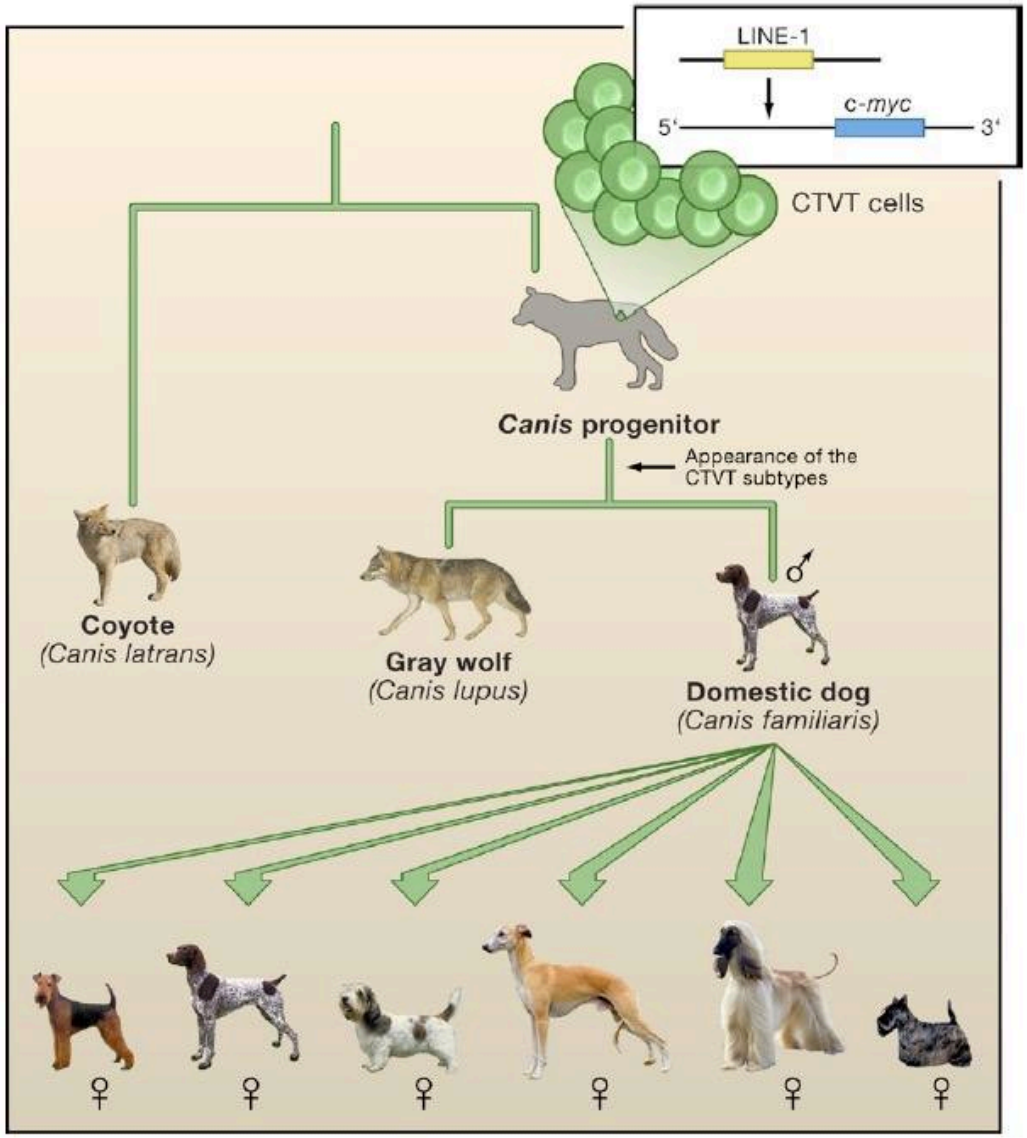


Figure 1. Ancestry of the Canine Transmissible Venereal Tumor Lineage

The canid phylogeny depicts the origins of canine transmissible venereal tumor (CTVT). The LINE-1 element was inserted upstream of c-*myc*, a proto-oncogene, in the cells of a wolf/dog progenitor. CTVT lineage divergence occurred soon after its emergence. The subtypes do not necessarily correspond to species. Once the CTVT tumor enters the dog lineage, an infected individual can rapidly transmit it (green arrows) by coitus. The tumor can potentially be transmitted among *Canis* species. Scottish terrier photo courtesy of the American Kennel Club (AKC); other dog photos courtesy of Mary Bloom, AKC. Wolf photo courtesy of Priscilla Barrett (D.W. MacDonald and P. Barrett, Mammals of Europe [Princeton University Press, Princeton, NJ, USA, 1993]). Coyote photo courtesy of Dr. Robert K. Wayne.

Transmission of a fatal clonal tumor by biting occurs due to depleted MHC diversity in a threatened carnivorous marsupial

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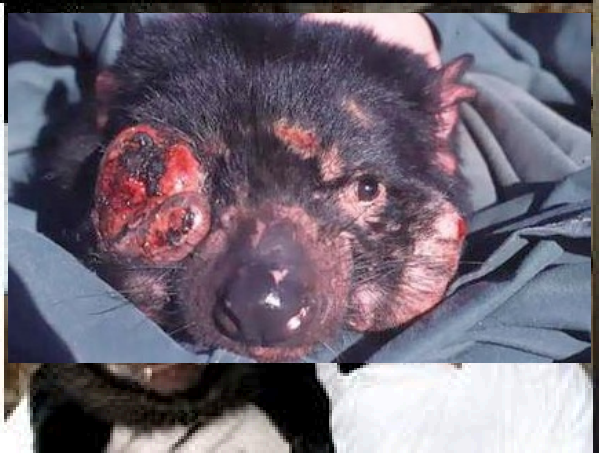
The Tasmanian devil, the largest living marsupial carnivore, earned its common name because of its blood-curdling nocturnal screams. But their true nature belies this reputation. Read more



Tasmanian devil facial tumour disease threatens the existence of the Tasmanian devil

A SPECIES AT RISK

The first signs of Tasmanian Devil Facial Tumour Disease (DFTD) were observed in 1996. It's a new and fatal condition in Tasmanian devils, characterised by cancers around the mouth and head. Tasmanian devils with the disease usually die within three to eight months of the lesions first appearing. Spotlight surveys indicate a decline in sightings of more than 50% statewide. Help now

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A transmissible cancer in clams!!