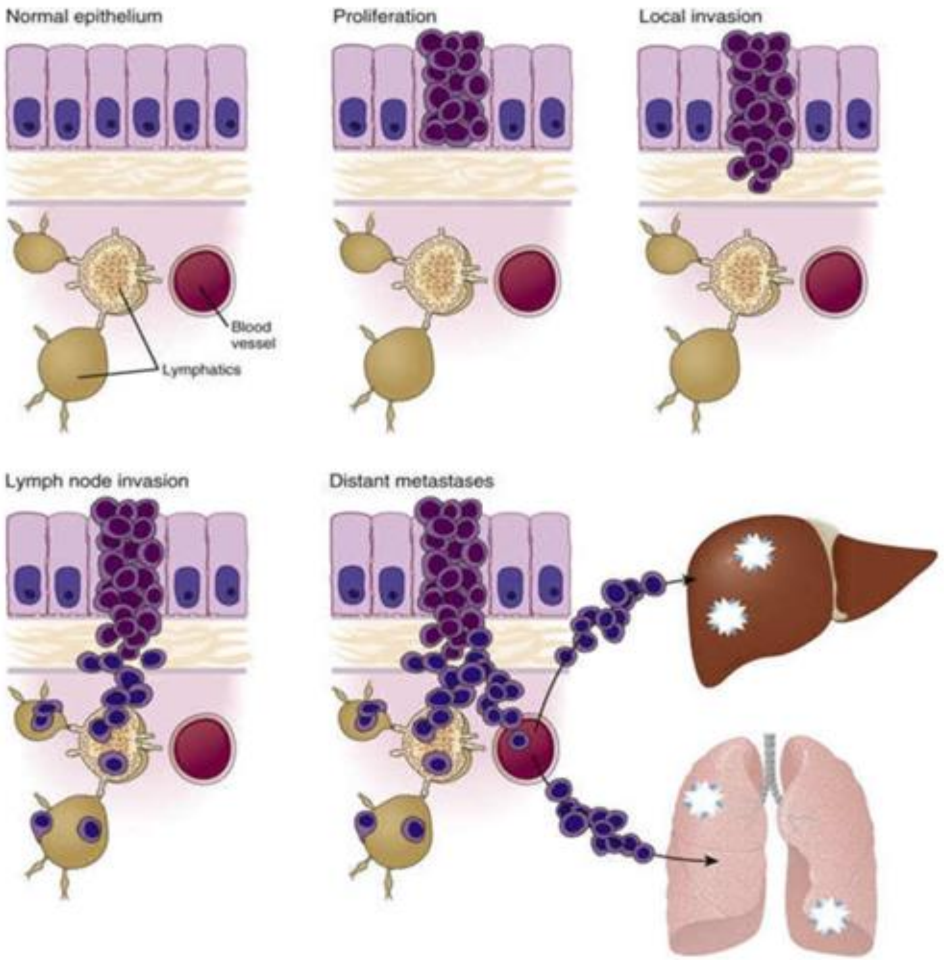
cancer is fundamentally a genetic disease

Dr. Bilal Azab

- **Neoplasia**: is a disease process characterized by uncontrolled cellular proliferation and growth leading to a mass or tumor (neoplasm).
- **Cancer** is the name used to describe the ***more virulent*** forms of neoplasia
- accumulation of cells in a neoplasm occurs because of an imbalance between the normal expression of genes involved in the processes of cellular proliferation and cellular attrition , which regulate the cell cycle and cell division.
- For a neoplasm to be a cancer, however, it must also be **malignant**, which means that not only is its growth uncontrolled, it is also capable of invading neighboring tissues that surround the original site (the primary site) and can spread (metastasize) to more distant sites

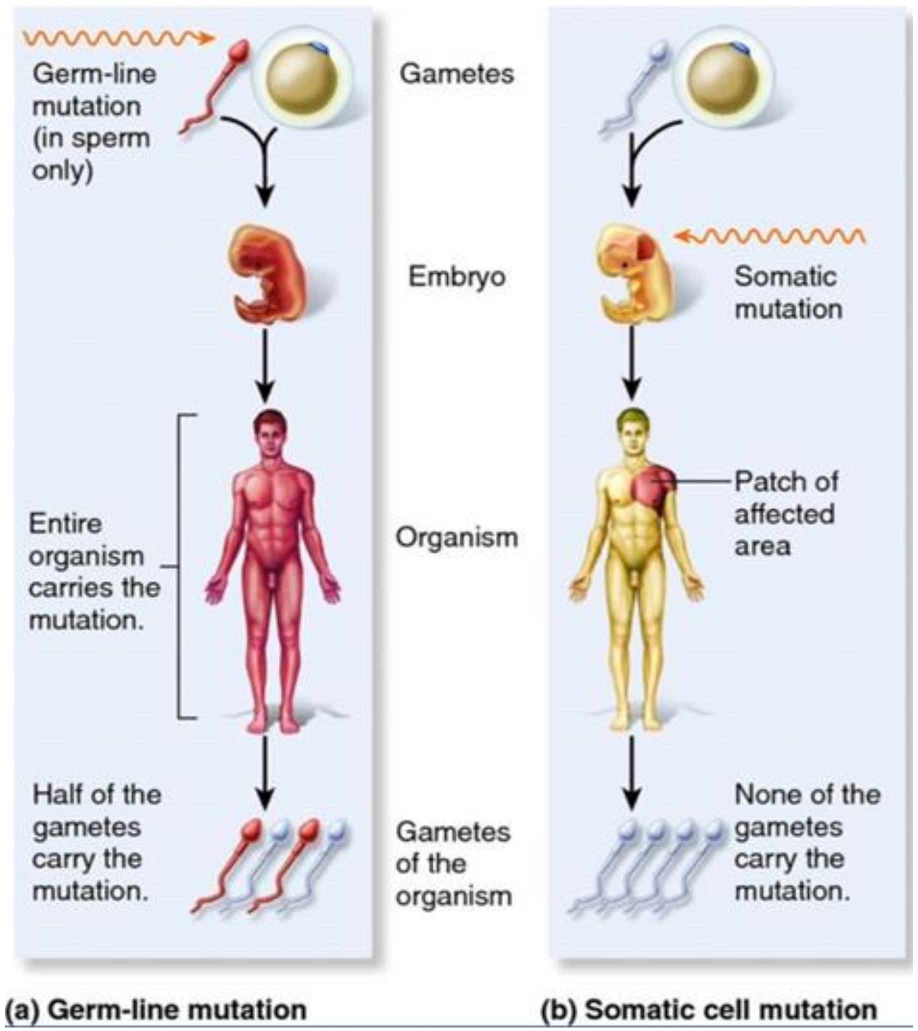
✓ The primary site is where it first starts, while the secondary site is where it spreads or metastasizes. Metastasis could be local near the primary site, or it could become invasive to secondary sites.

- Tumors that do not invade or metastasize are not cancerous but are referred to as **benign** tumors, although their abnormal function, size or location may make them anything but benign to the patient.



General scheme for development of a carcinoma in an epithelial tissue such as colonic epithelium. The diagram shows progression from normal epithelium to local proliferation, invasion across the lamina propria, spread to local lymph nodes, and final distant metastases to liver and lung.

Cells proliferate as they pass through the cell cycle and undergo mitosis. Attrition, due to programmed cell death



- Cancer is not a single disease but rather comes in many forms and degrees of malignancy.

There are three main classes of cancer:

- **Carcinomas**, which originate in epithelial tissue, such as the cells lining the intestine, glands, bronchi, or mammary ducts. Most common

- **Sarcomas**, in which the tumor has arisen in mesenchymal tissue, such as bone, muscle, or connective tissue, or in nervous system tissue

- **Hematopoietic** and **lymphoid** malignant neoplasms, such as leukemia and lymphoma, which spread throughout the bone marrow, lymphatic system, and peripheral blood.

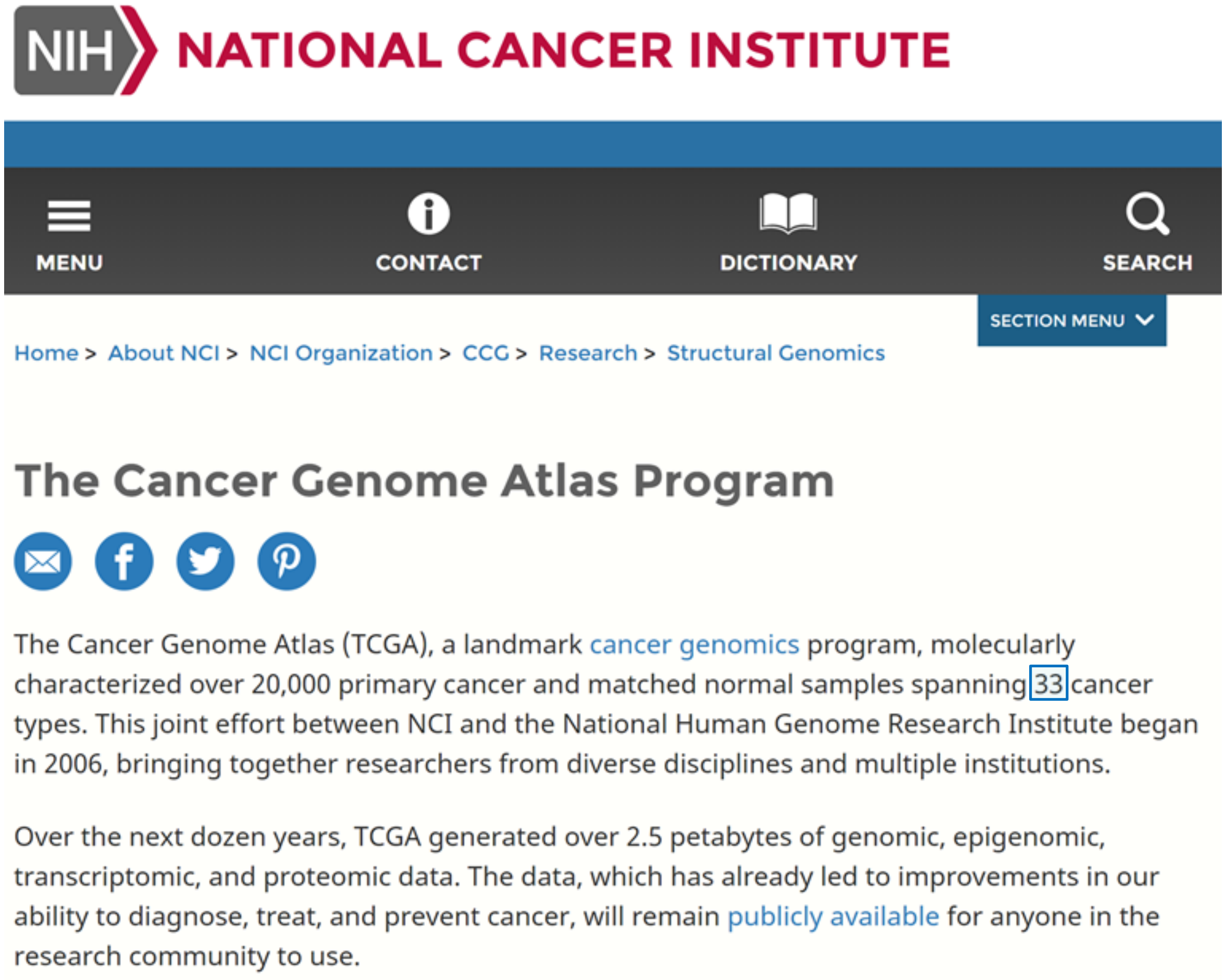
Categories of Cancer

- Carcinoma: Cancer that begins in the skin or in tissues that line or cover internal organs.
- Sarcoma: Cancer that begins in bone, cartilage, fat, muscle, blood vessels, or other connective or supportive tissue.
- Leukemia: Cancer that starts in blood-forming tissue such as the bone marrow & causes large numbers of abnormal blood cells to be produced & enter the blood.
- Lymphoma & myeloma: Cancers that begin in the cells of the immune system.

- Within each of the major groups, tumors are classified by site, tissue type, histological appearance, degree of malignancy, chromosomal aneuploidy, and, increasingly, by which gene mutations and abnormalities in gene expression are found within the tumor.

- Genomics—in particular the identification of mutations, altered epigenomic modifications, and abnormal gene expression in cancer cells—is vastly expanding our knowledge of why cancer develops and is truly changing cancer diagnosis and treatment.

✓ 33 samples were sequenced to identify the genetic alterations present in these tumors. Genetic mutations are increasingly used to guide diagnosis, prognosis, and treatment decisions, as they play an important role in clinical management.



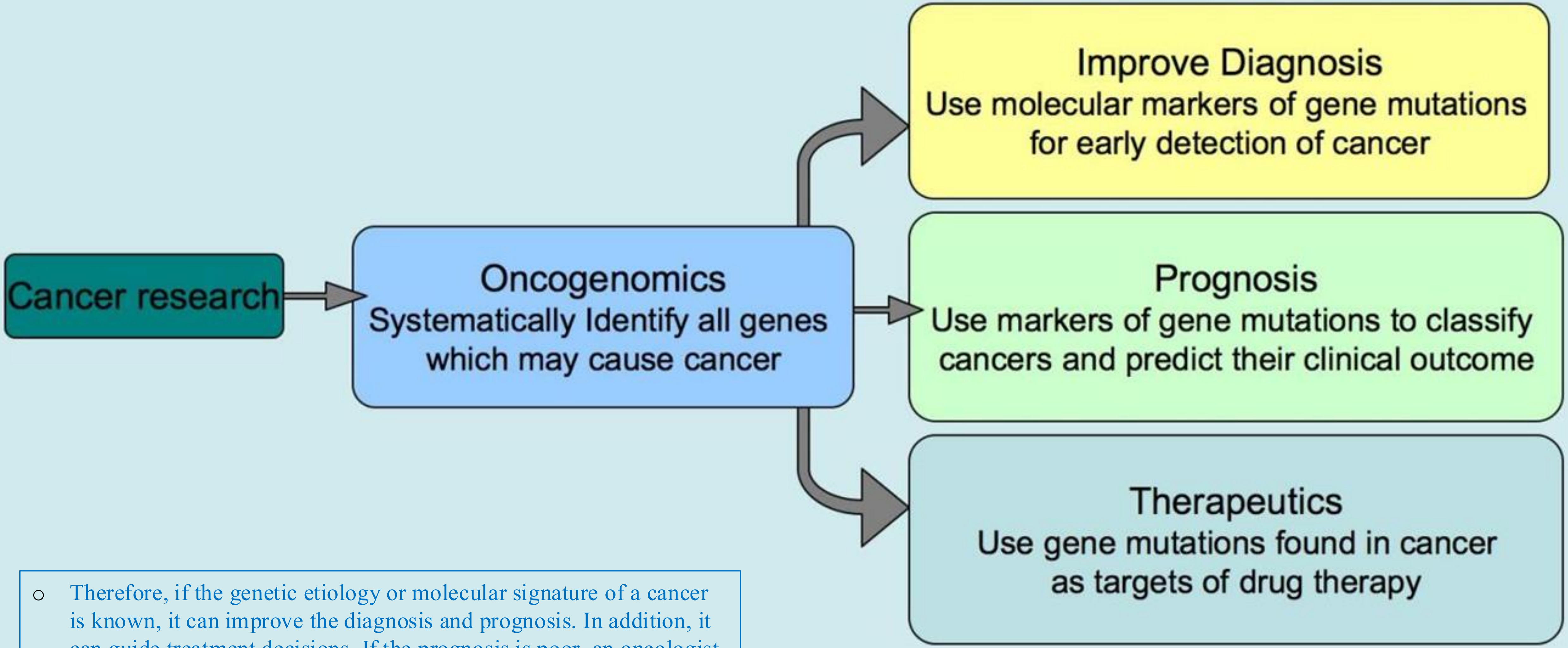
The Cancer Genome Atlas Program

The Cancer Genome Atlas (TCGA), a landmark cancer genomics program, molecularly characterized over 20,000 primary cancer and matched normal samples spanning 33 cancer types. This joint effort between NCI and the National Human Genome Research Institute began in 2006, bringing together researchers from diverse disciplines and multiple institutions.

Over the next dozen years, TCGA generated over 2.5 petabytes of genomic, epigenomic, transcriptomic, and proteomic data. The data, which has already led to improvements in our ability to diagnose, treat, and prevent cancer, will remain publicly available for anyone in the research community to use.

The Cancer Genome Atlas, a public catalog of mutations, epigenomic modifications, and abnormal gene expression profiles found in a wide variety of cancers.

Overall goals of oncogenomics



Cancer research

Oncogenomics
Systematically Identify all genes which may cause cancer

Improve Diagnosis
Use molecular markers of gene mutations for early detection of cancer

Prognosis
Use markers of gene mutations to classify cancers and predict their clinical outcome

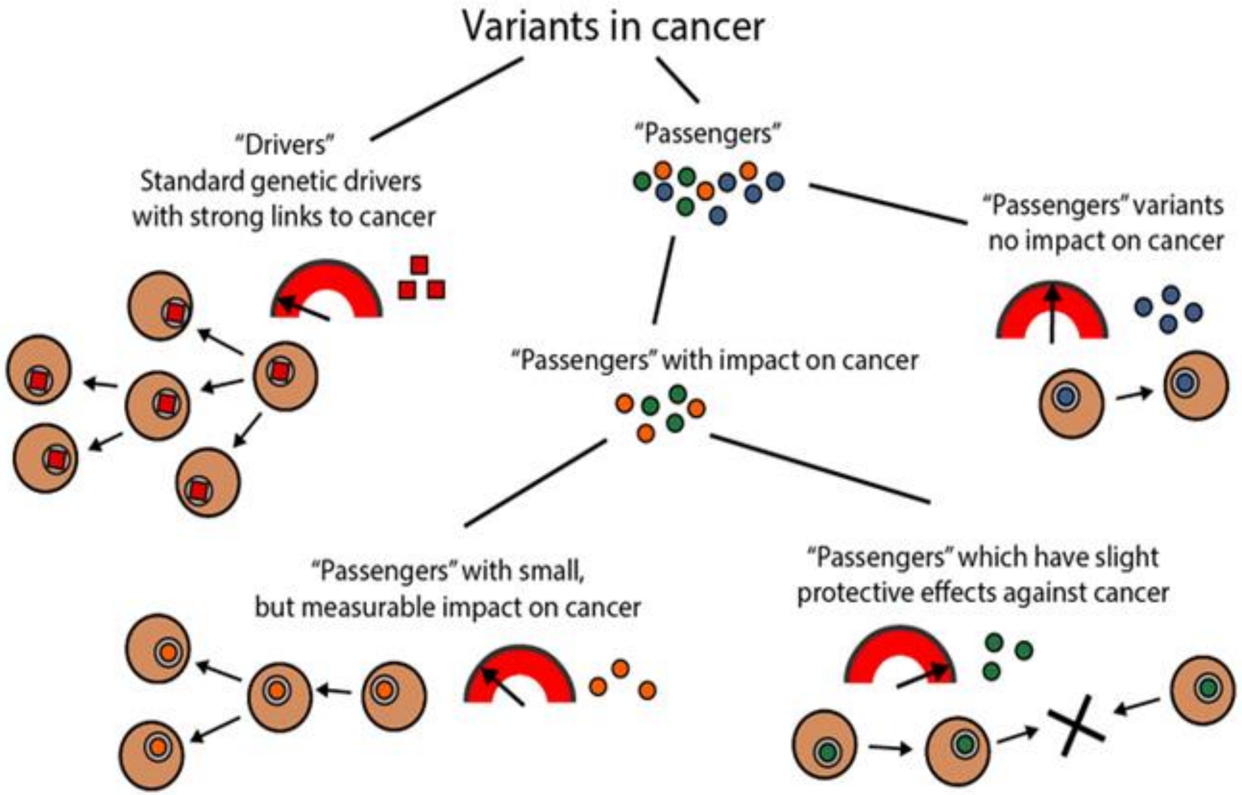
Therapeutics
Use gene mutations found in cancer as targets of drug therapy

- Therefore, if the genetic etiology or molecular signature of a cancer is known, it can improve the diagnosis and prognosis. In addition, it can guide treatment decisions. If the prognosis is poor, an oncologist may consider a more aggressive treatment approach. In some cases, the treatment itself is dictated by the specific mutation present.

Driver and Passenger Gene Variants

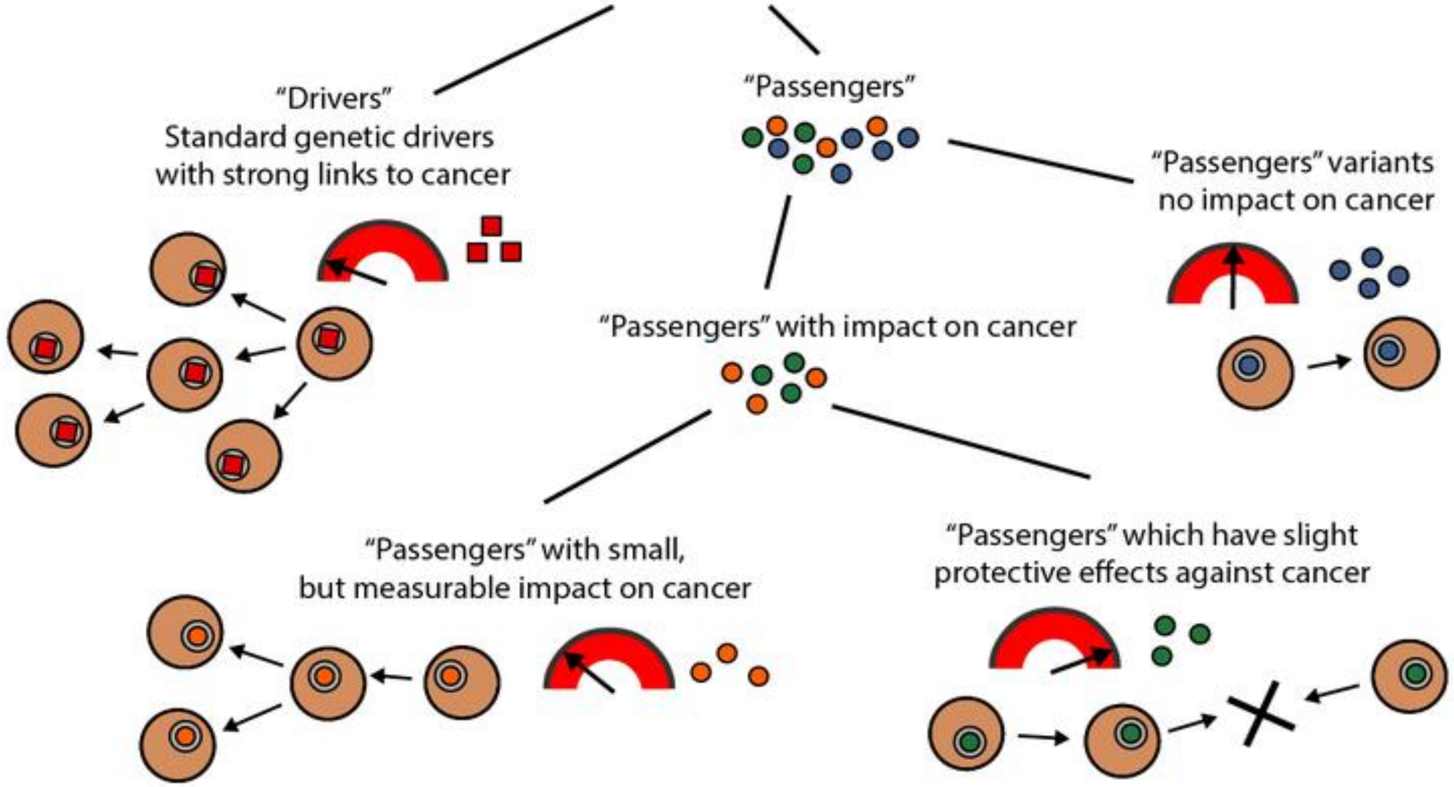
See the next slide

- The number of variants present in a tumor can vary from just a few to <u>many tens of thousands</u>.
- Most mutations found through sequencing of tumor tissue appear to be <u>random</u>, are <u>not recurrent</u> in particular cancer types (for the same tumor in other patients, they don't have those passenger mutations), and probably occurred as the cancer developed, rather than directly causing the neoplasia to develop or progress. Such mutations are referred to as "**passenger**" mutations
- However, a subset of a few hundred genes has been <u>repeatedly found</u> to be mutated at high frequency in many samples of the same type of cancer or even in multiple different types of cancers, mutated in fact far too frequently to simply be passenger mutations.
- These genes are thus presumed to be involved in the development or progression of the cancer itself and are therefore referred to as "**driver**" genes, that is, they harbor mutations (so-called driver gene mutations)



- ✓ Although many driver genes are specific to particular tumor types, some, such as those in the **TP53** gene (tumor suppressor gene) encoding the p53 protein, are found in the vast majority of cancers of many different types.
- ✓ Although the <u>most common driver genes are now known</u>, it is likely that additional, less abundant driver genes will be identified as The Cancer Genome Atlas continues to grow.

Variants in cancer



"Drivers"
Standard genetic drivers
with strong links to cancer

"Passengers"

"Passengers" variants
no impact on cancer

"Passengers" with impact on cancer

"Passengers" with small,
but measurable impact on cancer

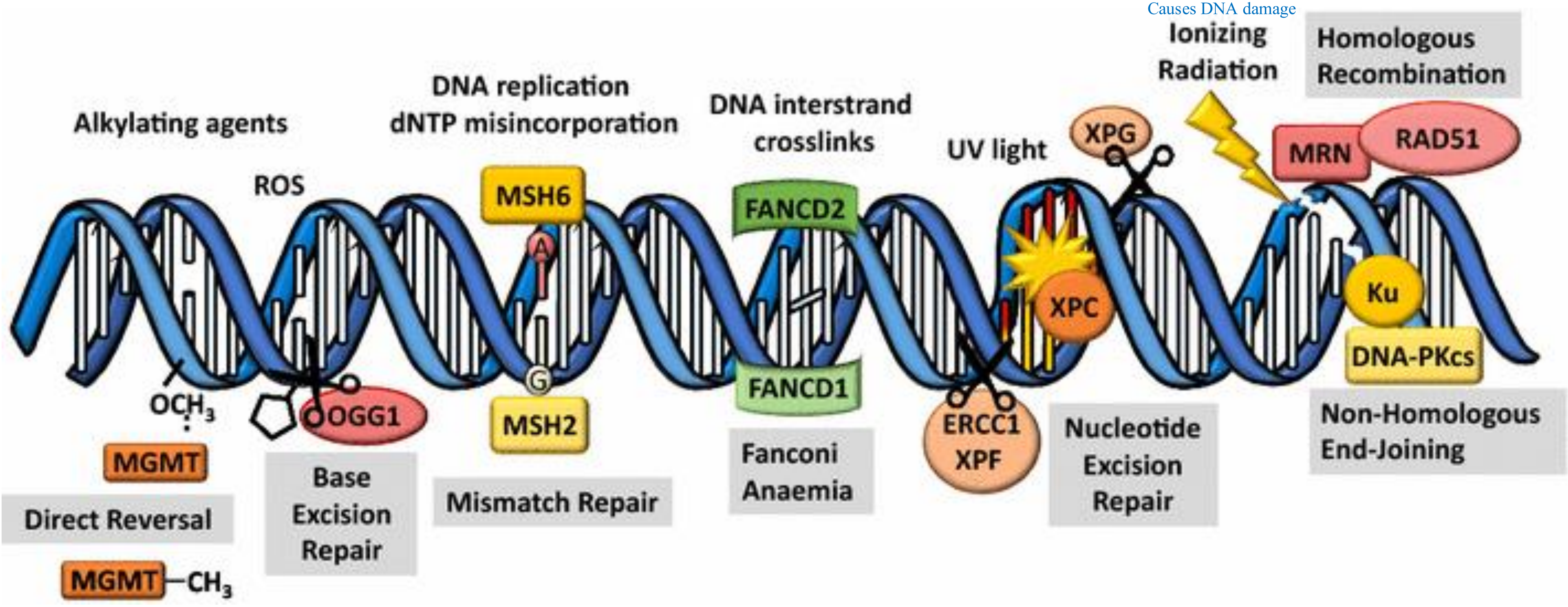
"Passengers" which have slight
protective effects against cancer

- If you compare and sequence the genes in tumor tissue versus normal tissue, you may find hundreds or even thousands of variants or mutations. However, not all of these mutations are clinically relevant or causative of the disease. In cancer biology, variants can be classified as driver or passenger mutations. **Driver mutations** are those that initiate and promote tumor formation. In contrast, **passenger mutations** are not responsible for initiating tumor development; they may have no effect on cancer, or they may have a small but measurable impact, or even an opposing effect that resists tumor progression. However, *tumor initiation is driven by driver mutations, not passenger mutations.*

Spectrum of Driver Gene Mutations

Replication errors (Not corrected), external environmental agents (radiation, UV light) and failure of DNA repair could occur to **dividing and arrested** cells will increase the rate of variants around the genome

Causes DNA damage



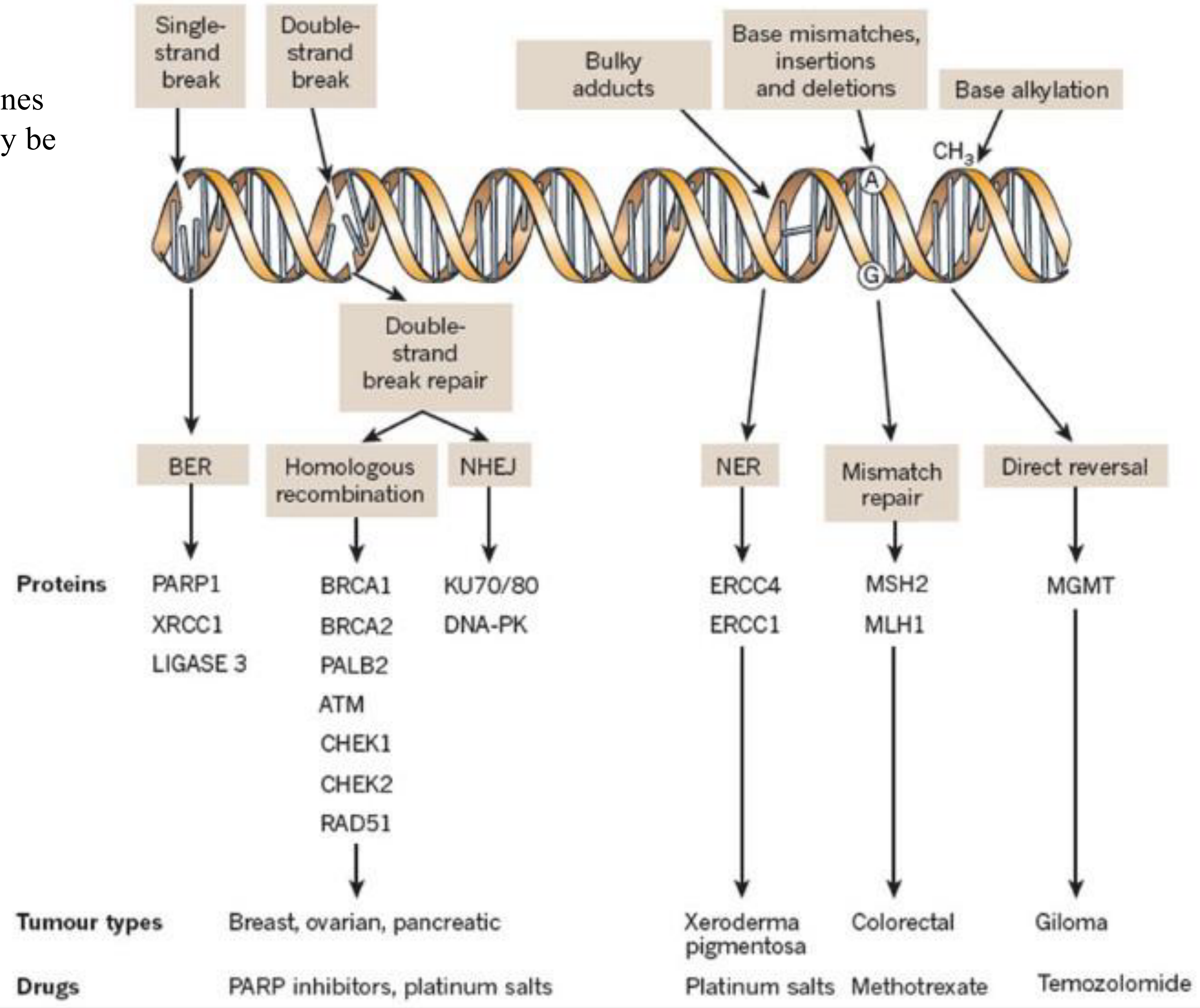
+ Abnormal covalent bonds forming

Spectrum of Driver Gene Mutations

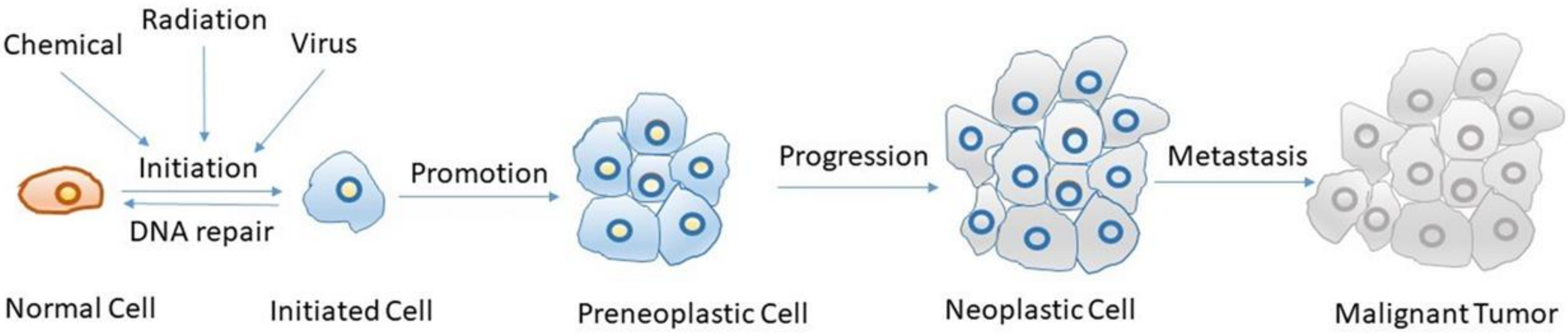
✓ If, by chance, mutations occur in critical driver genes in a particular cell, then the oncogenic process may be initiated.

○ DNA damage can occur as single-strand breaks or double-strand breaks, and there are different repair mechanisms depending on the type of damage, such as base excision repair (BER), homologous recombination, and non-homologous end joining (NHEJ). In general, these repair systems correct DNA damage caused by internal or external factors. However, if these repair mechanisms fail, and the damage occurs in genes involved in the cell cycle, cell division, or DNA repair, the cell may accumulate mutations. This can potentially lead to cellular transformation and the development of cancer.

Note: repair mechanisms are not required.



Multistep Carcinogenesis

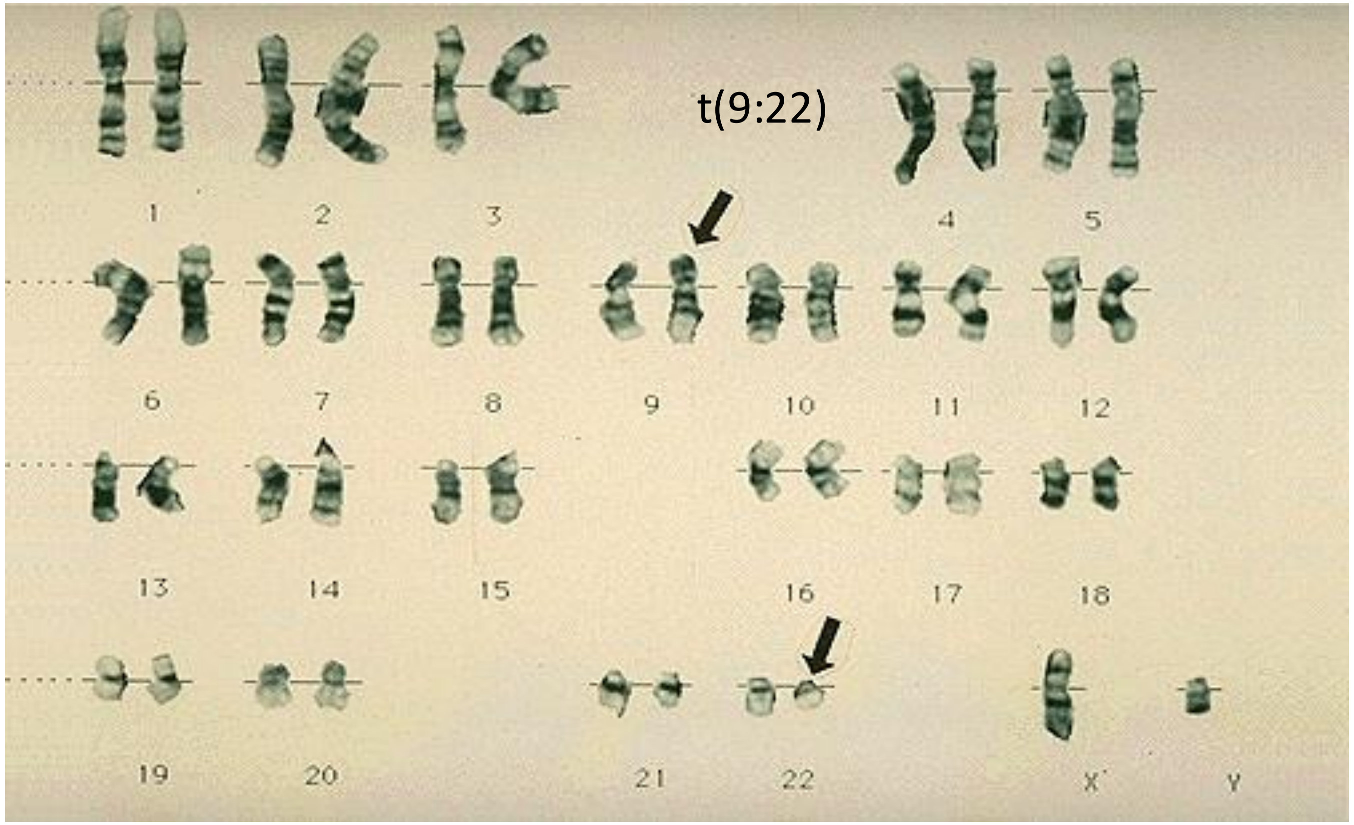


- **Oncogenesis (or carcinogenesis)** is a multistep process. It begins with a ***normal cell*** exposed to an insult such as chemical, radiation, or viral agents. If DNA repair mechanisms successfully correct the damage, the cell returns to a normal state. If repair fails, the process is called initiation, and the cell becomes an ***initiated cell***. However, initiation alone is not sufficient for tumor development. With the accumulation of additional mutations, the initiated cell progresses to a ***preneoplastic*** state. Further genetic alterations then lead to progression into a ***neoplastic cell***. When this neoplastic cell acquires the ability to invade surrounding tissues and metastasize to other organs, it becomes a ***malignant tumor***. Throughout this process, both driver and passenger mutations accumulate, with driver mutations playing the key role in tumor development.

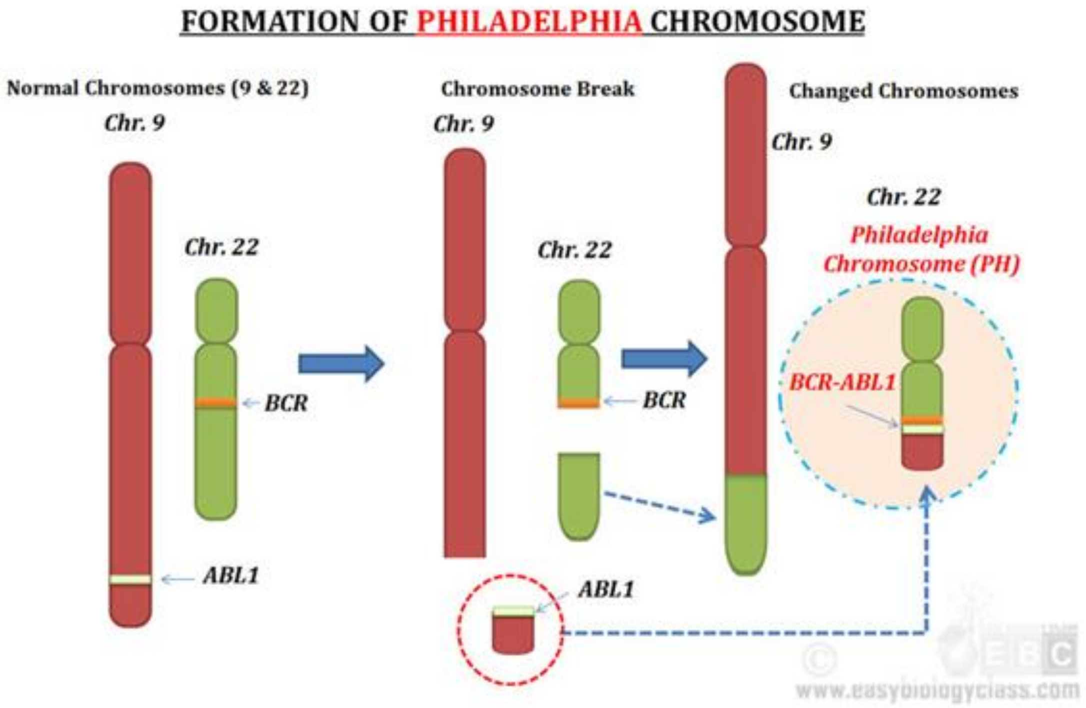
- **Driver mutations could occur on the chromosomal level**

- Chromosome and subchromosomal variants can also serve as driver mutations.

- Particular translocations are sometimes highly specific for certain types of cancer and involve specific genes
  - ✓ e.g., the BCR - ABL translocation in chronic myelogenous leukemia

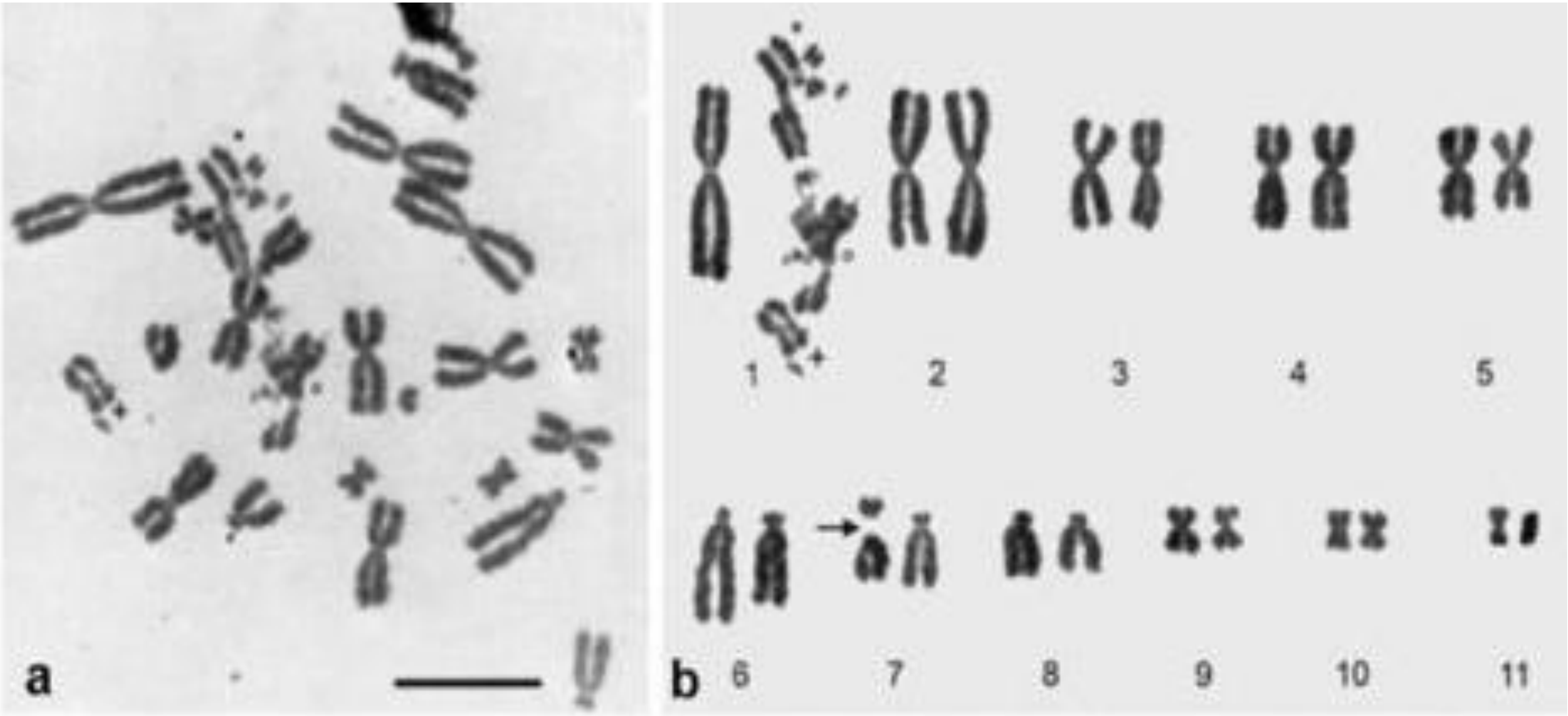


Myeloid cells of CML are also characterized by the Philadelphia chromosome (Ph1) on karyotyping. This is a translocation of a portion of the q arm of chromosome 22 to the q arm of chromosome 9, designated t(9:22).



- The Philadelphia chromosome is a cytogenetic translocation between chromosomes 9 and 22, t(9;22). This results in the fusion of the BCR gene on chromosome 22 with the ABL gene on chromosome 9. In this rearrangement, the ABL gene comes under the control of the BCR promoter, which is stronger than the normal ABL promoter, leading to increased expression of ABL tyrosine kinase. This causes increased kinase activity and higher phosphorylation of target proteins, resulting in accelerated cell cycle and uncontrolled cell proliferation. As a result, the cell divides rapidly, with less time for proper DNA repair, leading to the development of chronic myelogenous leukemia (CML).

Other cancers can show **complex rearrangements** in which chromosomes break into numerous pieces and rejoin randomly, forming novel and complex combinations (a process known as “**chromosome shattering** ”).

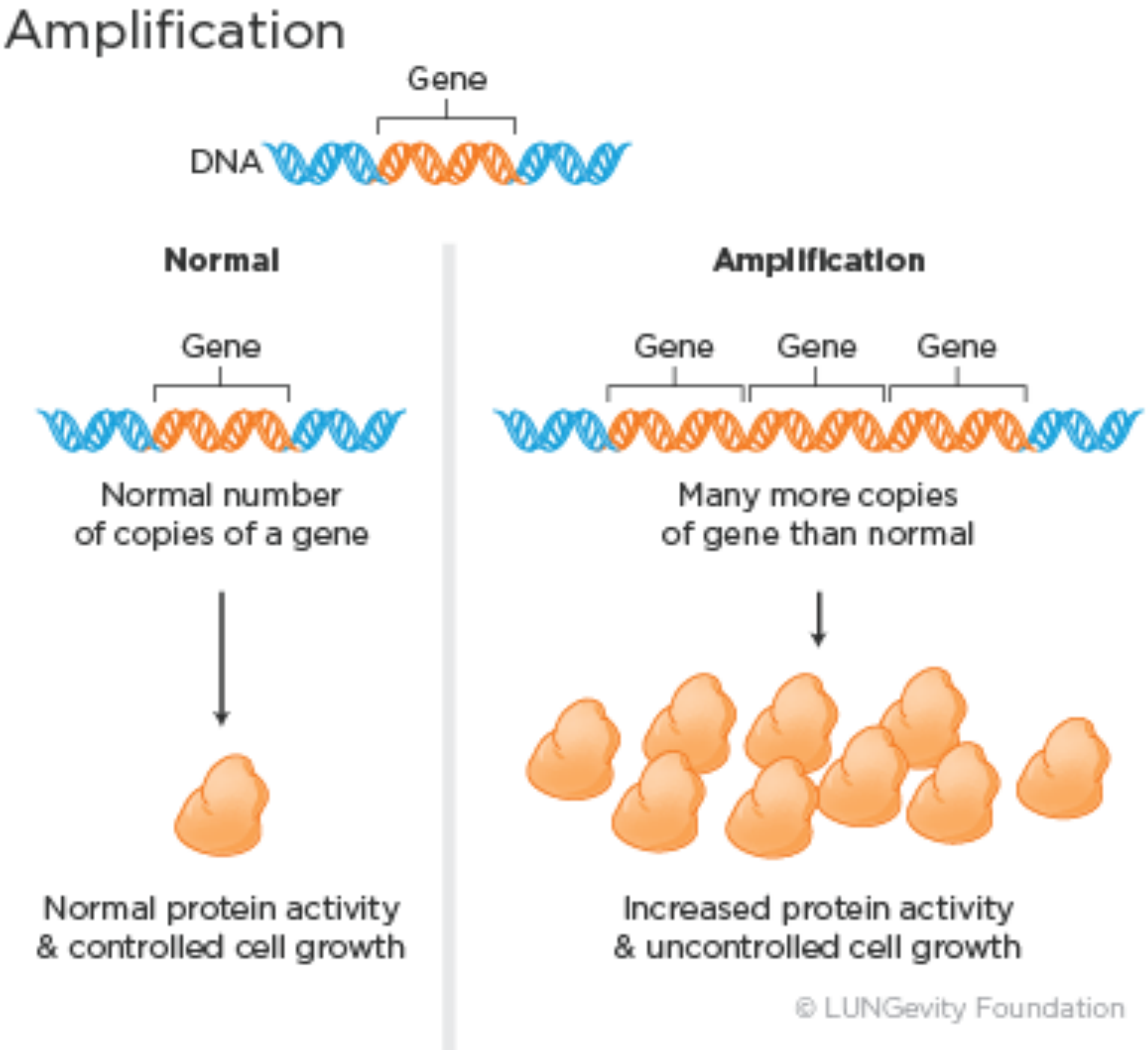


Metaphase spreads with damaged chromosomes obtained after laser **UV microirradiation** of nuclei in living Chinese hamster cells.
Nuclei in living Chinese hamster cells were microirradiated (k = 257 nm) at a single nuclear site comprising about 5% of the total nuclear area. Microirradiated cells were followed to the next mitosis (about 3-15 h) in medium with 1 mM caffeine.
a, b Metaphase spread (a) and the corresponding karyogram (b) from a diploid, fibroblastoid Chinese hamster cell reveal a shattered chromosome 1 and a break in a chromosome 7

large genomic alterations involving many kilobases of DNA can form the basis for **loss of function** or **increased function** of one or more driver genes.

Large genomic alterations include deletions of a segment of a chromosome or multiplication of a chromosomal segment to produce regions with many copies of the same gene (**gene amplification**).

- **Gene amplification** can also contribute to cancer development. One example is the **MYC gene**. In amplification, instead of having a single copy of the gene, there are many copies of the same gene. The gene itself may be normal, but because there are multiple copies, the expression level of the gene becomes much higher. If this gene promotes the cell cycle or cell division, the increased expression can lead to abnormal cell proliferation and potential cellular transformation. Therefore, cancer can result not only from loss of function mutations, but also from increased gene function or overexpression.



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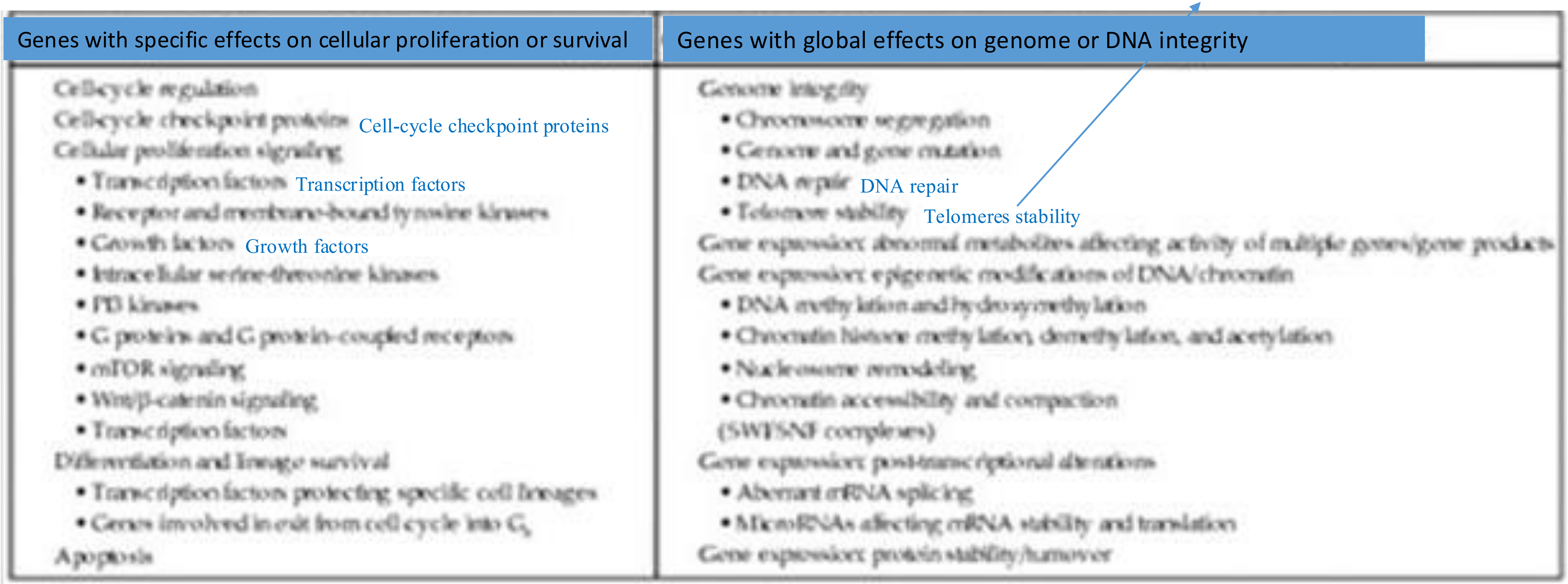
The Cellular Functions of Driver Genes

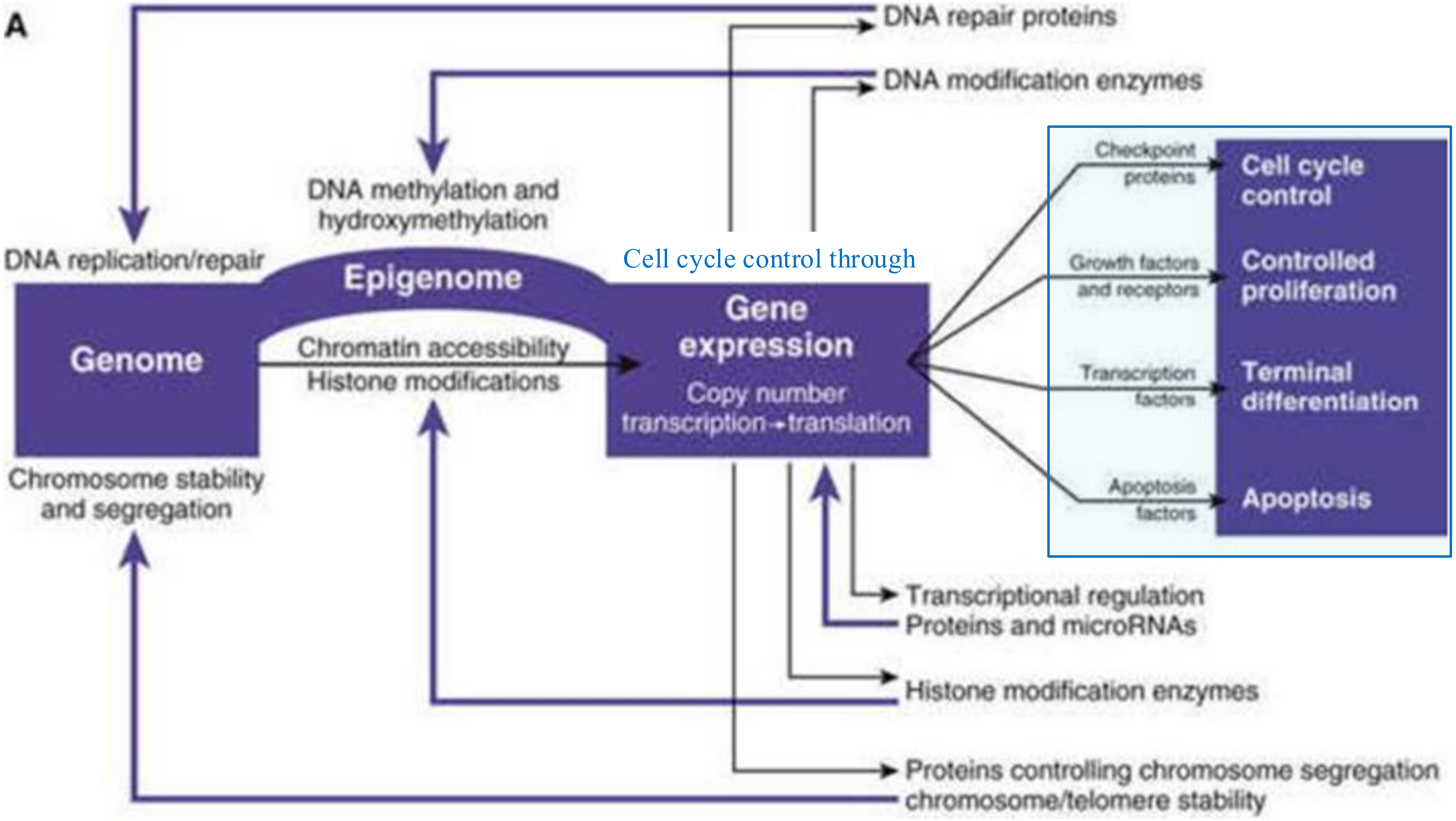
- The nature of some driver gene mutations comes as no surprise: the mutations directly affect specific genes that regulate processes that are readily understood to be important in oncogenesis.
- These processes include cell-cycle regulation, cellular proliferation, differentiation and exit from the cell cycle, growth inhibition by cell-cell contacts, and programmed cell death (apoptosis).

Remember, telomeres erode and shorten with time as people age, and the enzyme telomerase becomes inactive in older cells. However, in cancerous or malignant cells, telomerase remains active, so telomeres do not shorten. That is why cancer cells are considered immortal and can divide indefinitely. If tumor tissue is cultured in a Petri dish with adequate nutrients, the cells can continue living and dividing for a very long time, unlike normal cells, which die after a limited number of divisions.

Classes of driver genes



Genes with specific effects on cellular proliferation or survival	Genes with global effects on genome or DNA integrity
Cell-cycle regulation Cell-cycle checkpoint proteins Cell-cycle checkpoint proteins Cellular proliferation signaling • Transcription factors Transcription factors • Receptor and membrane-bound tyrosine kinases • Growth factors Growth factors • Intracellular serine-threonine kinases • PI3 kinases • G proteins and G protein-coupled receptors • mTOR signaling • Wnt/β-catenin signaling • Transcription factors Differentiation and lineage survival • Transcription factors protecting specific cell lineages • Genes involved in exit from cell cycle into G_0 Apoptosis	Genome integrity • Chromosome segregation • Genome and gene mutation • DNA repair DNA repair • Telomere stability Telomeres stability Gene expression: abnormal metabolites affecting activity of multiple genes/gene products Gene expression: epigenetic modifications of DNA/chromatin • DNA methylation and hydroxymethylation • Chromatin histone methylation, demethylation, and acetylation • Nucleosome remodeling • Chromatin accessibility and compaction (SWI/SNF complexes) Gene expression: post-transcriptional alterations • Aberrant mRNA splicing • MicroRNAs affecting mRNA stability and translation Gene expression: protein stability/turnover



Cell cycle control through

Occurs in certain highly differentiated tissues, such as neurons and skeletal muscle cells.

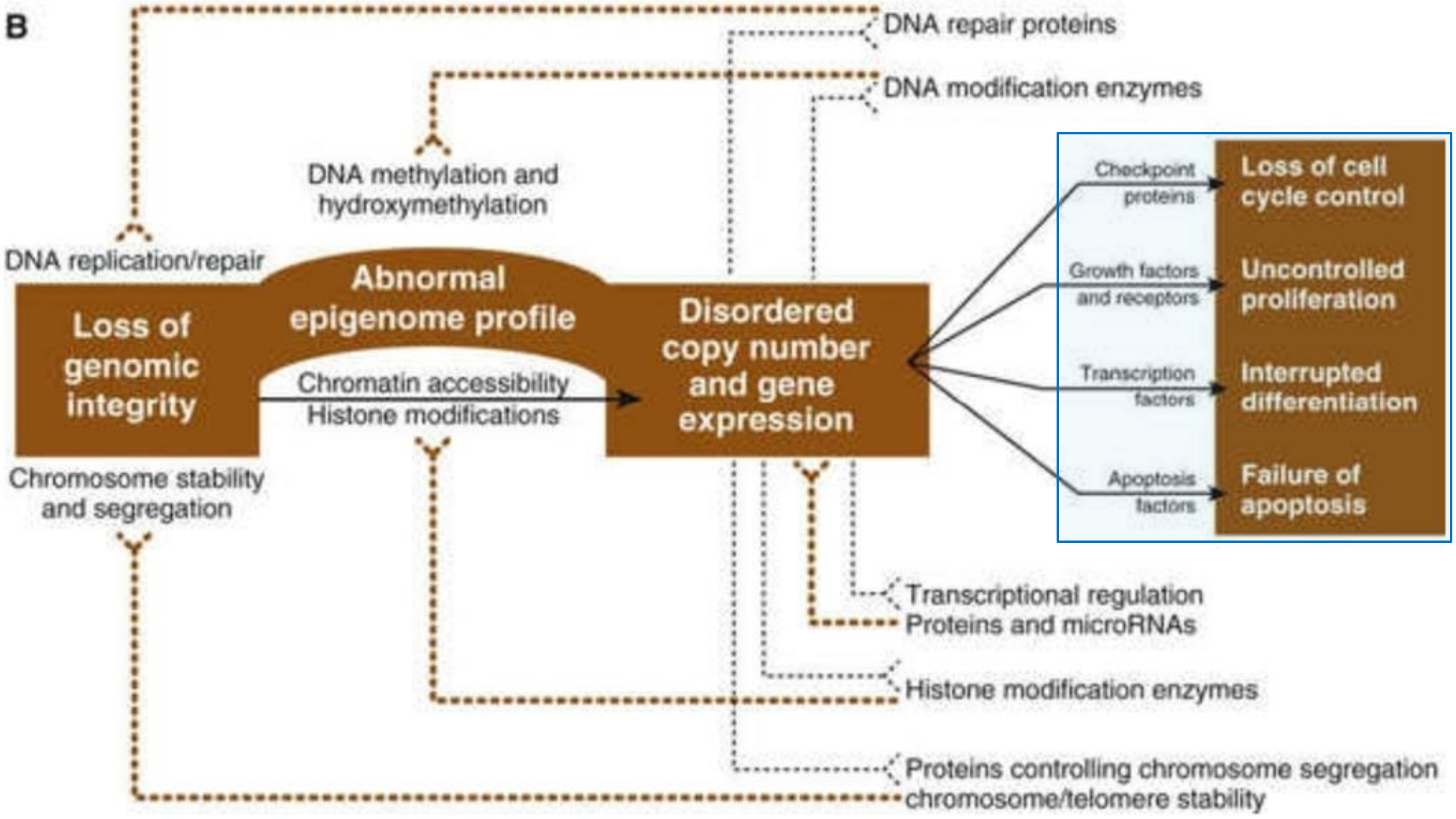
When expressed, they induce programmed cell death.

Overview of normal genetic pathways controlling normal tissue homeostasis.

- ✓ If those groups of genes are mutated, these mechanisms are impacted. See the next slide for the consequences.

The information encoded in the genome (black arrows) results in normal gene expression, as modulated by the epigenomic state.

Many genes provide negative feedback (purple arrows) to ensure normal homeostasis.



It is not the shape of these tissues; this is not how the cells look in normal tissue.

The cell is not dying anymore.

Perturbations in neoplasia.

Abnormalities in gene expression (dotted black arrows) lead to a vicious cycle of positive feedback (brown dotted lines) of progressively more disordered gene expression and genome integrity.

Activated Oncogenes and Tumor Suppressor Genes

Both classes of driver genes—those with specific effects on cellular proliferation or survival and those with global effects on genome or DNA integrity —can be further **subdivided** into one of two functional categories depending on how, if mutated, they drive oncogenesis.

The first category includes **proto-oncogenes**
These are normal genes that, that promotes growth and survival of cells.

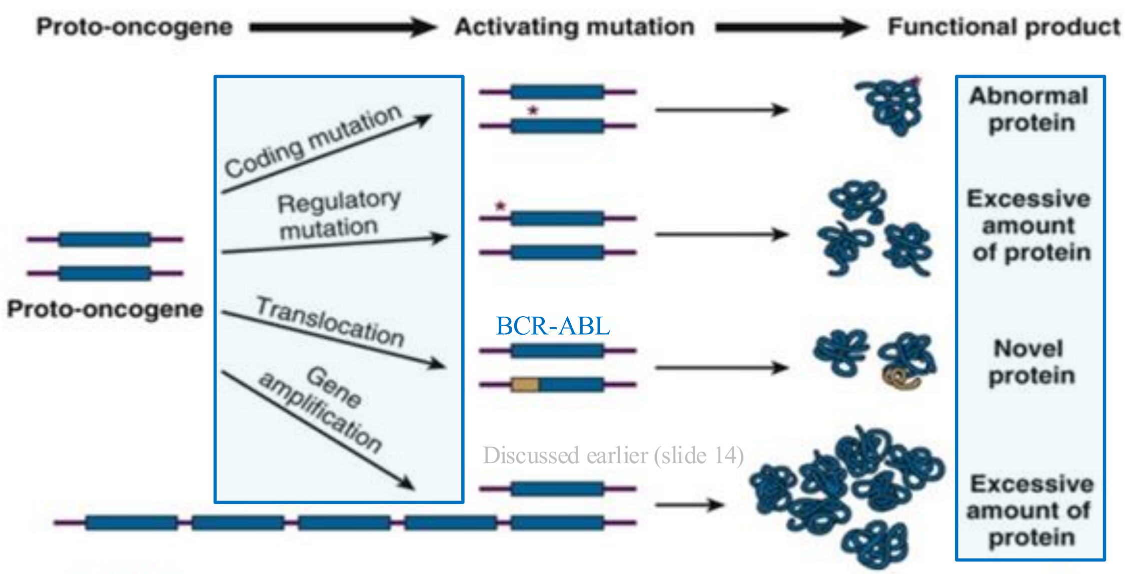
when mutated in very particular ways, become driver genes through alterations, the expression level is interrupted and that leads to ***excessive levels of activity.*** Therefore, the promotion of growth and survival of cells becomes higher.

Once mutated in this way, driver genes of this type are referred to as **activated oncogenes** .

Only a **single mutation at one allele** can be sufficient for activation

The mutations that activate a proto-oncogene can **range** from highly specific point mutations causing dysregulation or hyperactivity of a protein, to chromosome translocations that drive overexpression of a gene, to gene amplification events that create an overabundance of the encoded mRNA and protein product

✓ *Sometimes the protein structure itself is affected and becomes abnormal, while in other cases the protein structure remains normal, but the quantity of the protein is excessively increased.*



BCR-ABL

Discussed earlier (slide 14)

FIGURE 15-3 Different mutational mechanisms leading to proto-oncogene activation. These include a single point mutation leading to an amino acid change that alters protein function, mutations or translocations that increase expression of an oncogene, a chromosome translocation that produces a novel product with oncogenic properties, and gene amplification leading to excessive amounts of the gene product.

- Regarding **translocation**, the gene itself may undergo translocation or inversion, where one coding region becomes attached to another coding region. As a result, when the gene is expressed, it produces a single fusion protein that is novel and abnormal, often with increased activity.
- While discussing **regulatory mutations**, a variant in non-coding regions such as the promoter or UTR may lead to increased gene expression, resulting in an excessive amount of the protein.
- On the other hand, regarding **coding-region mutations**, variants within the coding sequence may alter the amino acid sequence, producing a structurally abnormal protein.

Oncogenes encode proteins such as the following:

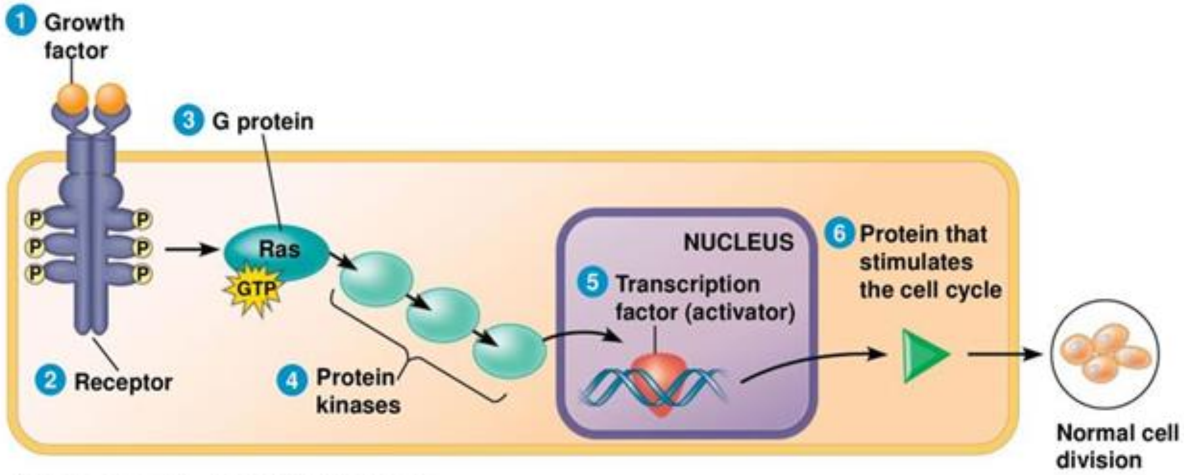
- Proteins in signaling pathways for cell proliferation

- Transcription factors that control the expression of growth-promoting genes

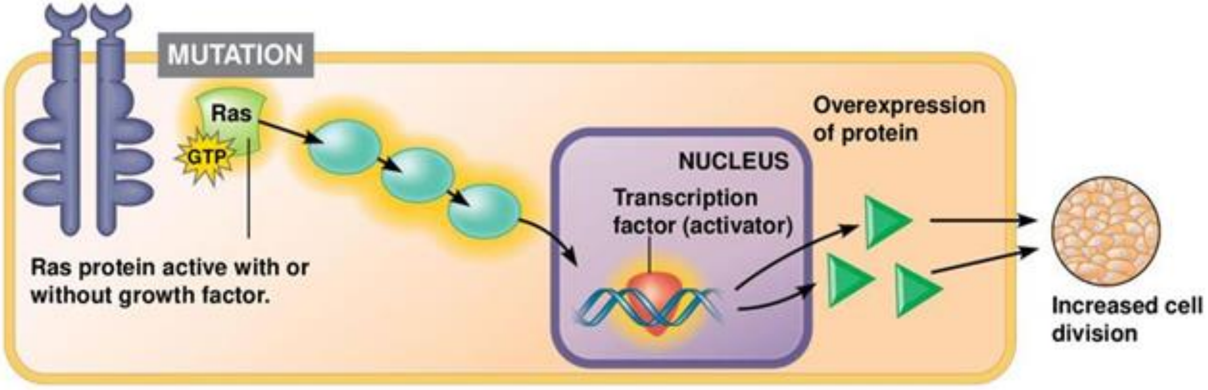
- Inhibitors of programmed cell death machinery

- Let’s take RAS as an example. **RAS** is normally a proto-oncogene. Under normal conditions, a growth factor binds to a receptor on the cell surface, which activates RAS by converting it into its active **GTP-bound form**. Activated RAS then phosphorylates downstream proteins, which in turn activate additional proteins through signaling cascades. Eventually, these signals influence transcription factors and induce the expression of genes involved in **stimulating the cell cycle** and cell division.

- However, when RAS is mutated into an oncogene, it becomes constitutively active, meaning it remains active even in the absence of a growth factor. As a result, it **continuously stimulates** the expression of genes that promote the cell cycle, leading to abnormal cell proliferation and increasing the likelihood of **cellular transformation into cancer**. This is an example of a proto-oncogene being converted into an oncogene with continuous activity.



Normal cell cycle–stimulating pathway.

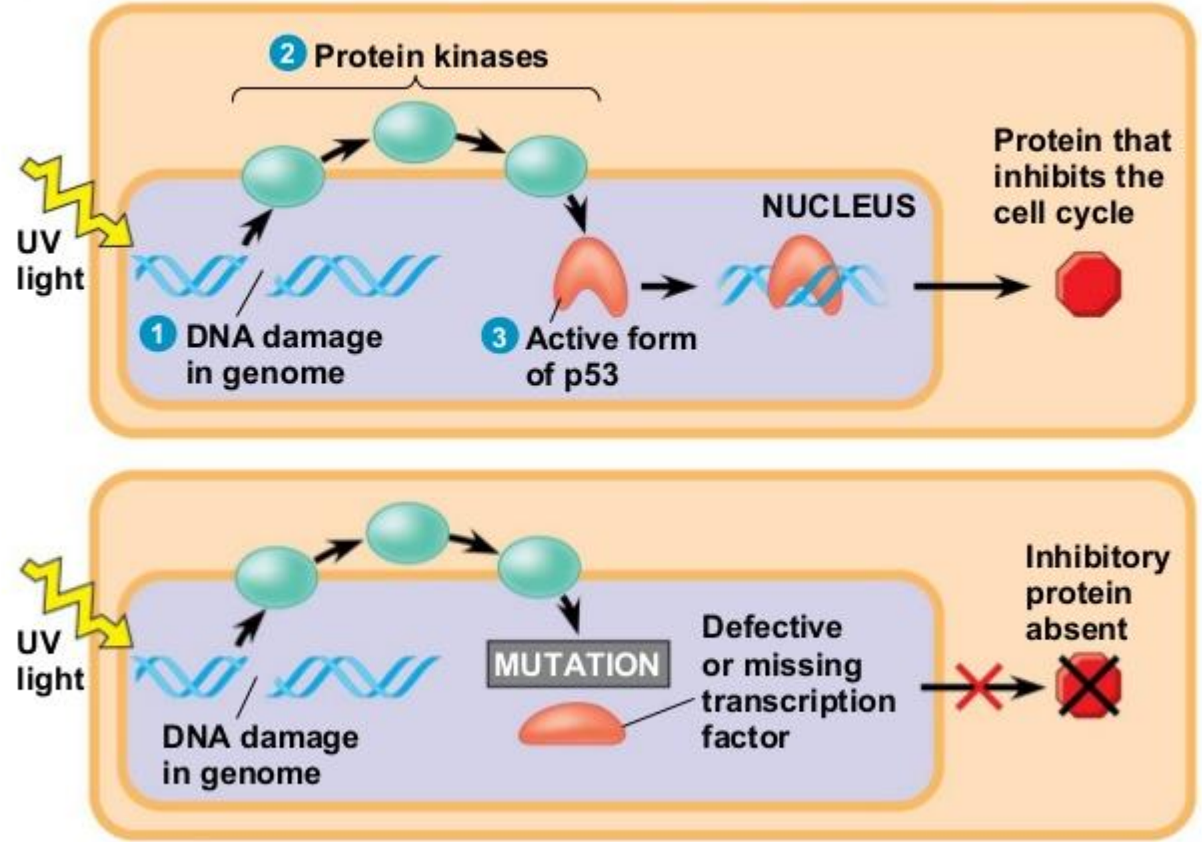


Mutant cell cycle–stimulating pathway.

The second, and more common, category of driver genes includes **tumor suppressor genes** (**TSGs**), variants in which cause a *loss of expression* of proteins necessary to control the development of cancers.

To drive oncogenesis, loss of function of a TSG typically requires mutations at both alleles. In contrast, oncogenes undergo gain of function mutations.

Figure 16.18



See the next slide

Loss-of-function mechanisms can range from missense, nonsense, or frame-shift mutations to gene deletions or loss of a part or even an entire chromosome.

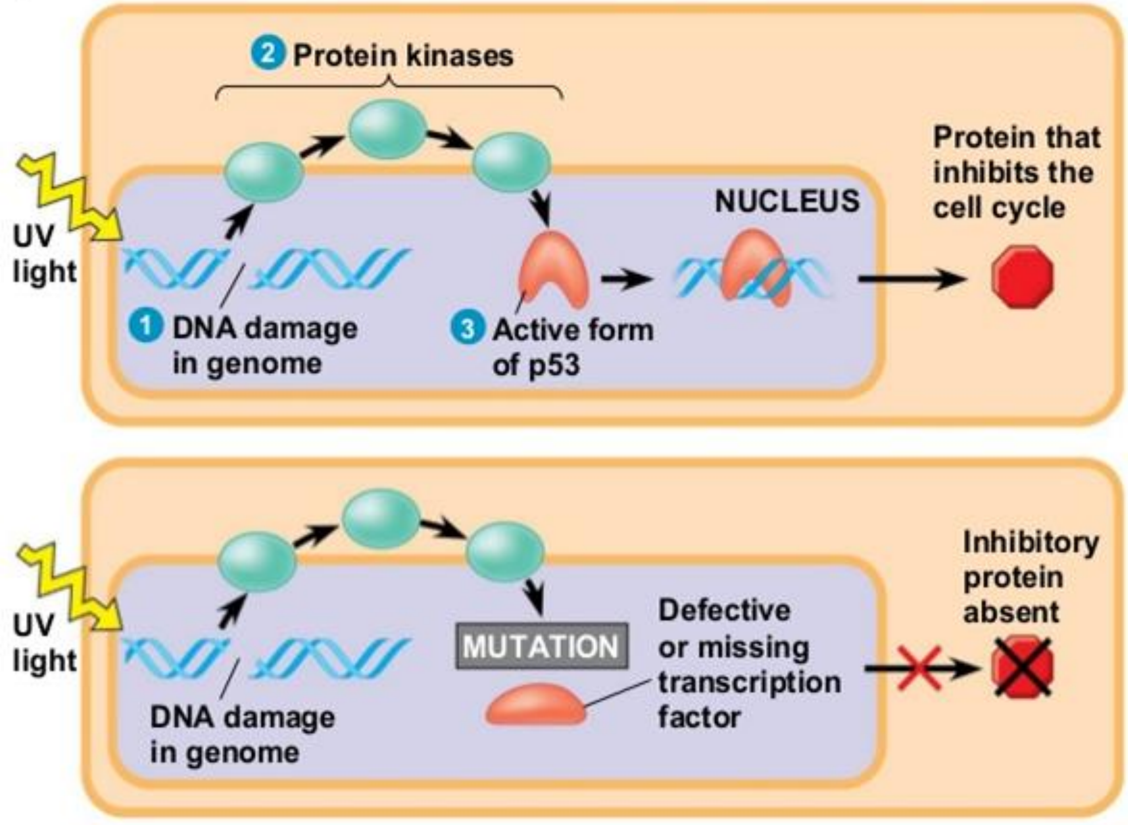
Loss of function of TSGs can also result from epigenomic transcriptional silencing due to:

- altered chromatin conformation
- promoter **methylation**
- translational silencing by miRNAs or disturbances in other components of the translational machinery

TSGs encode proteins involved in many aspects of cellular function, including but not limited to:

- maintenance of correct chromosome number and structure
- DNA repair proteins
- proteins involved in regulating the cell cycle, cellular proliferation, or contact inhibition

Figure 16.18



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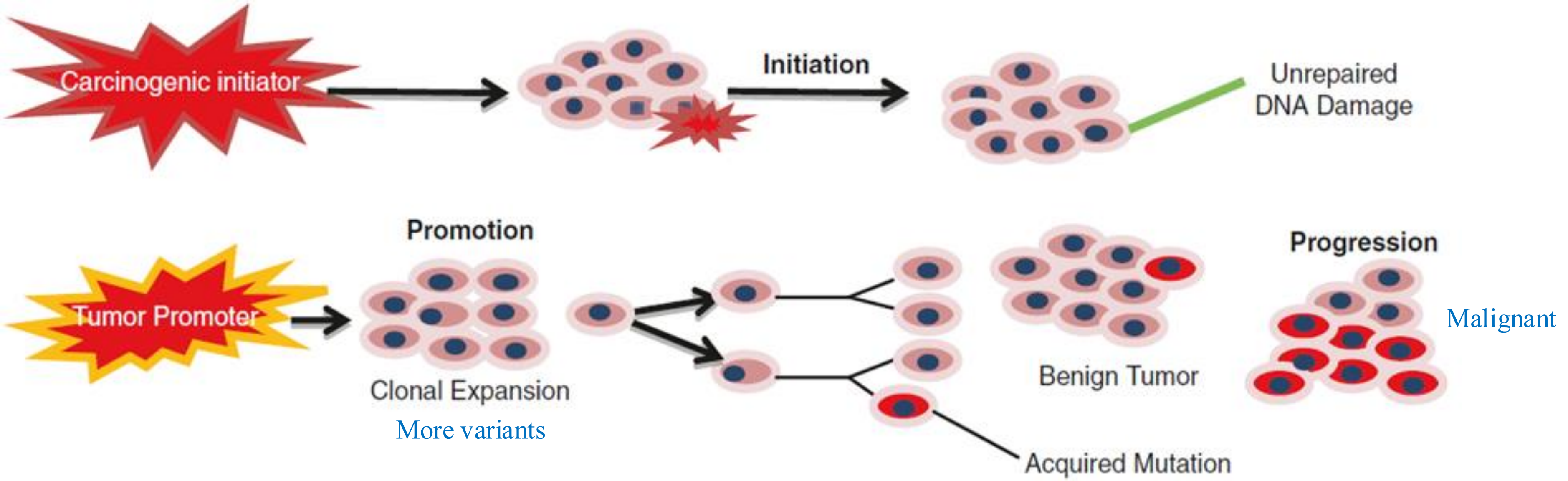
- For example, **TP53** is a tumor suppressor gene. Normally, UV light damages DNA, and this damage is detected by cellular proteins, which then induce the expression of TP53. The p53 protein moves to the nucleus and **inhibits the expression of genes involved in the cell cycle**, thereby preventing cell division until DNA repair is completed.

- **When TP53 is mutated**, a non-functional protein is produced due to a loss of function mutation. In this case, even though DNA damage is detected and TP53 is expressed, the protein **cannot inhibit the cell cycle**. As a result, the cell continues to divide without repairing the damage, leading to *accumulation of mutations*.

Cellular Heterogeneity within Individual Tumors

- The accumulation of driver gene mutations does not occur synchronously (all at once), in lockstep, in every cell of a tumor.
- To the contrary, cancer evolves along multiple lineages within a tumor
- Multiple cellular lineages are required to accumulate mutations in oncogenes or tumor suppressor genes. A single mutation alone is not sufficient for malignant transformation. The cell may divide and acquire additional mutations over time, including multiple driver mutations. Only after sufficient accumulation of these genetic alterations can a daughter cell become malignant.
- mutational and epigenetic events in different cells activate proto-oncogenes and cripple the machinery for maintaining genome integrity, leading to more genetic changes in a vicious cycle of more mutations and worsening growth control.
- The lineages that experience an enhancement of growth, survival, invasion, and distant spread will come to predominate as the cancer evolves and progresses

This is why tumor cell populations are ***heterogeneous****, as some cells have acquired mutations that other cells have not yet developed.*



A paradigm for the development of cancer

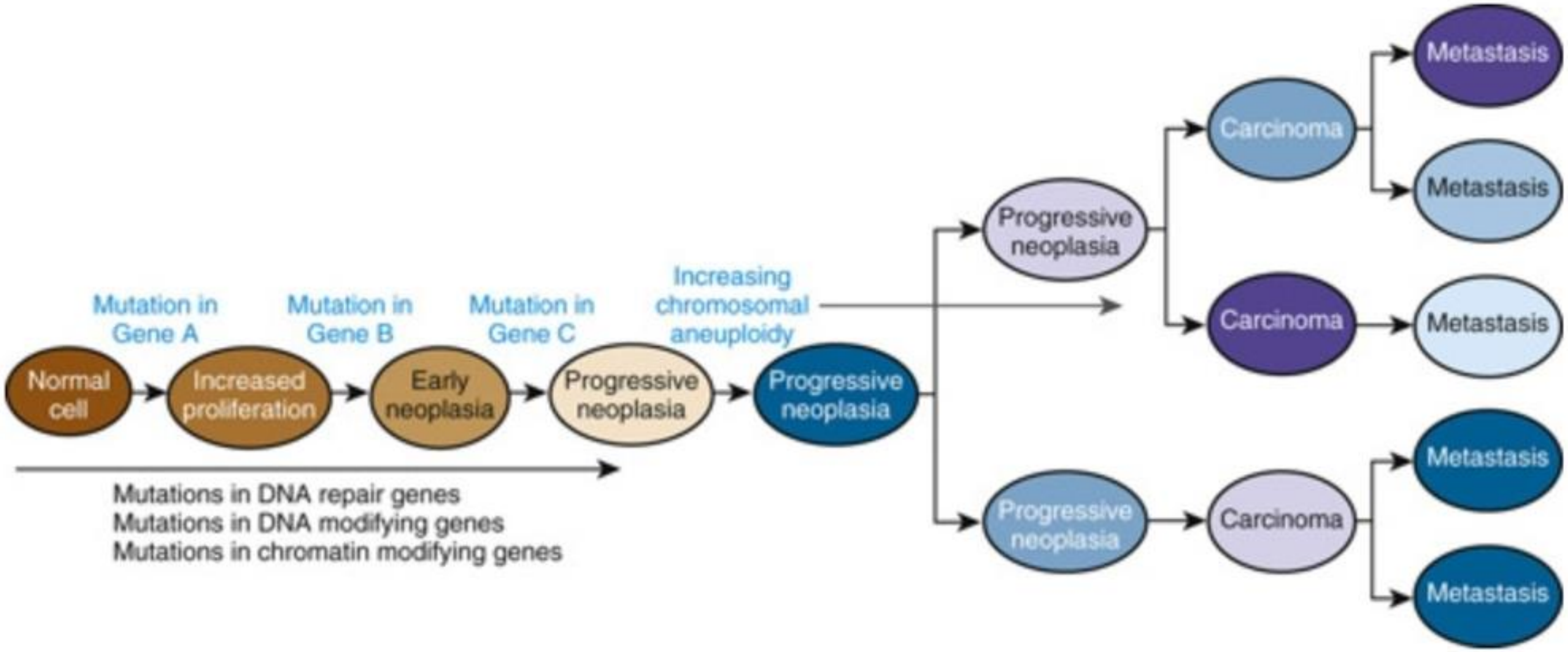


FIGURE 15-4 **Stages in the evolution of cancer. Increasing degrees of abnormality are associated with sequential loss of tumor suppressor genes from several chromosomes and activation of proto-oncogenes, with or without a concomitant defect in DNA repair. Multiple lineages, carrying different mutations and epigenomic profiles, occur within the primary tumor itself, between the primary and metastases and between different metastases.**

the original clone of neoplastic cells evolves and gives rise to multiple sublineages

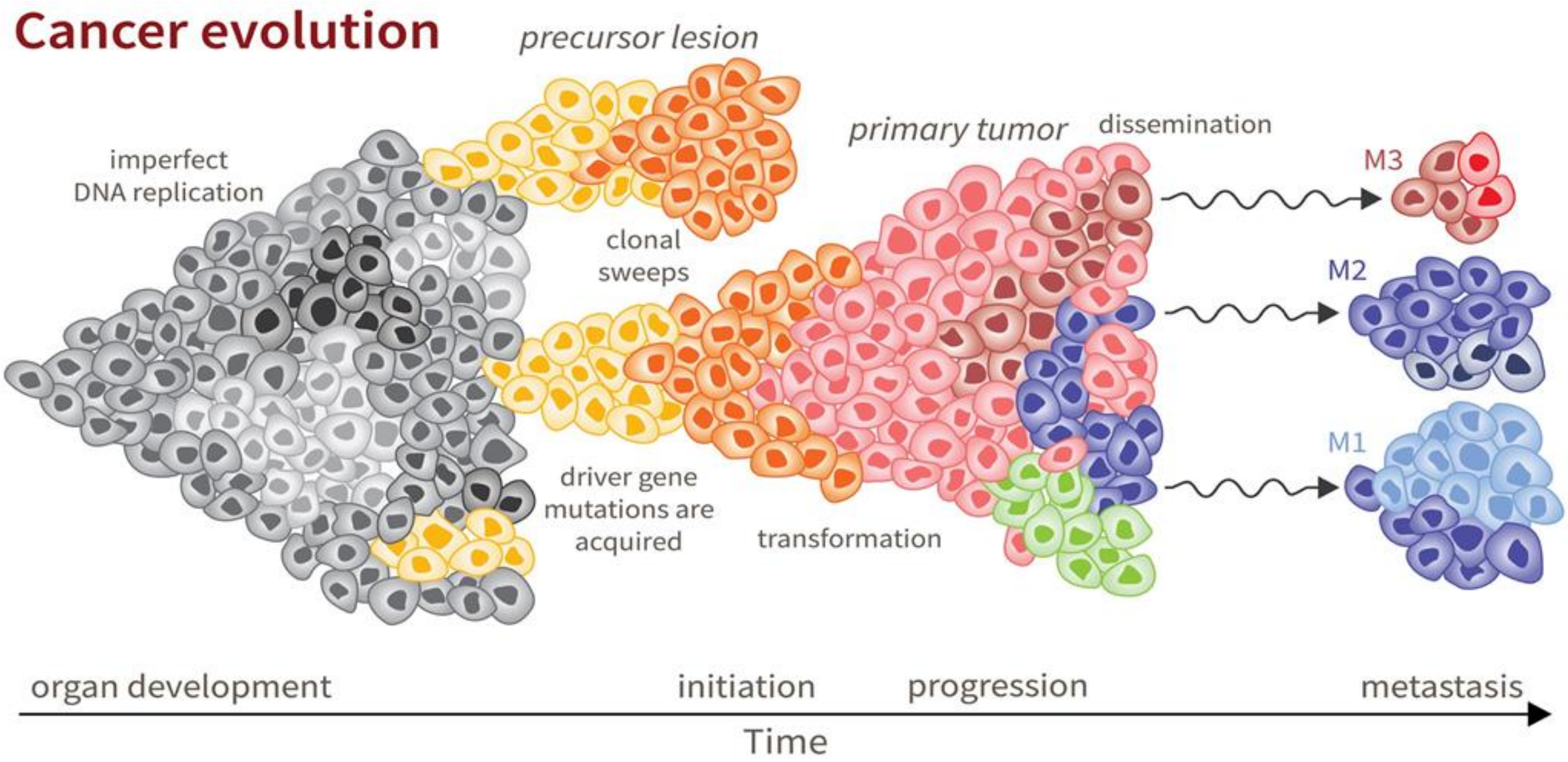
each carrying a set of mutations and epigenomic alterations that are different from but overlap with what is carried in other sublineages.

The profile of mutations and epigenomic changes can differ:

Between the primary and its metastases

Between different metastases,

Between the cells of the original tumor or within a single metastasis.



- **Cancer evolution** shows that even from the same origin, tumor cells acquire different mutations over time in oncogenes and tumor suppressor genes as they continue to divide. This leads to multiple cellular colonies within the same tumor, each with distinct genetic profiles, resulting in ***tumor heterogeneity***. Therefore, it is important to understand the concept of tumor heterogeneity.

Please click here and let me know if there's any mistake.
Good Luck ☺