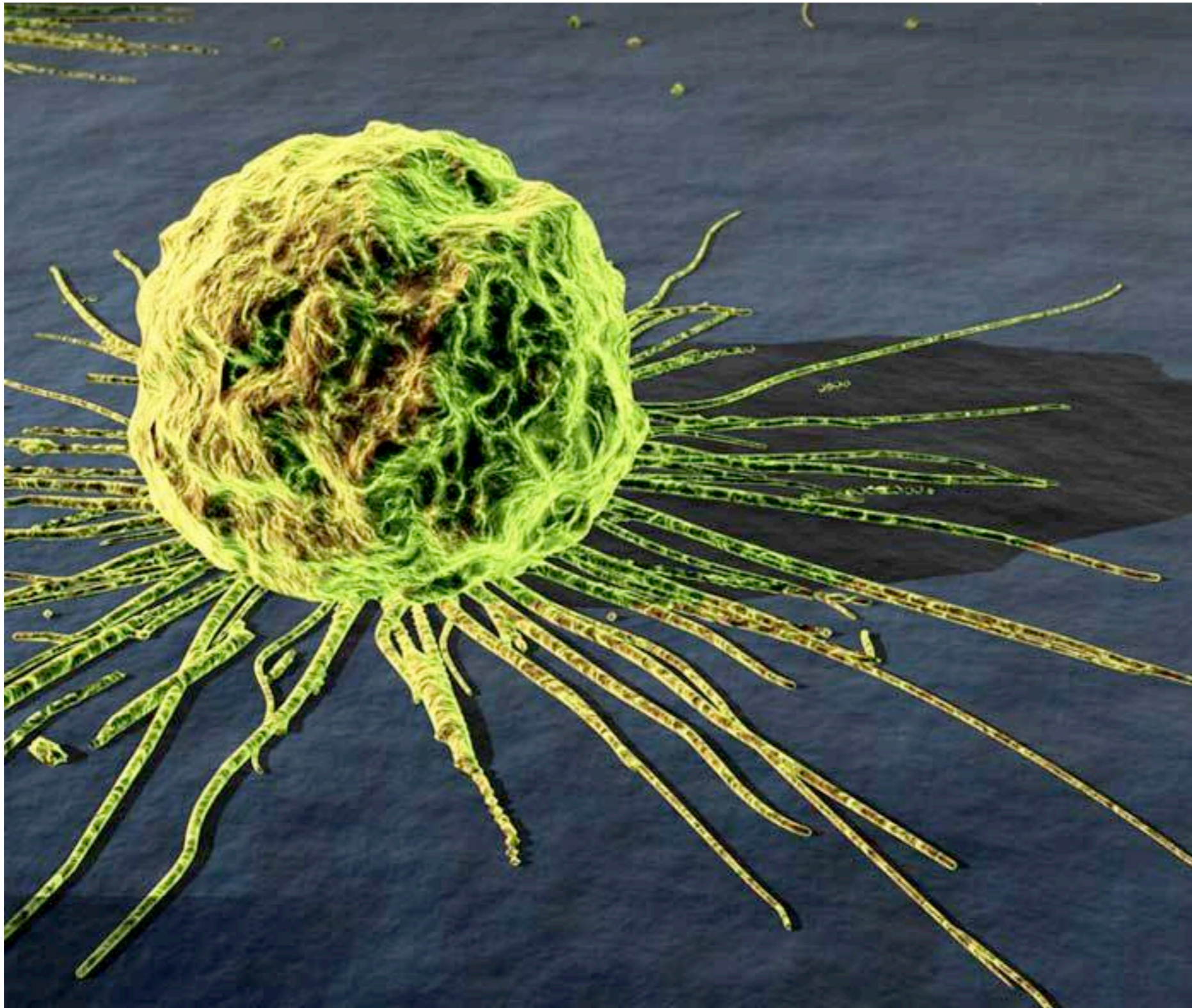
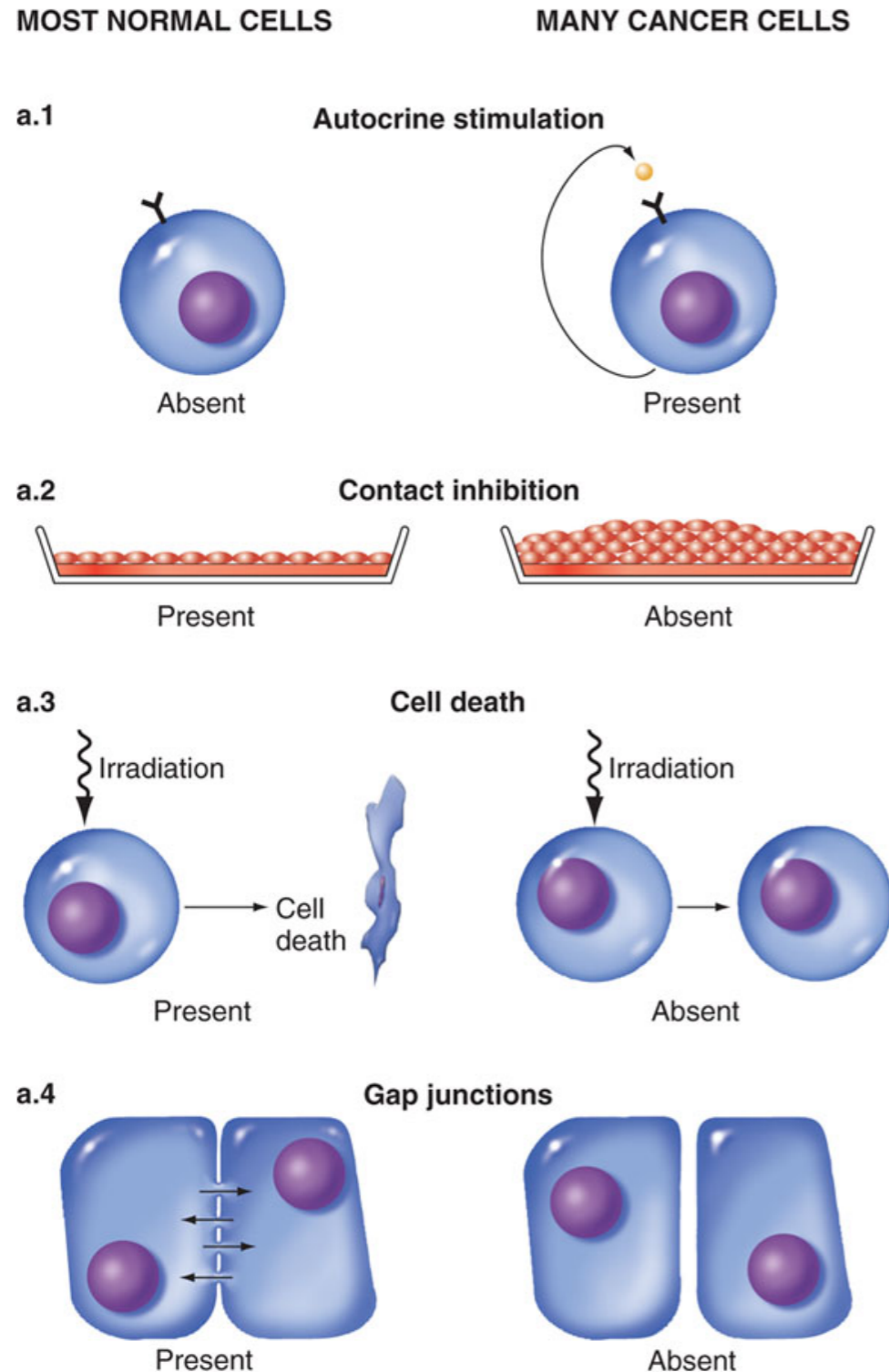


Cancer is a diverse disease with common cellular themes



Phenotypes that distinguish cancer cells from normal cells

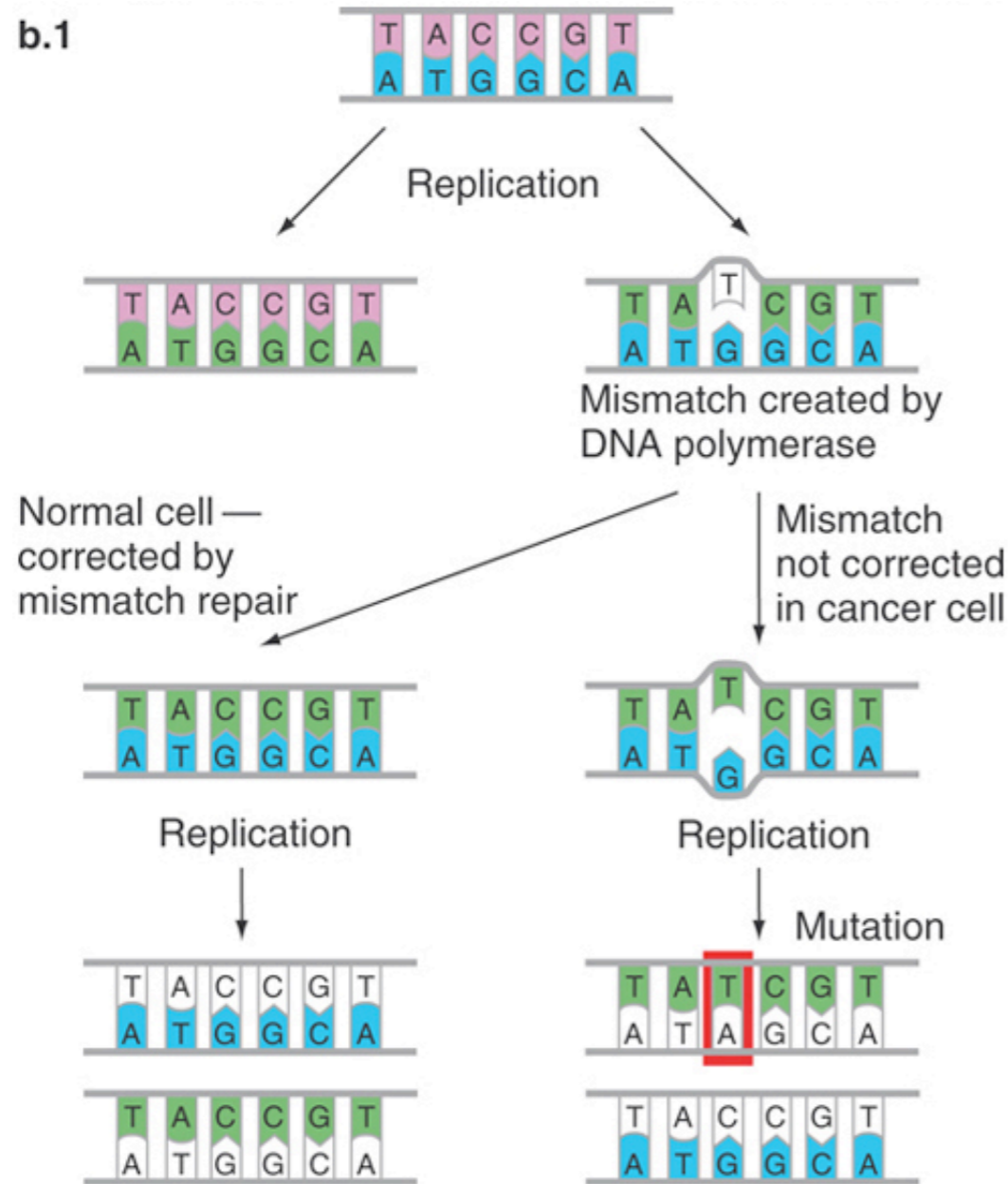


Cancer cells have typically lost multiple regulatory pathways that enable normal cells to respond appropriately to their environment.

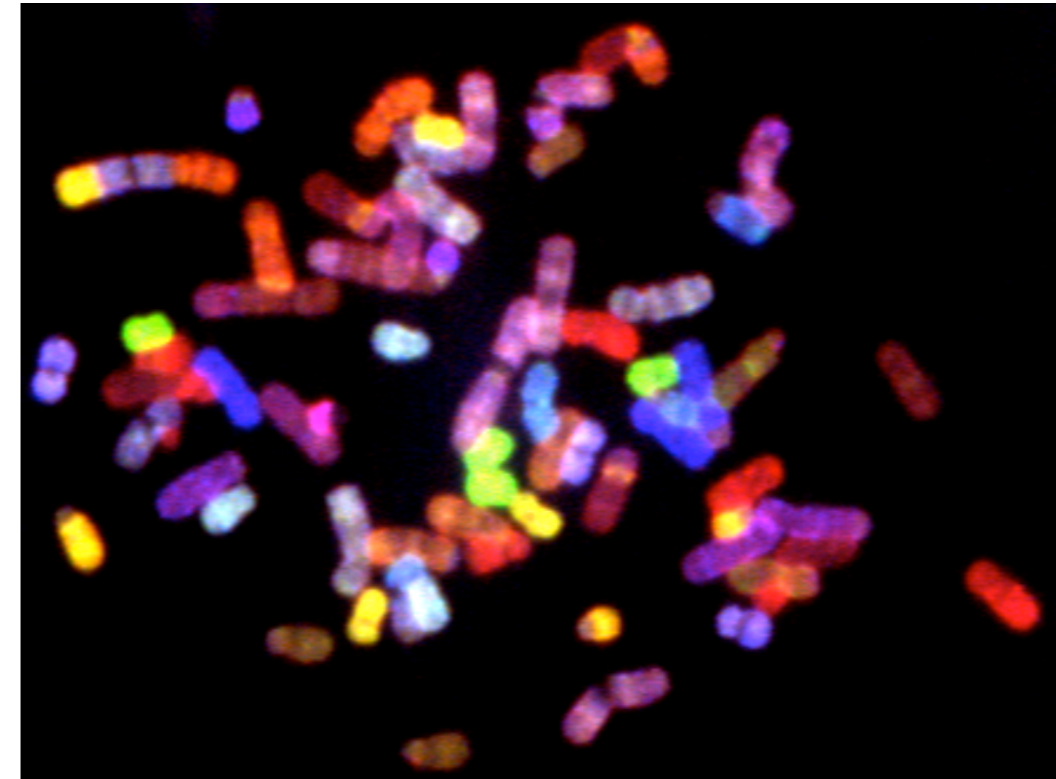
- Autocrine stimulation – tumor cells make their own signals to divide
- Loss of contact inhibition – normal cells stop dividing when contacted by another cell
- Loss of cell death – apoptosis normally eliminates cells with potentially serious problems
- Loss of gap junctions – normal cells have channels for communicating with neighbor cells

Phenotypes that distinguish cancer cells from normal cells

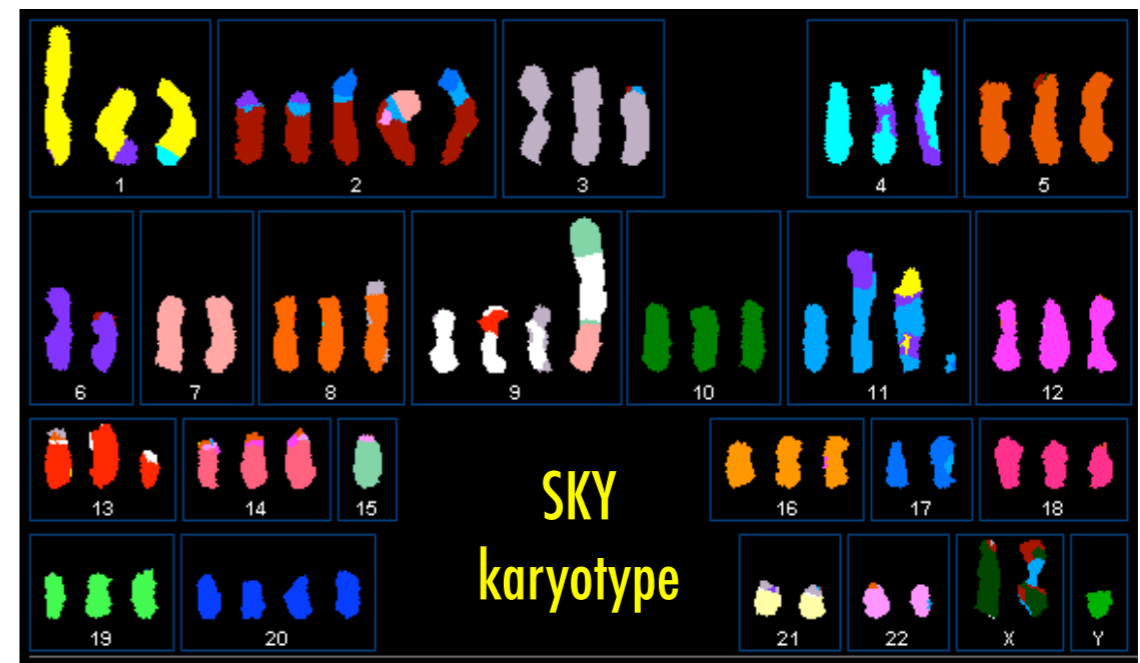
Cancer cells are characterized by “genome instability” - they do not replicate and segregate their genetic information as faithfully as normal cells



Cancer cells often have mutations in genes required for DNA replication, repair, or segregation.

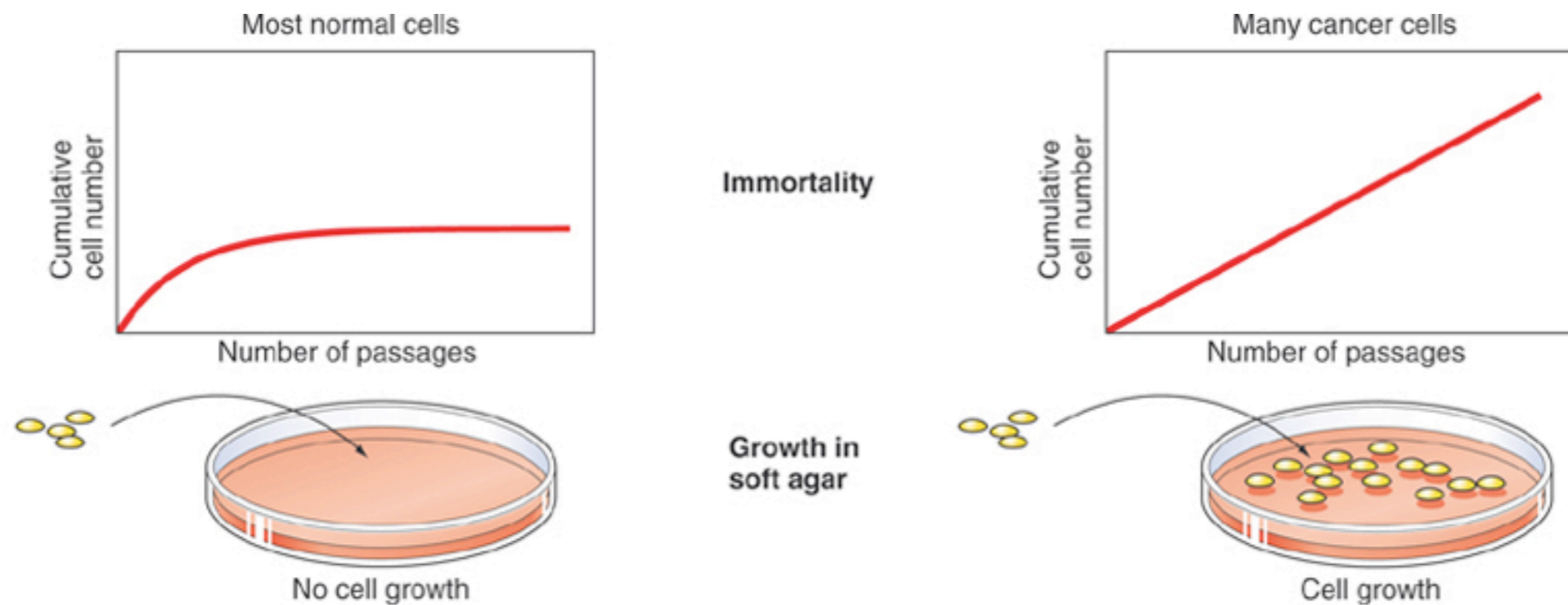


Chromosome painting or spectral karyotyping (SKY), reveals extensive chromosome rearrangements and aneuploidy



Phenotypes that distinguish cancer cells from normal cells

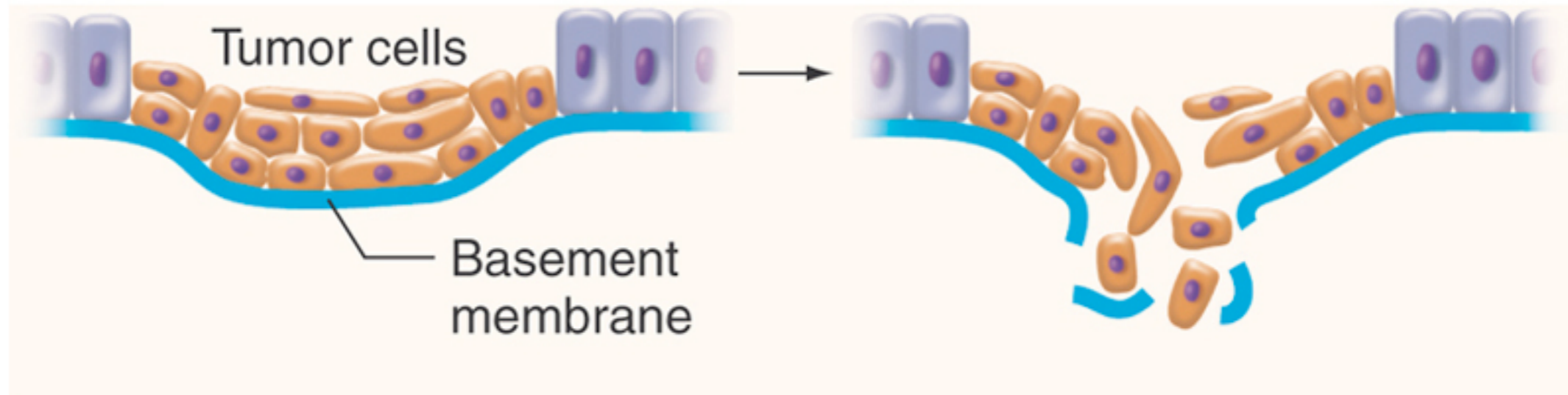
Cancer cells also become immortal -
unlike most cells, they have the ability to divide indefinitely



Phenotypes that distinguish cancer cells from normal cells

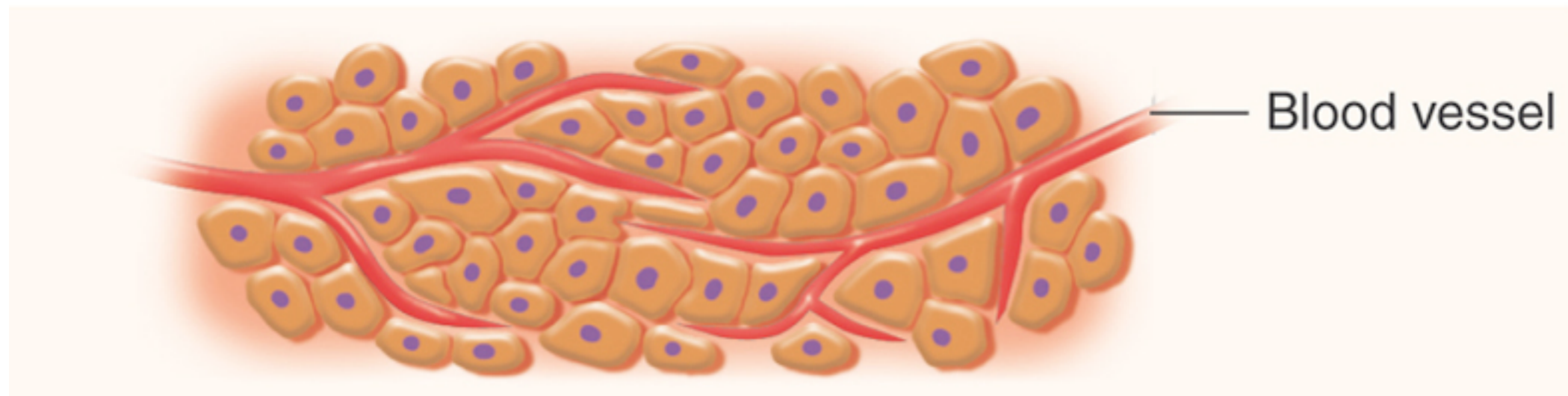
Tumor cells also gain the capacity to invade through barriers that would block the growth or movement of normal cells

d.1 Metastasis



...and they acquire the ability to feed themselves by secreting growth factors to promote blood vessel development

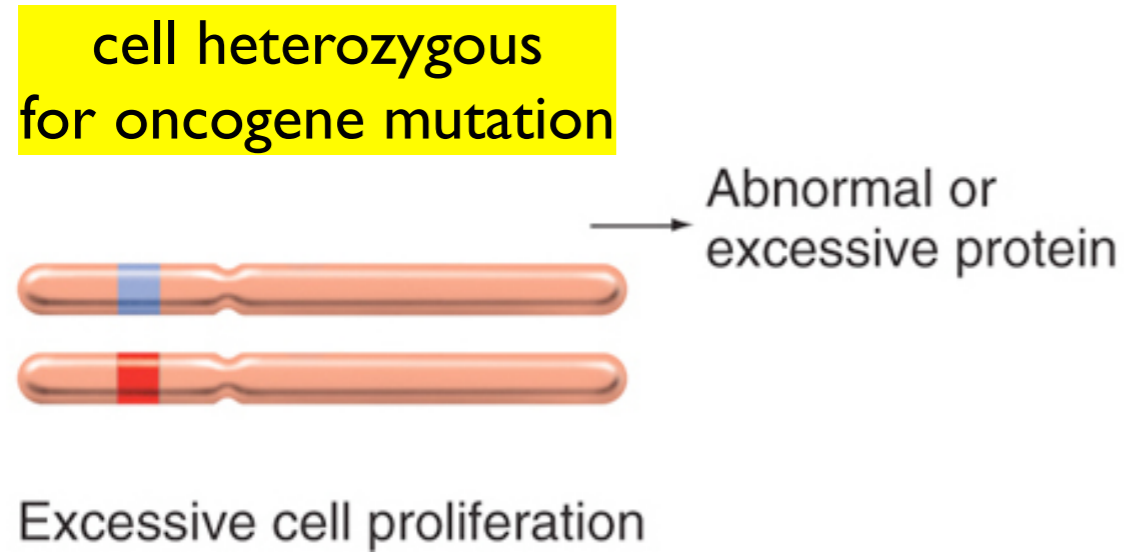
d.2 Angiogenesis



Two classes of cancer-causing mutations

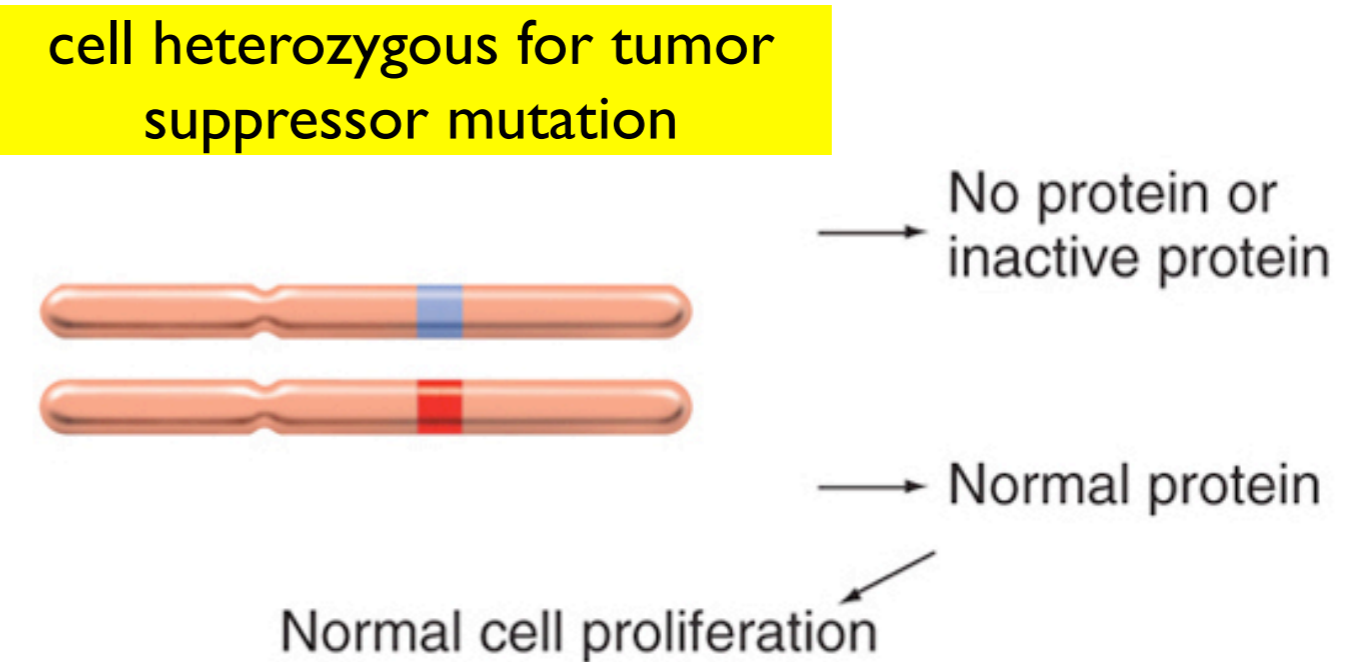
Oncogenes

gain-of function, dominant mutations

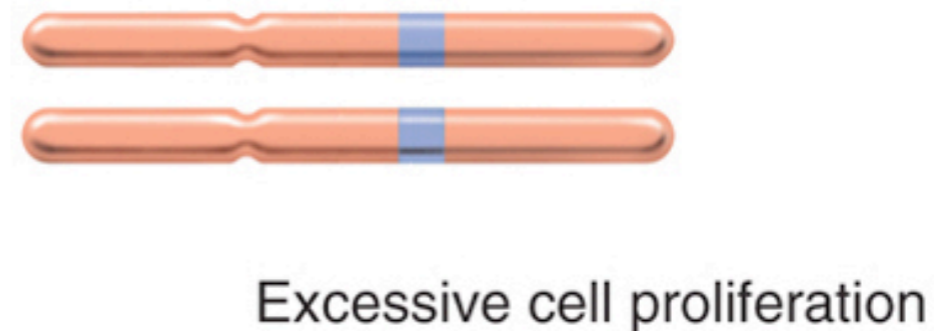


Mutant tumor-suppressor genes

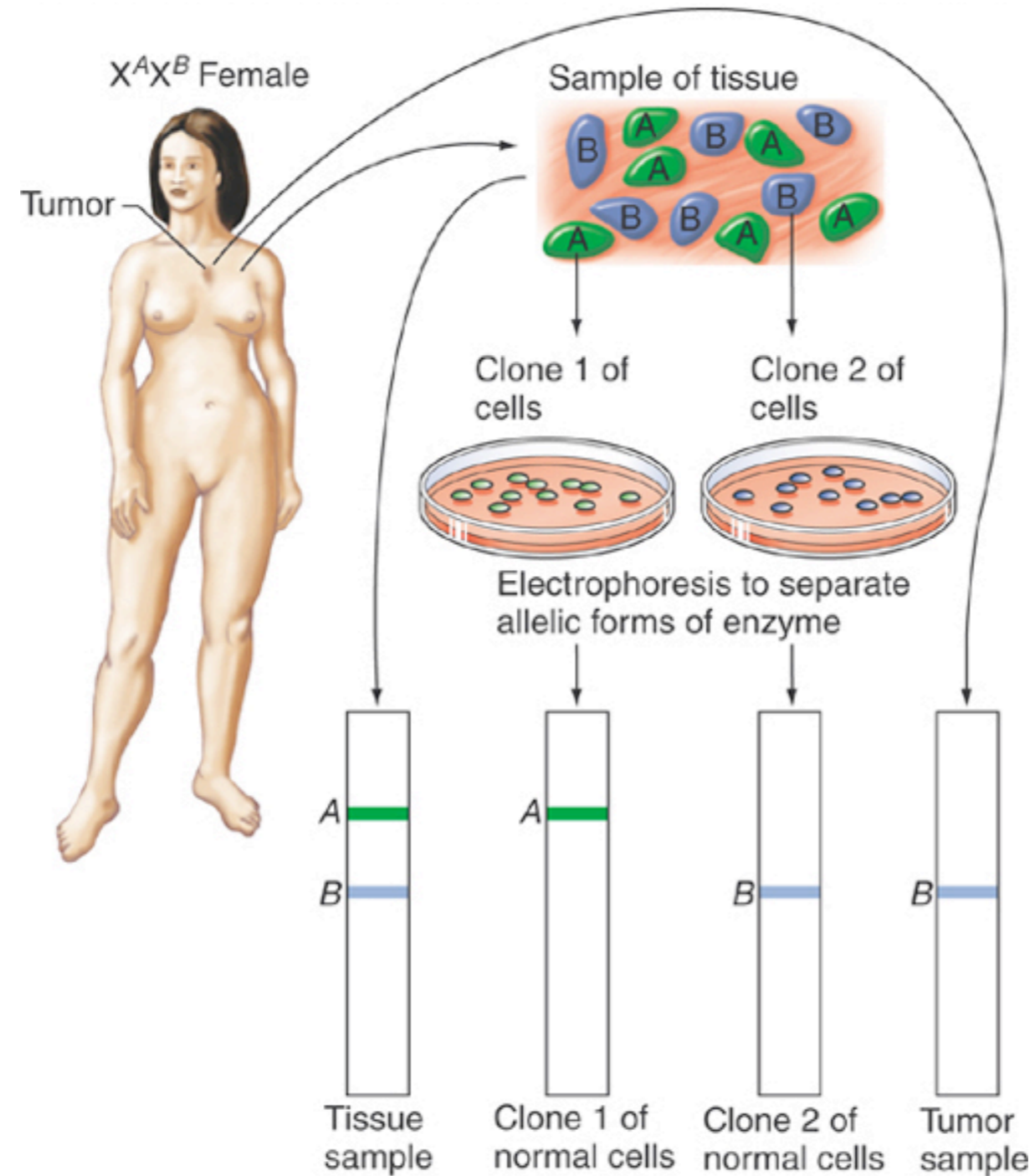
loss-of-function, recessive mutations



cell homozygous for tumor suppressor mutation

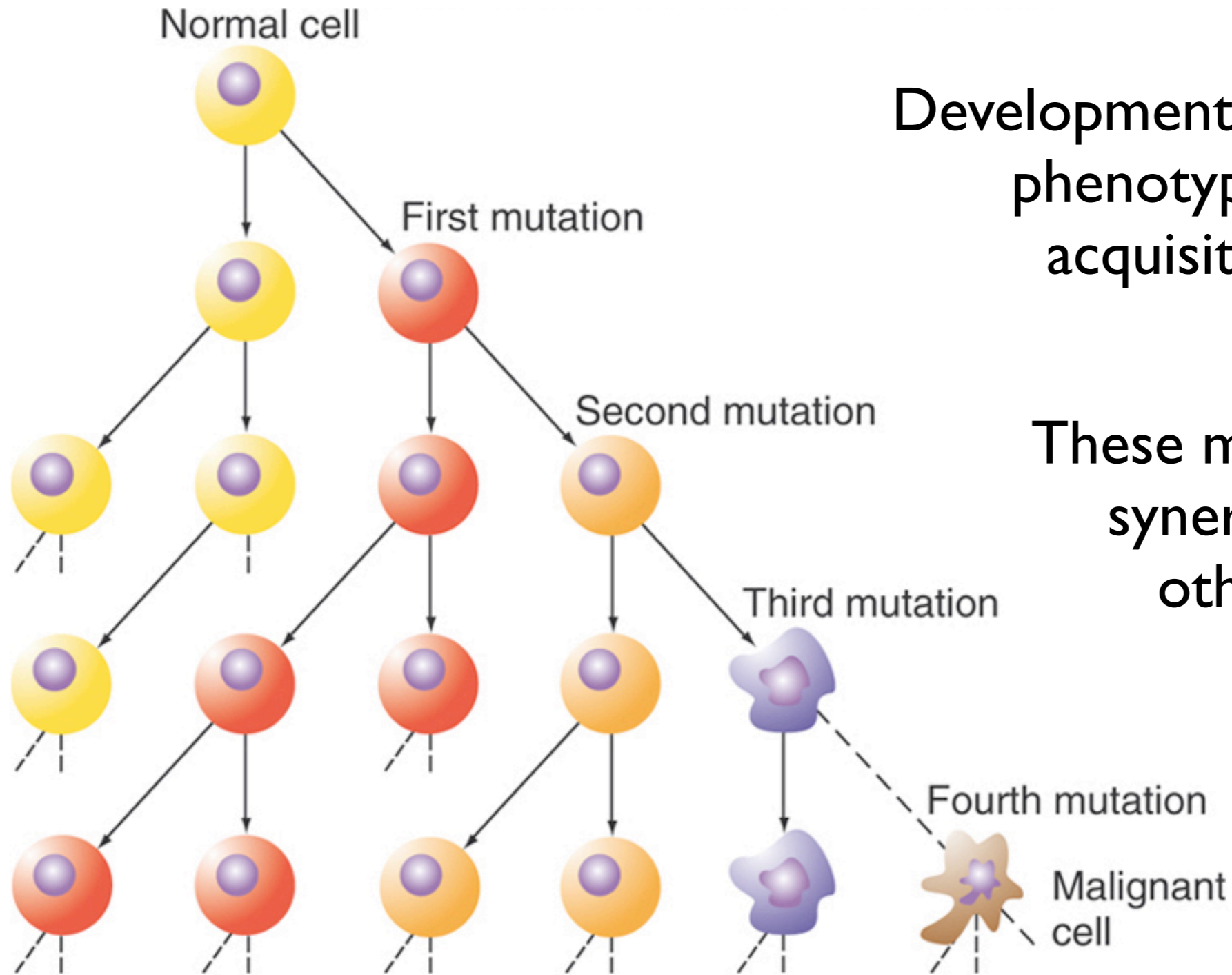


How do cancer-causing mutations arise?



Evidence indicates that most tumors are the descendants of a single normal cell

How do cancer-causing mutations arise?

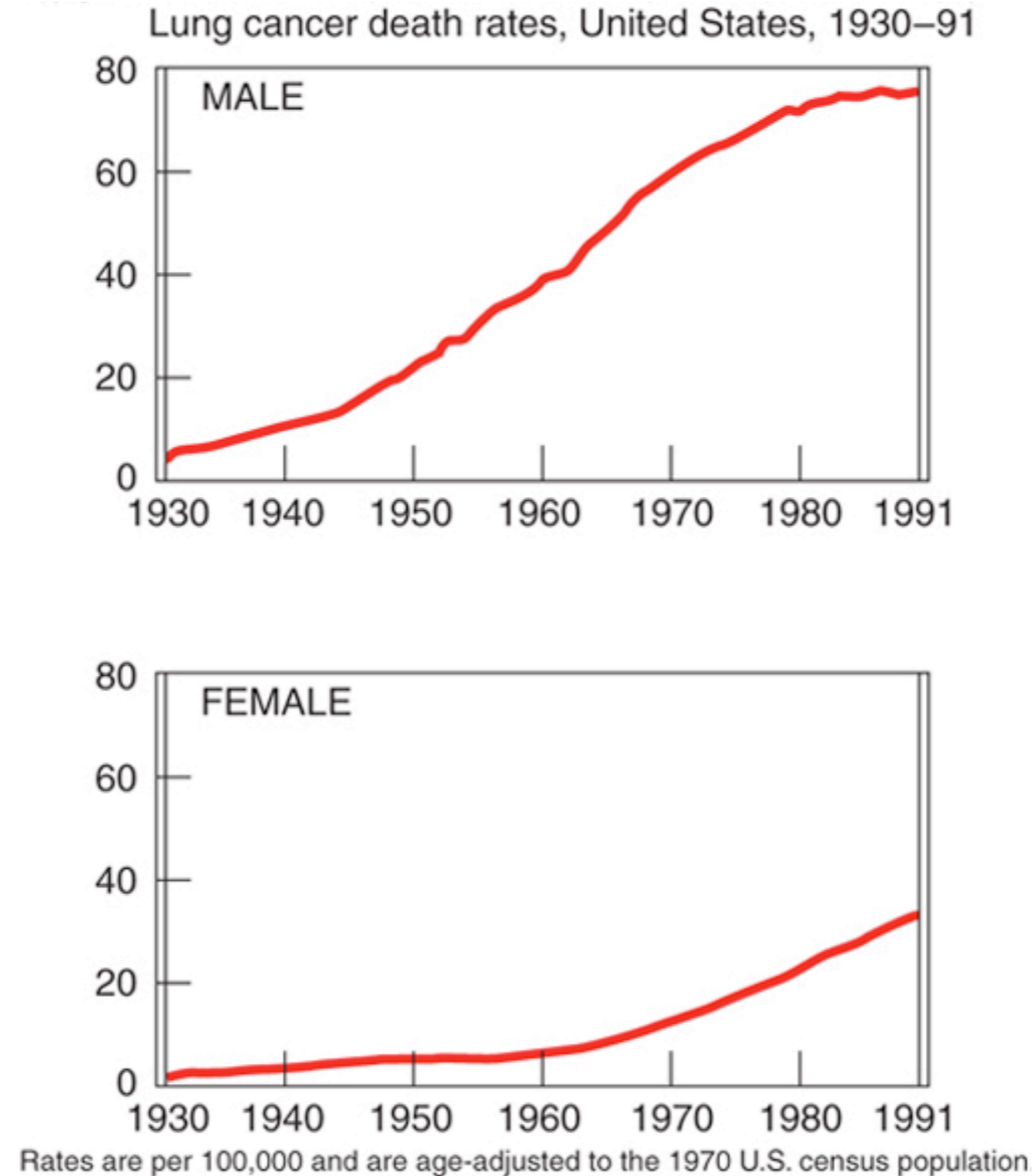


Development of a malignant phenotype requires the acquisition of multiple mutations.

These mutations often synergize with each other (remember enhancers?)

Evidence indicates that most tumors are the descendants of a single normal cell

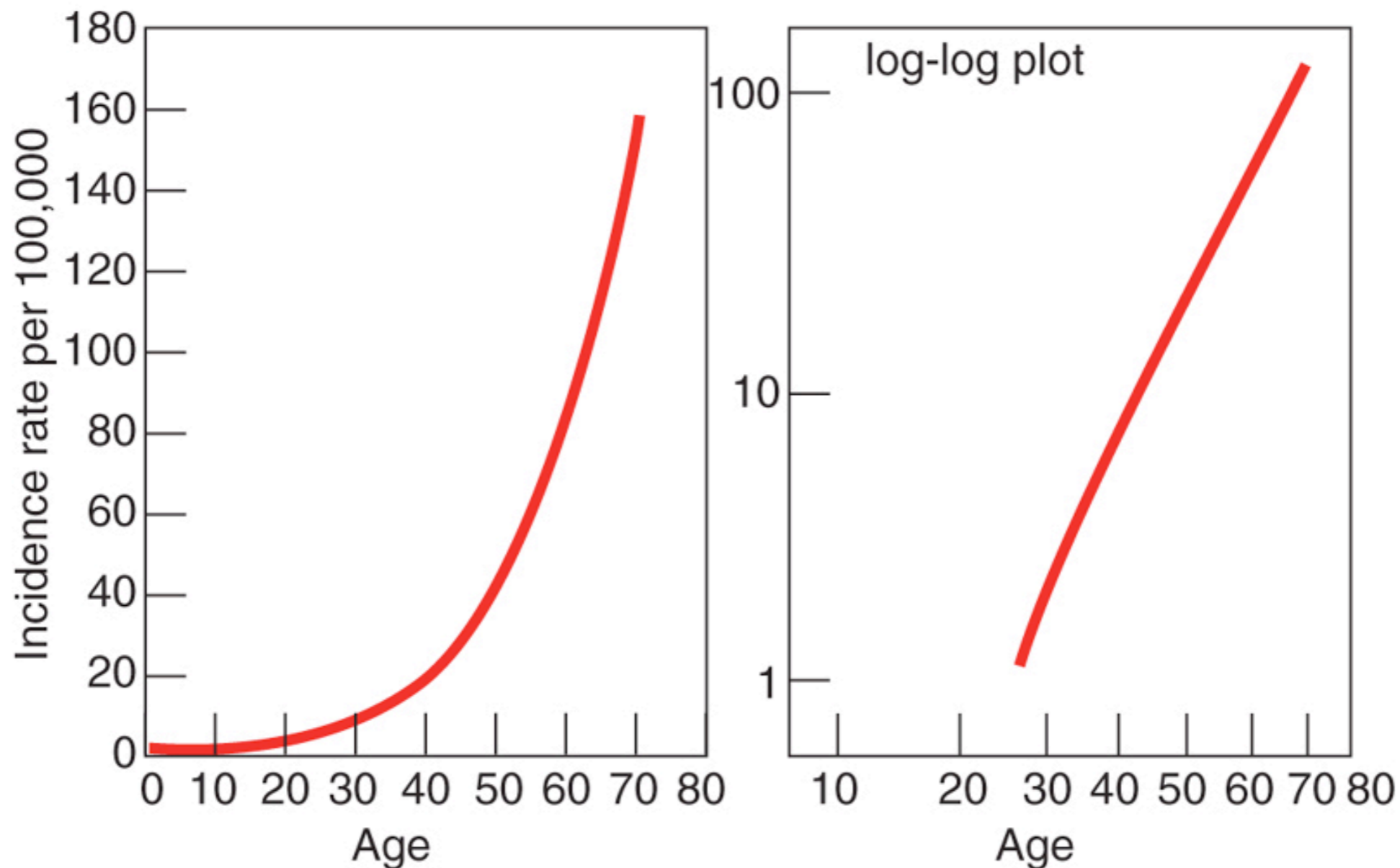
How do cancer-causing mutations arise?



exposure to mutagens stimulates the development of cancer-causing mutations

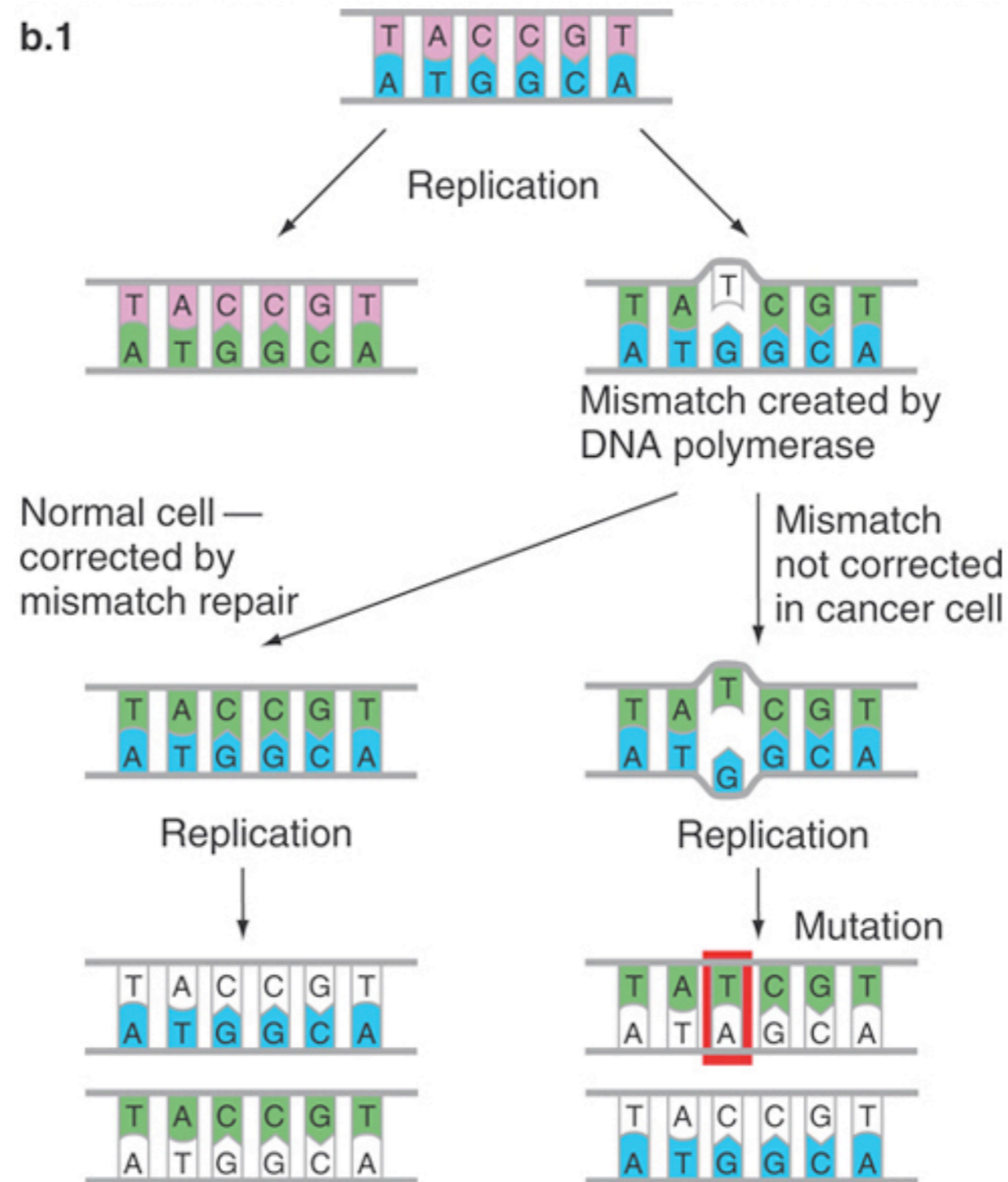
How do cancer-causing mutations arise?

It takes time for cells to acquire the multiple mutations that result in malignancy



The incidence of human cancer rises sharply with age

Tumor Suppressors are genes whose NORMAL function protects a cell from genomic instability



For example: DNA replication, DNA repair, chromosome segregation, cell cycle checkpoint, and apoptosis-promoting genes.

Tumor Suppressors are genes whose NORMAL function protects a cell from genomic instability

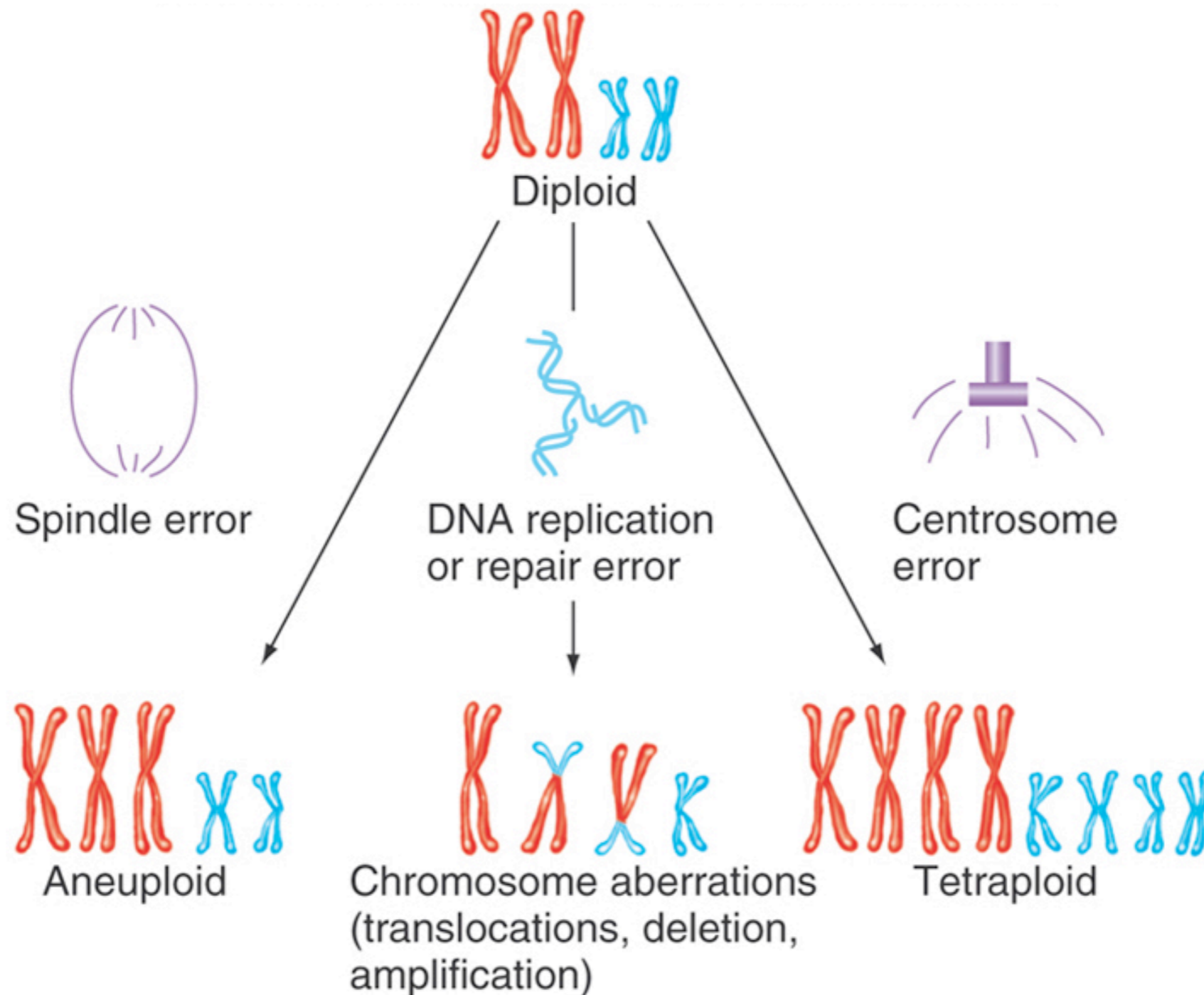
TABLE 19.5 Mutant Alleles of These Tumor-Suppressor Genes Decrease the Accuracy of Cell Reproduction*

Gene	Normal Function of Gene (if known), or Disease Syndrome Resulting from Mutation	Function of Normal Protein Product
<i>p53</i>	Controls G ₁ -to-S checkpoint	Transcription factor
<i>RB</i>	Controls G ₁ -to-S transition	Inhibits a transcription factor
<i>ATM</i>	Controls G ₁ -to-S phase, and G ₂ -to-M checkpoint	DNA-dependent protein kinase
<i>BS</i>	Recombinational repair of DNA damage	DNA/RNA ligase
<i>XP</i>	Excision of DNA damage	Several enzymes
<i>hMSH2, hmLH1</i>	Correction of base-pair matches	Several enzymes
<i>FA</i>	Fanconi anemia	Unknown
<i>BRCA1</i>	Repair of DNA breaks	Unknown
<i>BRCA2</i>	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.

For example: DNA replication, DNA repair, chromosome segregation, cell cycle checkpoint, and apoptosis-promoting genes.

Tumor Suppressors are genes whose NORMAL function protects a cell from genomic instability

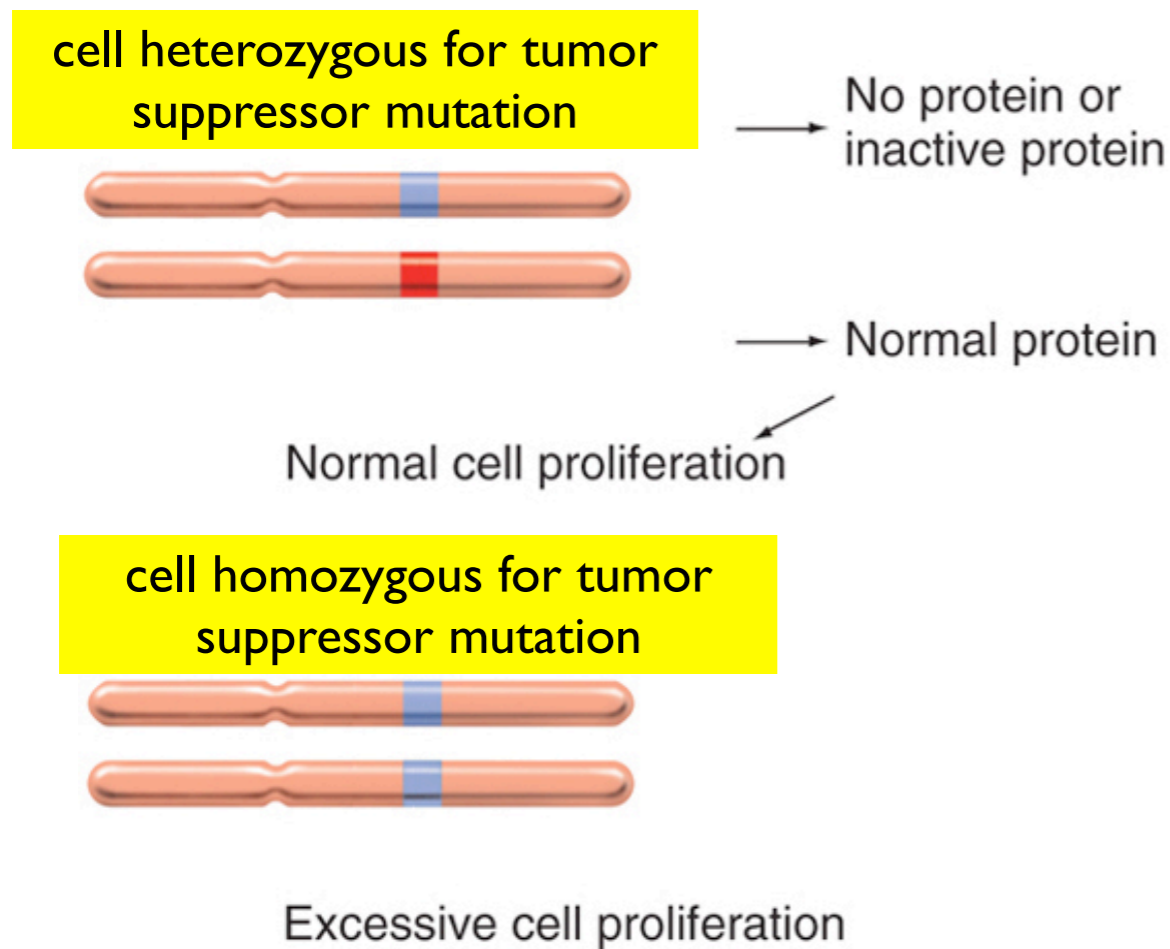


For example: DNA replication, DNA repair, chromosome segregation, cell cycle checkpoint, and apoptosis-promoting genes.

Tumor Suppressors are genes whose NORMAL function protects a cell from genomic instability

Because mutations in tumor suppressors usually act recessively to promote cancer, both copies of the gene must be mutated.

How does this happen?



Usually, a mutation in one of the two copies is followed by *loss-of-heterozygosity (LOH)*. The “good” copy gets lost due to...

- ☞ a spontaneous mutation,
- ☞ a chromosome segregation error,
- ☞ mitotic recombination,
- ☞ or some other rare event.

Tumor Suppressors are genes whose **NORMAL** function protects a cell from genomic instability

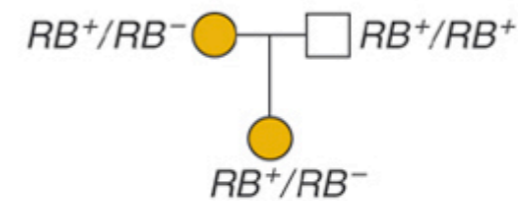
Most *inherited* cancers are due to mutations in tumor suppressor genes.

Inherited mutations in tumor suppressor genes can cause a dominant predisposition to cancer, even though they behave recessively on a cell-by-cell basis. This is an important concept!

Retinoblastoma is inherited as a dominant trait, even though both alleles must be mutated for the tumor to develop

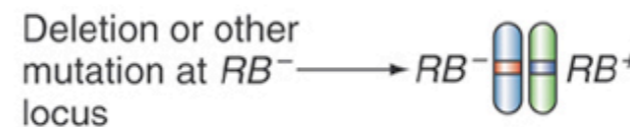


Retinoblastoma pedigree



(b)

Chromosome 13 in the normal cells of a person with predisposition to retinoblastoma



Nondisjunction (loss)



Nondisjunction and replication



Mitotic recombination



Gene conversion



Deletion



Point mutation



A heterozygote for a mutation in the *RB* gene (RB^+/RB^-) is 36,000 times more likely to develop the disease than a RB^+/RB^+ individual

“Cancer Free at 33, but Weighing a Mastectomy”

The New York Times, Sunday, Sep. 16, 2007



Deborah Lindner, 33, did intensive research as she considered having a preventive mastectomy after a DNA test.

Heterozygous mutations in the *BRCA1* or *BRCA2* tumor suppressor genes lead to a 36-85% chance of developing breast cancer (compared to 12.7% for all women)

ONCOGENES are *normal* genes (protooncogenes) in which a gain-of-function mutation leads to to unregulated cell proliferation

Many oncogenes encode components of signal transduction systems

TABLE 19.4 Oncogenes Are Members of Signal Transduction Systems*

Name of Oncogene	Tumor Associations	Mechanism of Activation	Properties of Gene Product
<i>hst</i>	Stomach carcinoma	Rearrangement	Growth factor
<i>erb-B</i>	Mammary carcinoma, glioblastoma	Amplification	Growth factor receptor
<i>trk</i>	Papillary thyroid carcinomas	Rearrangement	Growth factor receptor
<i>Ha-ras</i>	Bladder carcinoma	Point mutation	GDP/GTP binding signaling protein
<i>raf</i>	Stomach carcinoma	Rearrangement	Cytoplasmic serine/threonine kinase
<i>myc</i>	Lymphomas, carcinomas	Amplification, chromosomal translocation	Nuclear transcription factor

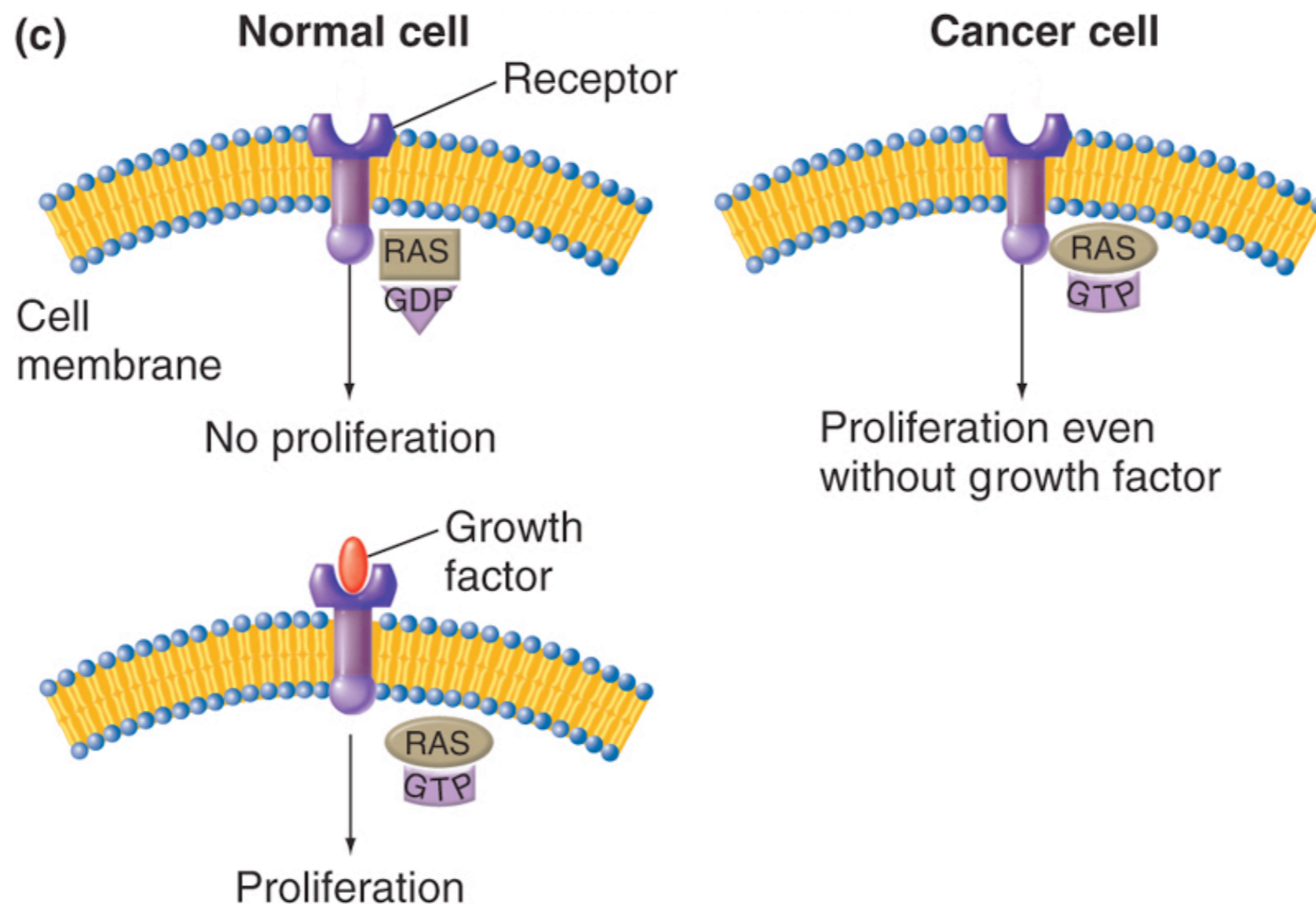
*The roles of several oncogene products that are members of the signal transduction pathway and the ways in which they get activated in human cells are shown.

We've talked about how gain-of-function mutations can make one protein no longer dependent on another, or can simply hyperactivate a particular function.

ONCOGENES are *normal* genes (protooncogenes) in which a gain-of-function mutation leads to to unregulated cell proliferation

Many oncogenes encode components of signal transduction systems

We've talked about how gain-of-function mutations can make one protein no longer dependent on another for its function, or can simply upregulate a particular function.



ONCOGENES are *normal* genes (protooncogenes) in which a gain-of-function mutation leads to to unregulated cell proliferation

Oncogenes can arise in several ways:

- A protooncogene (the normal version of the gene) can mutate, usually by translocation, amplification, or other rearrangement

- A virus can carry an oncogene into a cell

Viruses often harness oncogenes as a way to promote the proliferation of the cells they infect

The replication mechanism of retroviruses makes them particularly prone to pick up genetic material from their host during an infection cycle

- A viral infection can insert a strong promoter next to a cellular gene

A combination of unregulated growth and genome instability creates enormous potential for new mutations to arise

...in other words, oncogenes *enhance* tumor suppressor mutations, and vice versa.

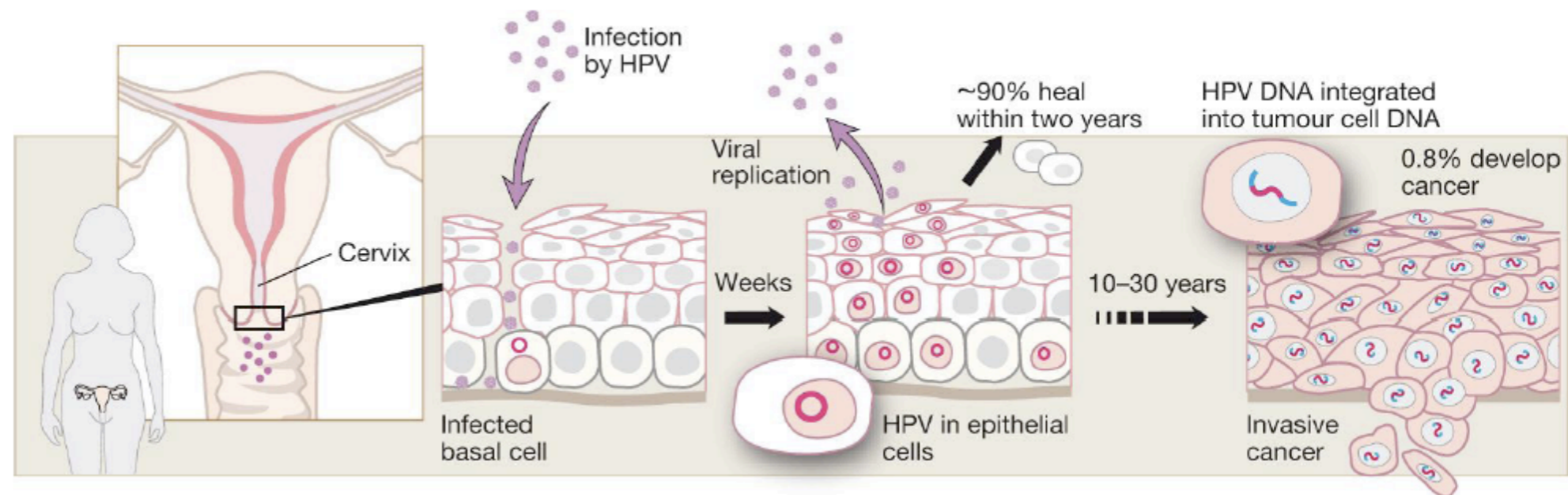
Some cancers are caused by viruses that carry oncogenes

Cervical cancer is caused by HPV (human papilloma virus)

Because HPV is a DNA virus, not a retrovirus, it took a while to convince people that this was true



Harald zur Hausen
won 1/2 of the 2008 Nobel Prize
in Physiology or Medicine



The HPV genes E6 and E7 are oncogenes.
They inactivate p53 and Rb, respectively, in infected cells.