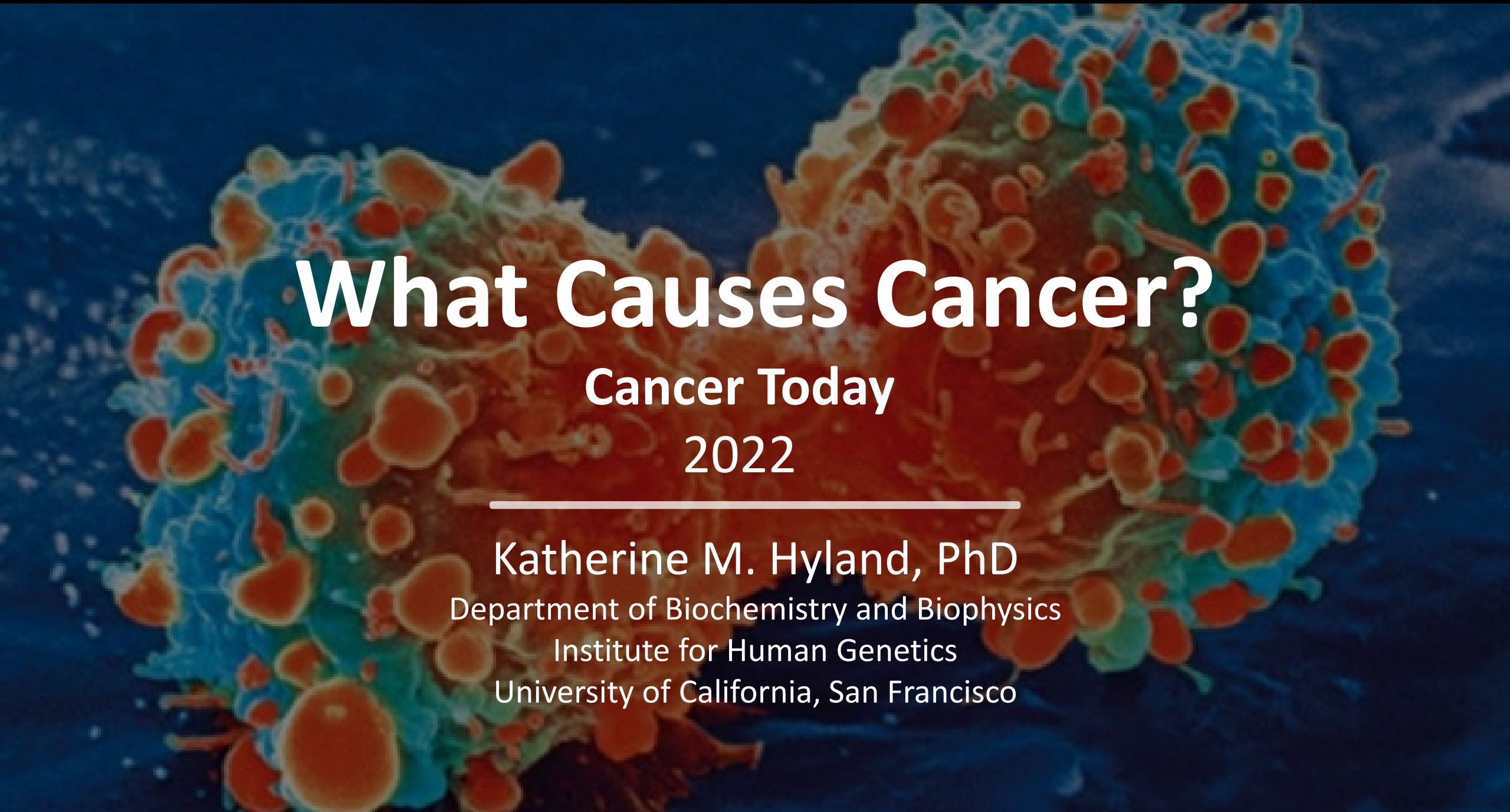

What Causes Cancer?

Cancer Today

2022

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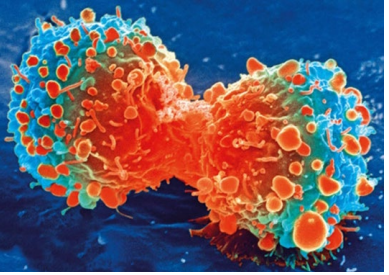
Disclosures

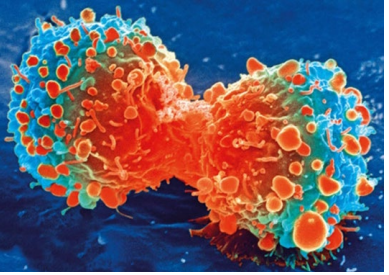
I have no conflict of interest, and nothing to declare regarding the content in this lecture.

-Katherine M. Hyland, PhD



OUTLINE

1. What is Cancer - from a molecular genetic perspective
2. Sporadic vs. inherited cancers
3. Genes that prevent and cause cancer
   - Examples of Tumor Suppressor Genes and Oncogenes
4. How cancer-causing mutations occur



OUTLINE

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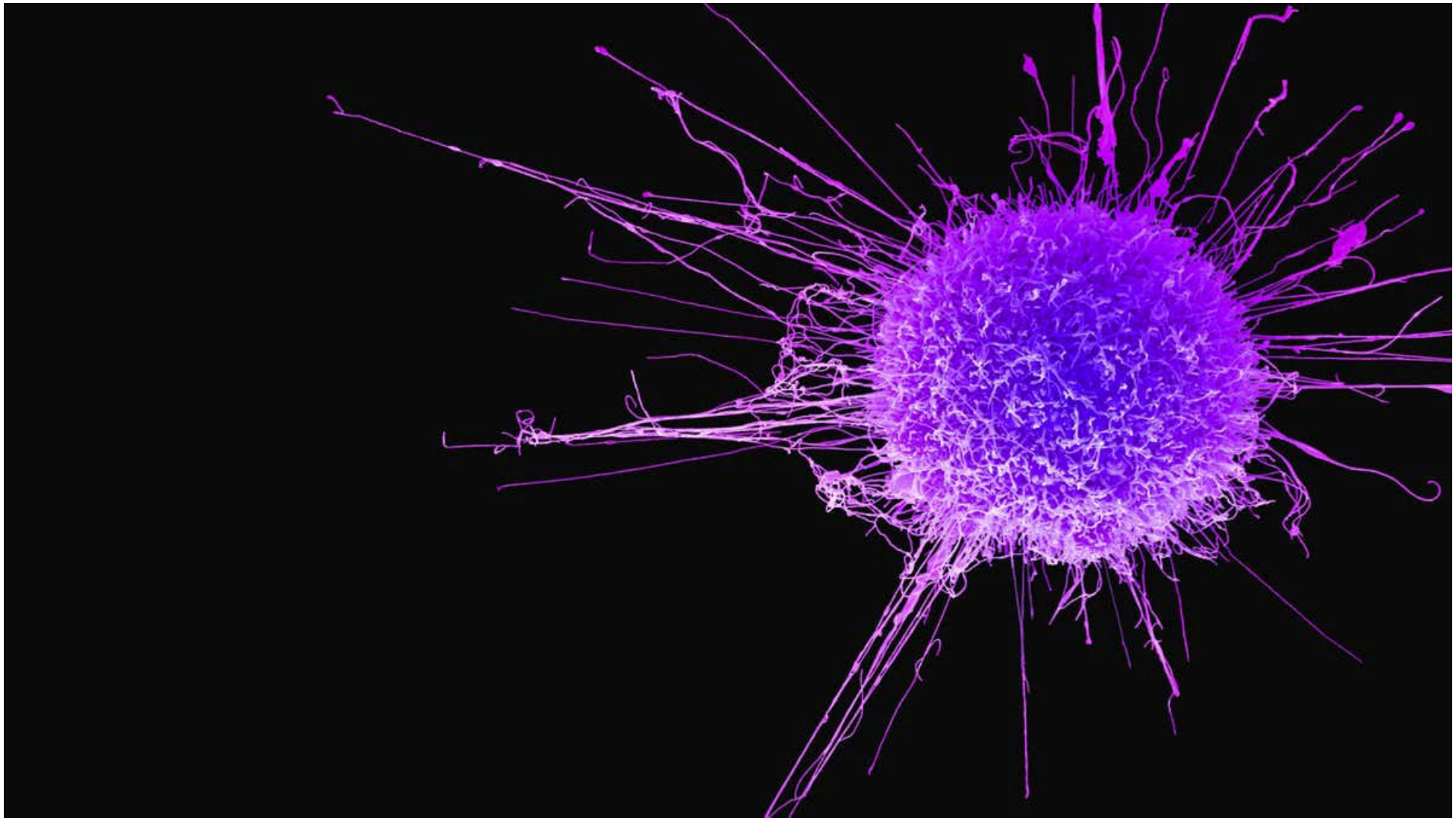
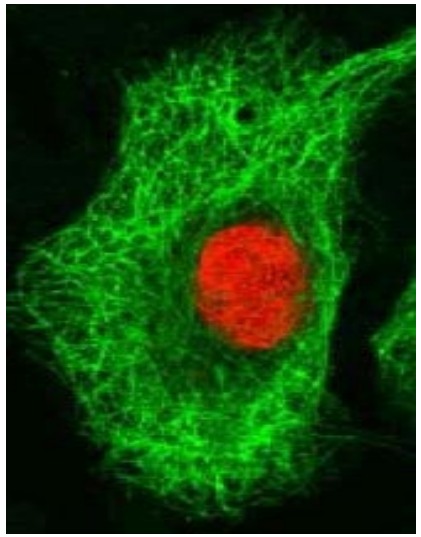
One word that comes to mind when you hear CANCER?

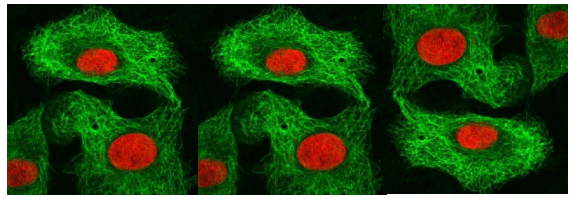


Tissue Homeostasis



Normal Cell

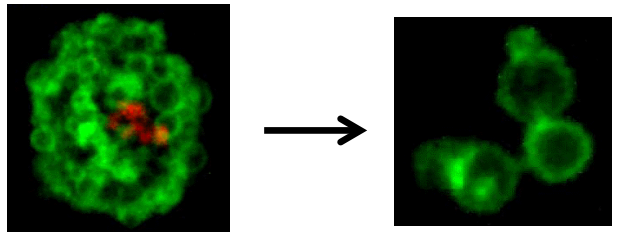
Cell Proliferation



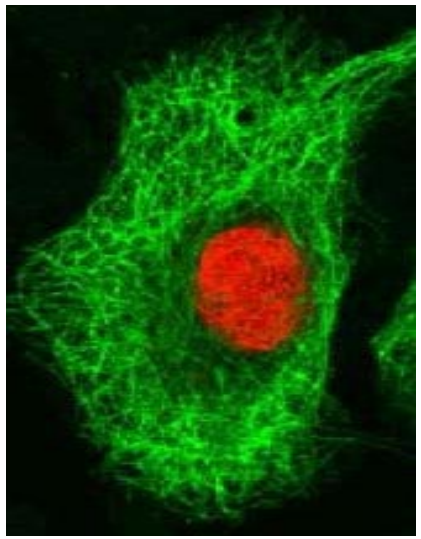
||

Cell Death

Apoptosis



Normal cells have safeguards to maintain homeostasis



growth factors (mitogens)

growth suppressors

Proliferation

=

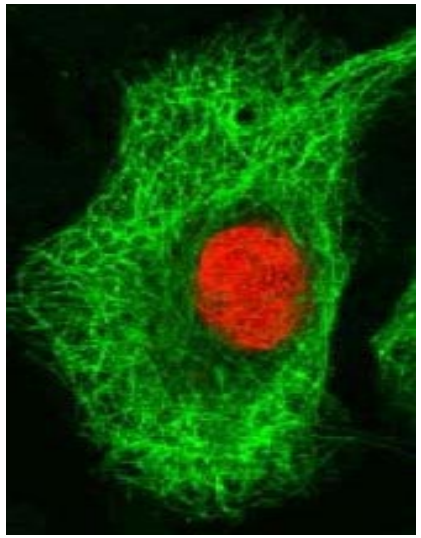
Cell Death

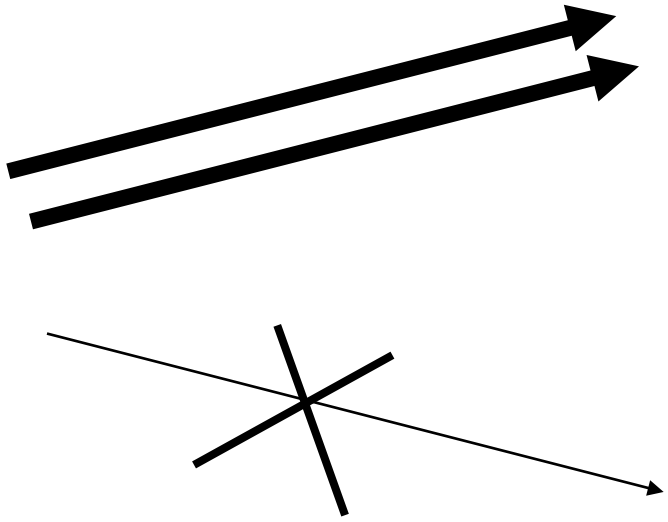
death signals

survival factors

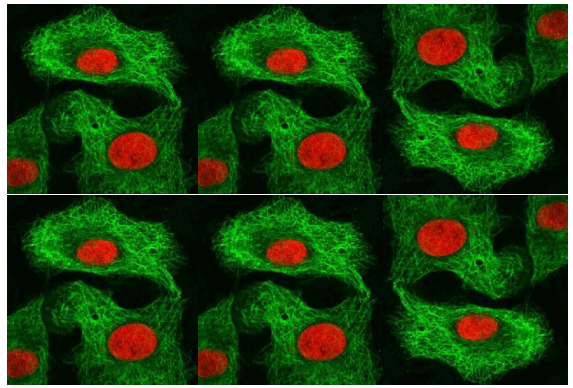
Tumor Formation

results from a disruption of normal tissue homeostasis

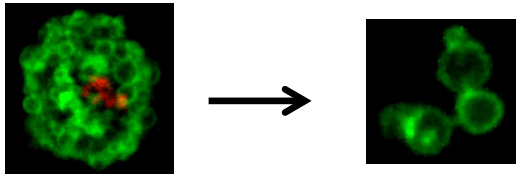


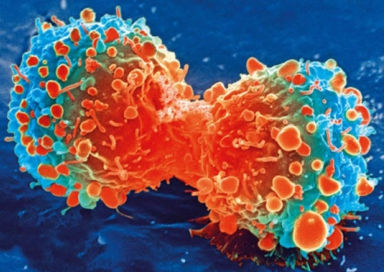


Proliferation



Cell Death

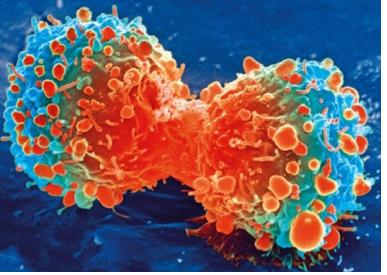




What is CANCER?

- Collection of many heterogeneous diseases
  - Share common cell biological characteristics and similar molecular pathogenesis
  - Yet each individual's cancer has a unique molecular profile

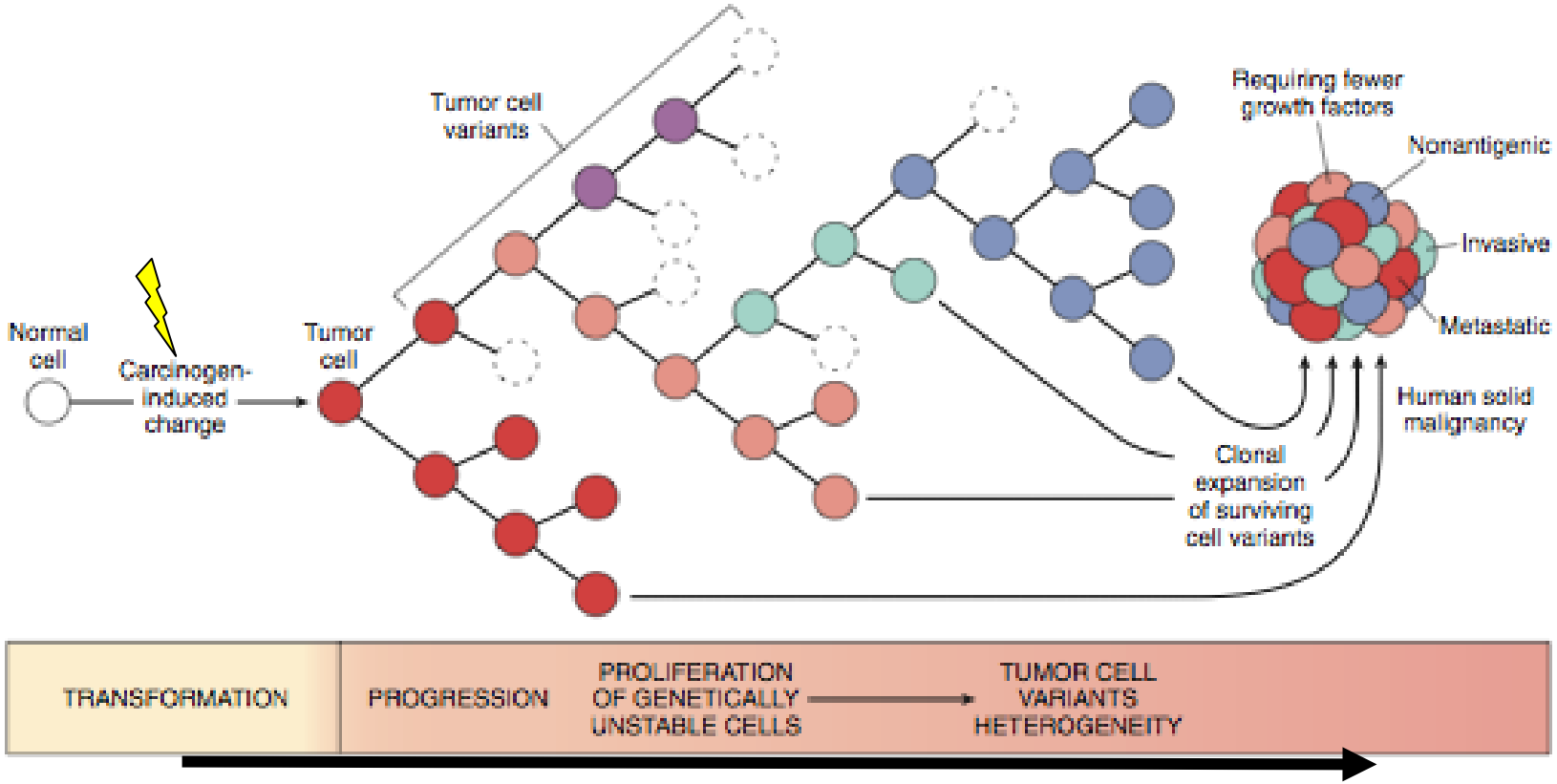
- Common feature: Inappropriate and rapid proliferation of cells



What is CANCER?

- At its root cause, cancer is a **genetic** disease
- Accumulation of **genetic mutations** that **disrupt** normal tissue homeostasis
- Several mutations are required
  - e.g., lag time between carcinogen exposure and cancer development

Tumor Progression through step-wise mutation and expansion

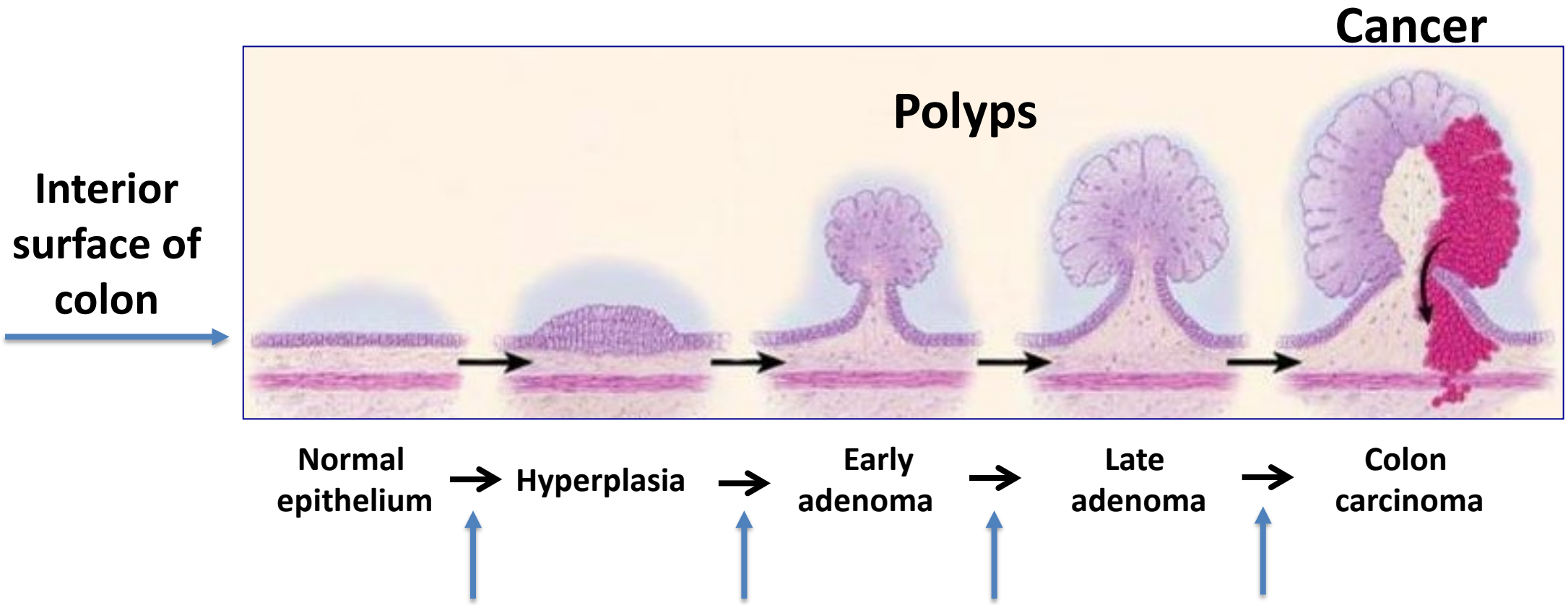


Multistep carcinogenesis

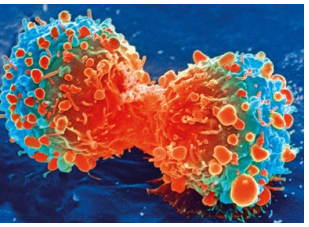
A **clone** = arises from a single cell, genetically identical

*Fig 6-15, **Robbins Basic Pathology**. 8th edition, Kumar, Abbas, Fausto, and Mitchell. Saunders/Elsevier, 2007.*

Colorectal Cancer: Example of multistep process



Mutations knocking out normal cellular "safe-guards"



Cancer is a Genetic disease

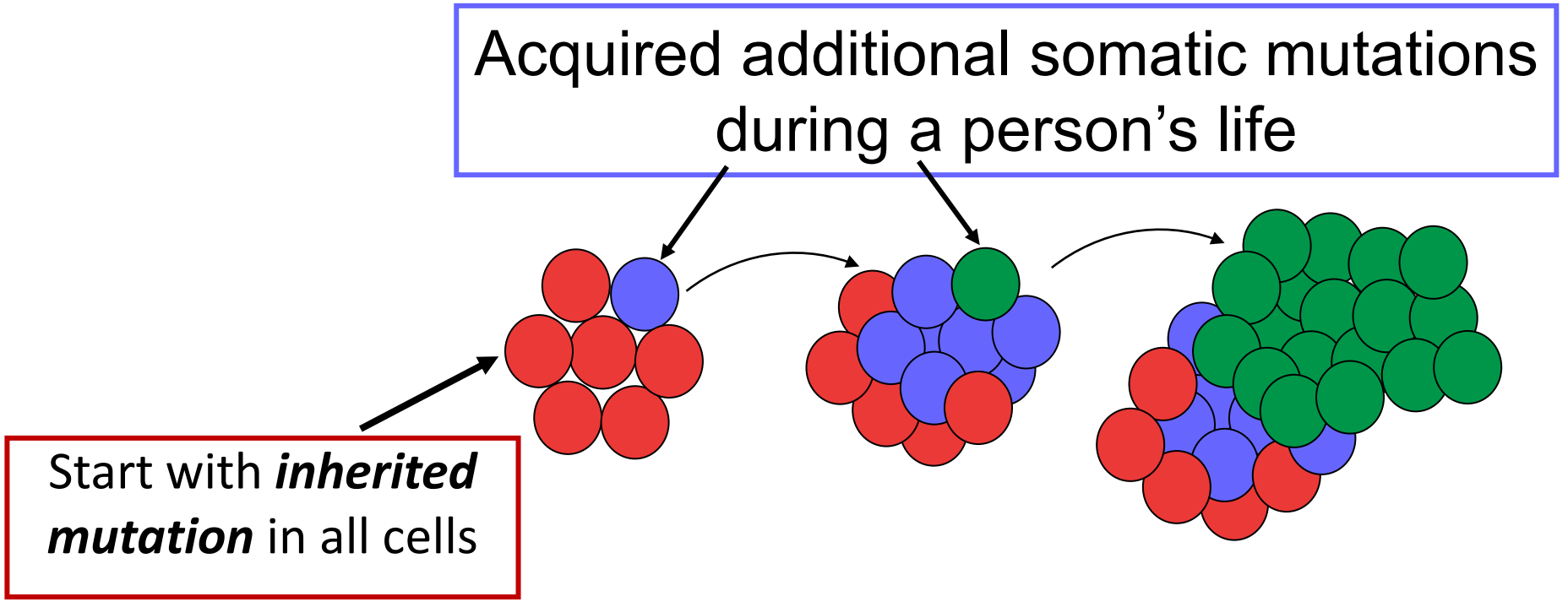
- ***Sporadic*** = common, >90% of cancers
  - Accumulation mutations in a person's cells over a lifetime (somatic)
  - Complex interaction of genetic & environmental factors
  - Develop at older age

- ***Inherited*** = less common, ~10% of cancers

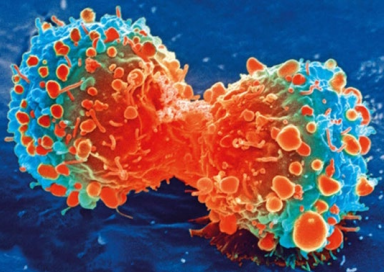
  (but very common within affected family!)

  - Inherited susceptibility via germline mutation
  - Gives tumor a 'head start'
  - Develop at younger age, at risk for multiple cancers throughout life

Familial and Inherited Cancers



- "Head start" in tumor progression pathway
- Higher risk of tumor development & multiple tumors, and at younger age



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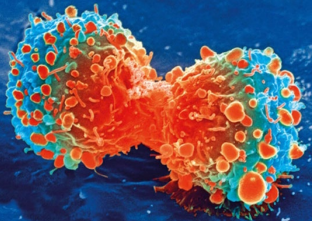
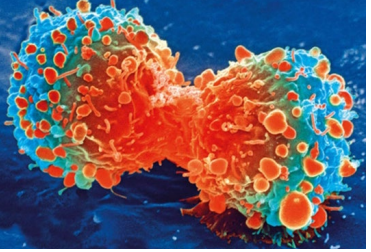


Types of genes involved in cancer development

- **Tumor Suppressor Genes**
  - **Inhibit** cell proliferation
- **Oncogenes**
  - **Promote** cell proliferation

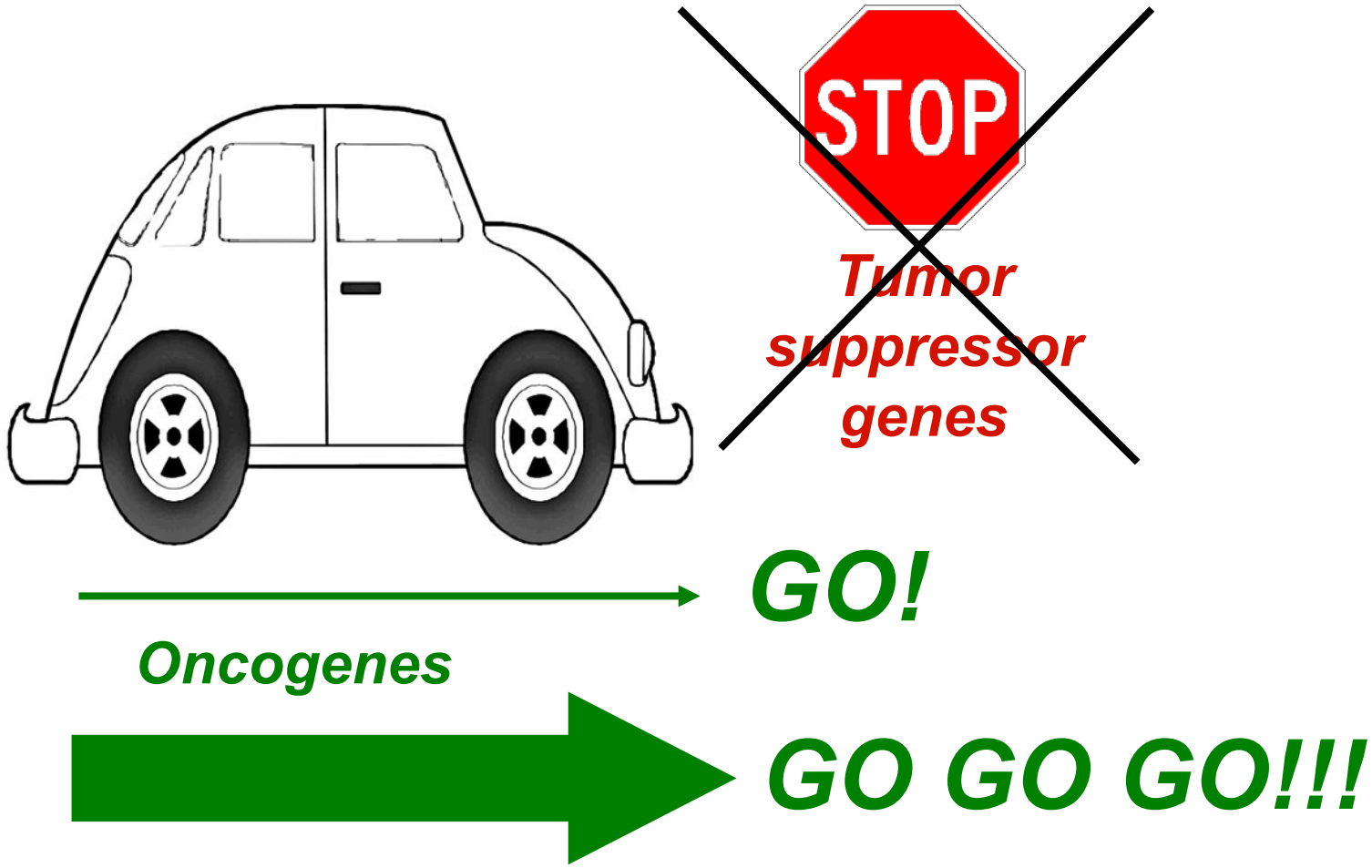


Tumor Suppressor Genes and Oncogenes act through 3 main processes

1. **Regulate cell cycle**
   - Directly promote or inhibit cell proliferation
2. **Control cell death (Apoptosis)**
   - Pro-apoptotic/anti-apoptotic
3. **Repair damaged DNA**
   - Indirectly affect cell proliferation

TUMOR FORMATION is promoted by defects in these genes!

Types of genes involved in cancer development

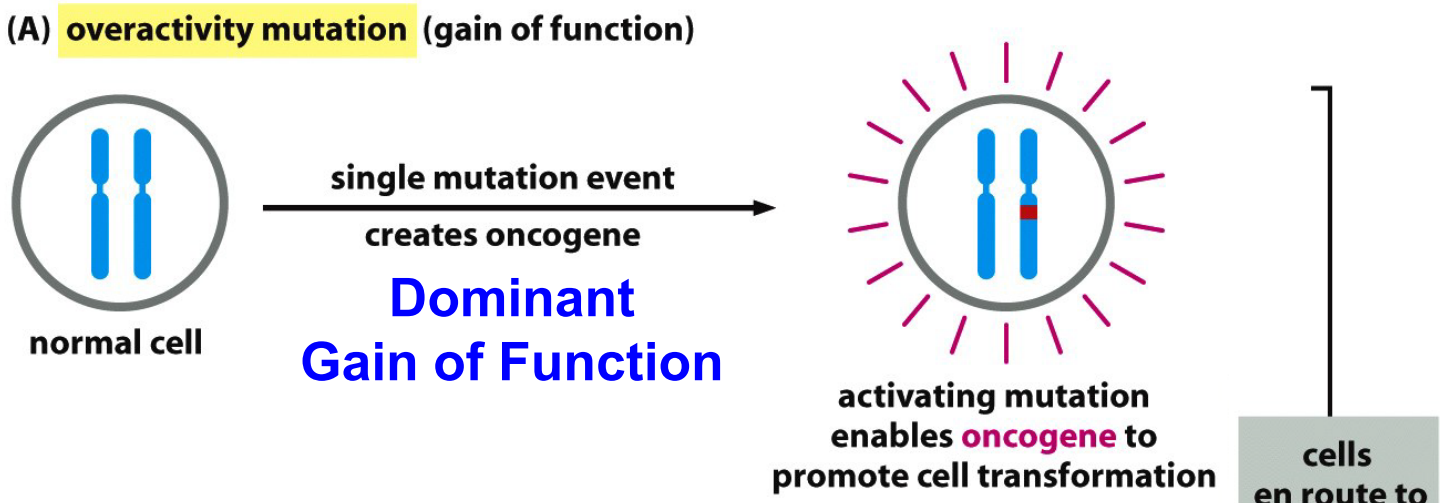


Types of genes involved in cancer development

- Mutation of "**Caretaker genes**" leads to a "**Mutator Phenotype**"
  - Control rate of mutation
  - Disruption of DNA repair system(s)
  - Leads to accumulation of more mutations
    - some of which are in TS genes and oncogenes

Cancer-Causing Mutations

Oncogene



Tumor Suppressor gene

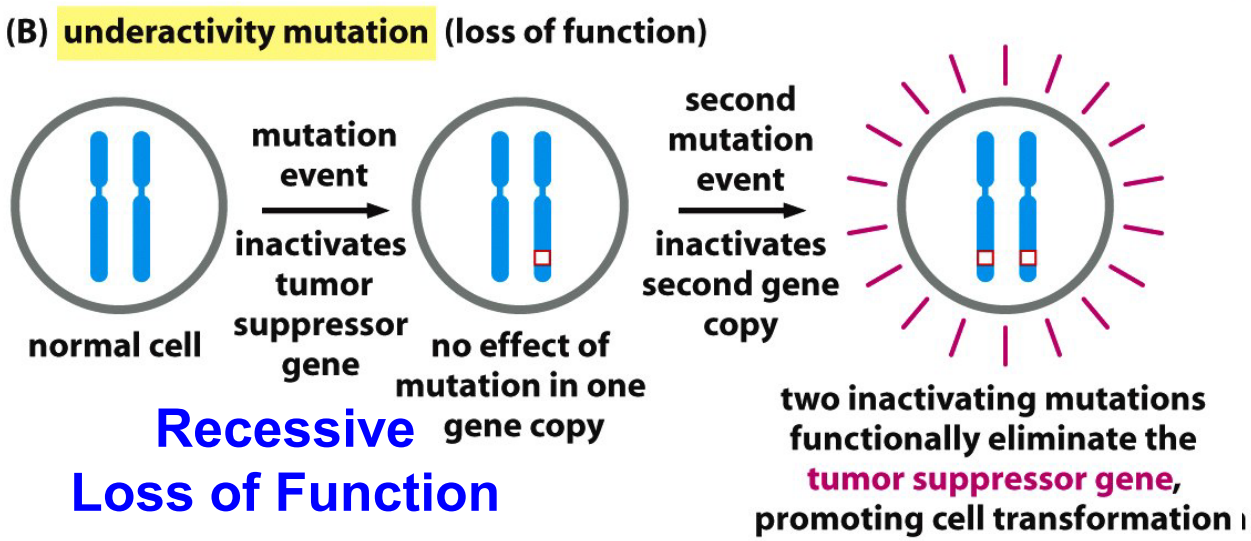
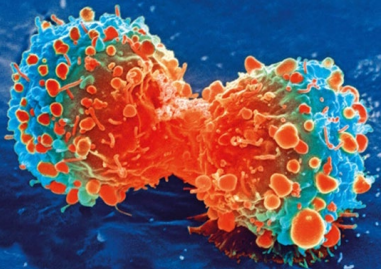


Figure 20-27 Molecular Biology of the Cell 5/e (© Garland Science 2008)



TS Genes & Oncogenes: SUMMARY

➢ Tumor Suppressor Genes

- **Inhibit cell proliferation**
  - Directly inhibit cell cycle
  - Promote cell death (apoptosis)
- **Repair DNA damage**
- **Both copies <u>inactivated/lost</u> in cancer = unregulated cell proliferation**

➢ Oncogenes

- **Promote cell proliferation**
  - Directly promote cell cycle
  - Block cell death (apoptosis)
- **Single copy <u>activated</u> in cancer = unregulated cell proliferation**

1989 Nobel Prize

UCSF Faculty

Dr. J.M. Bishop &

Dr. H.E. Varmus

* First suggestion that cancer can be caused by **normal genes** becoming hyperactive

The Nobel Prize in Physiology or Medicine 1989

"for their discovery of the cellular origin of retroviral oncogenes"

J. Michael Bishop

◑ 1/2 of the prize

USA

University of California
School of Medicine
San Francisco, CA, USA

b. 1936

Harold E. Varmus

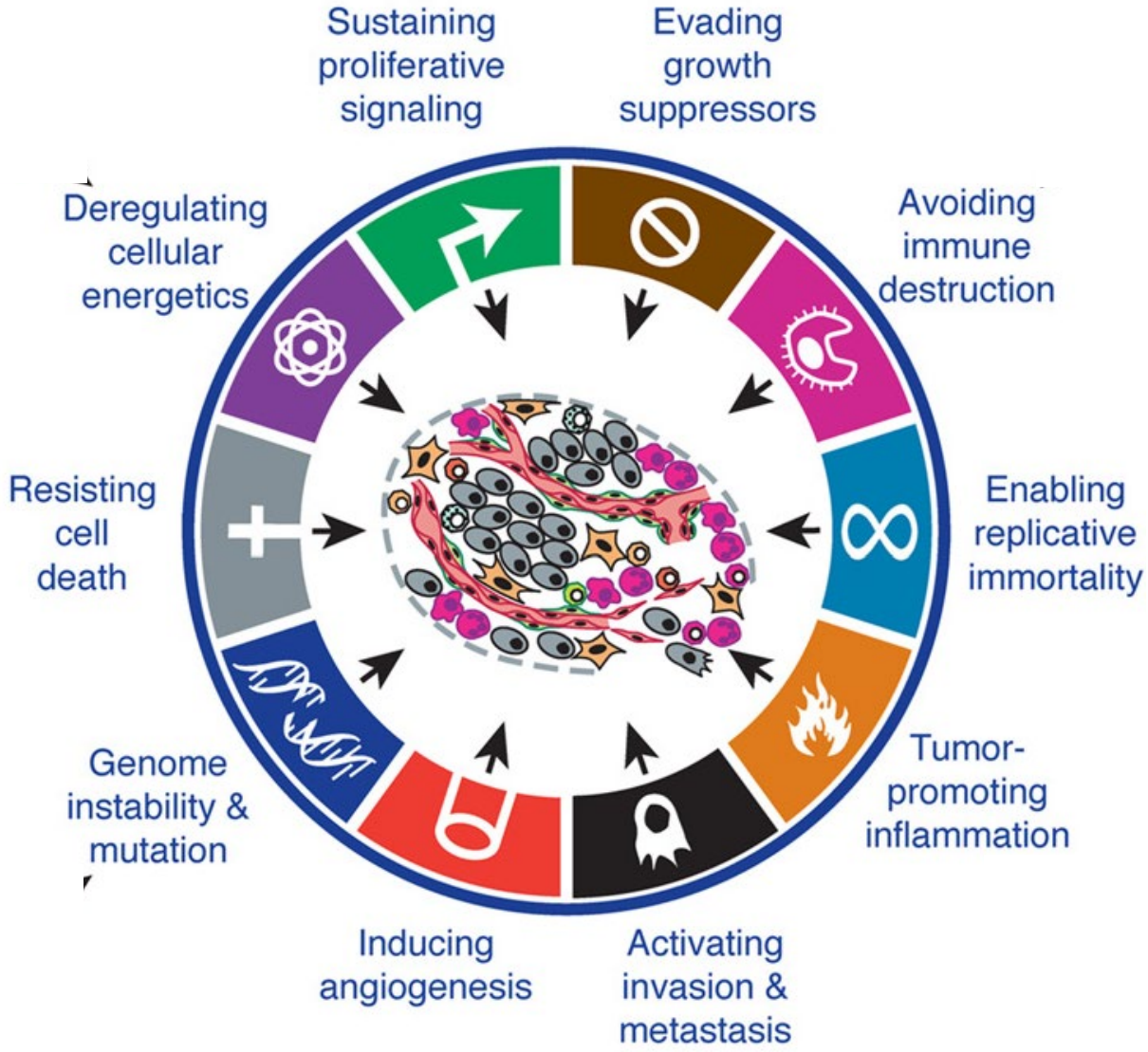
◑ 1/2 of the prize

USA

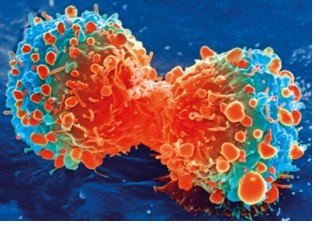
University of California
School of Medicine
San Francisco, CA, USA

b. 1939

Hallmarks of Cancer



Hanahan and Weinberg (2000, 2011)

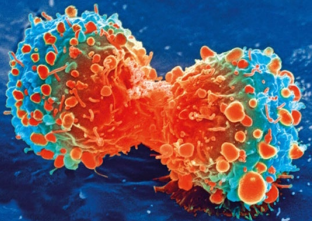


TP53 Tumor Suppressor

- "Guardian of the genome"; responds to DNA damage

- Germline mutation in Li-Fraumeni syndrome
  - Autosomal dominant pattern of inheritance (every generation)
  - Patients inherit one copy of *TP53* with a pathogenic variant (mutation), resulting in a strong predisposition to large variety of tumors, typically <45 y/o:
    - Bone cancer, breast cancer, brain tumors, leukemia (blood cancers), cancers in soft tissues like muscles, etc
  - In tumors, 2nd copy of TP53 gene is lost or inactivated

- ***TP53* is lost or inactivated in >50% of ALL sporadic human tumors!**

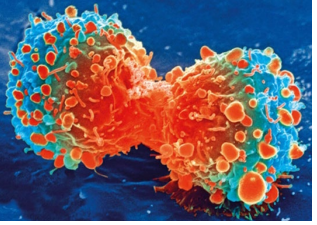


BRCA1 & BRCA2 Tumor Suppressors

- Normally function to repair a specific type of DNA damage (double-stranded breaks)
- Susceptibility genes for hereditary breast and ovarian cancer, autosomal dominant inheritance
- Germline mutations account for majority of familial breast and ovarian cancer (typically diagnosed <50 years of age)
- Also mutated in many sporadic breast and ovarian cancers

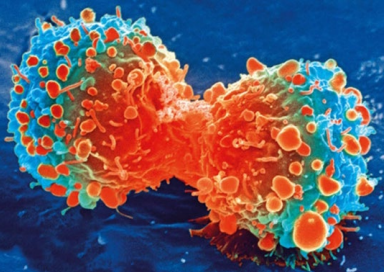
DNA Mismatch Repair Genes

- Loss of MMR leads to the accumulation of mutations
- Early step in development of **many sporadic colorectal cancers**
- Germline mutations in MMR genes cause **Lynch Syndrome**
- **Lynch Syndrome**:
  - Dominantly inherited **colorectal cancer predisposition syndrome**
  - Also at risk for uterine, stomach, prostate and other cancers
  - Mean age of onset early 40s, may be as early as 20's or teens



RAS Oncogenes

- Three human genes *H-ras, K-ras*, and *N-ras*
- Mutations lock the Ras protein in its **active** state, so it no longer turns off in the absence of growth signals, and keeps promoting cell proliferation
- 30% of human tumors contain dominant mutations in a *ras* gene!
- 90% of pancreatic cancers & 35-50% of CRC have a *K-ras* mutation



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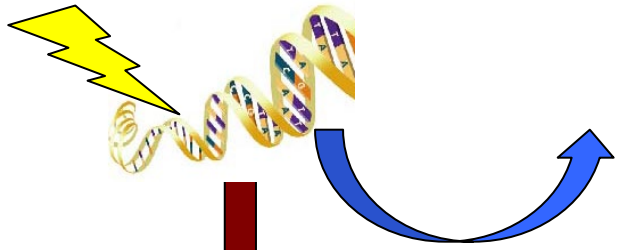
4. **How cancer-causing mutations occur**

How do cancer-causing mutations occur?

DNA Damage



Repair

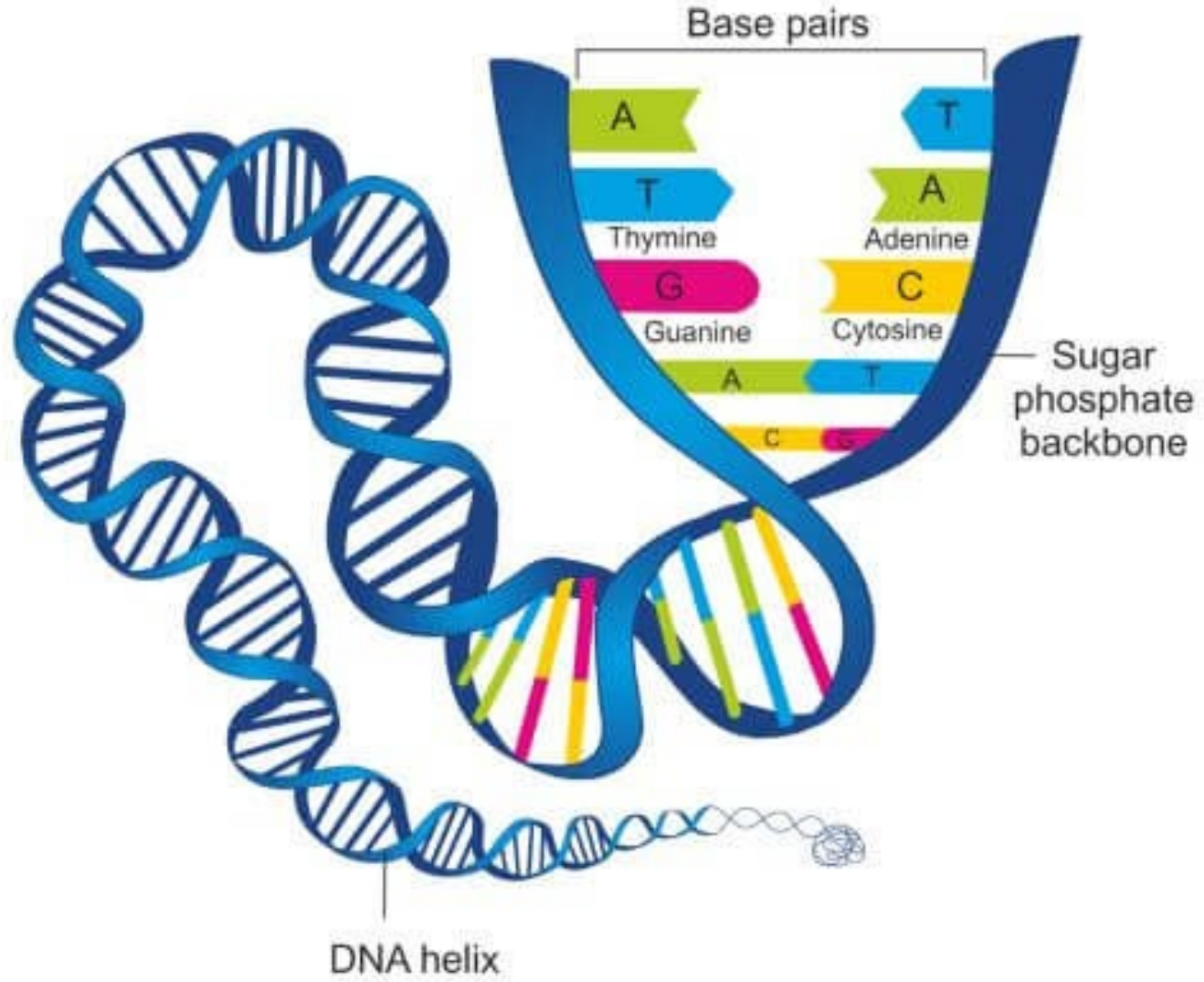
Loss of Repair Mechanisms (Genome Caretakers)

Un-Repaired DNA Damage,
Accumulation of Mutations

Genomic Instability

CANCER

Base Pairs in DNA Double Helix

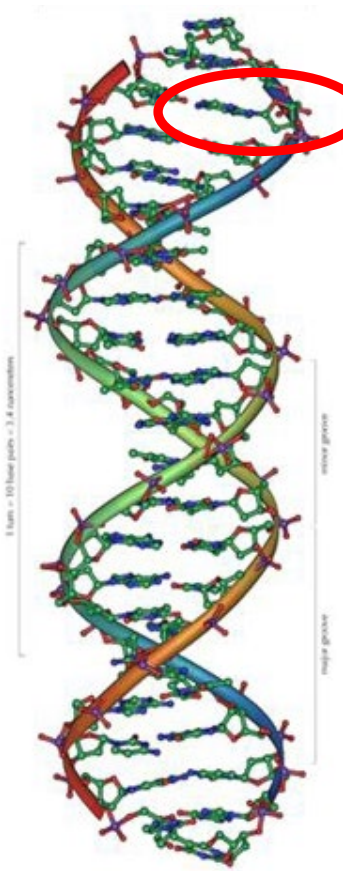


How does DNA damage occur?

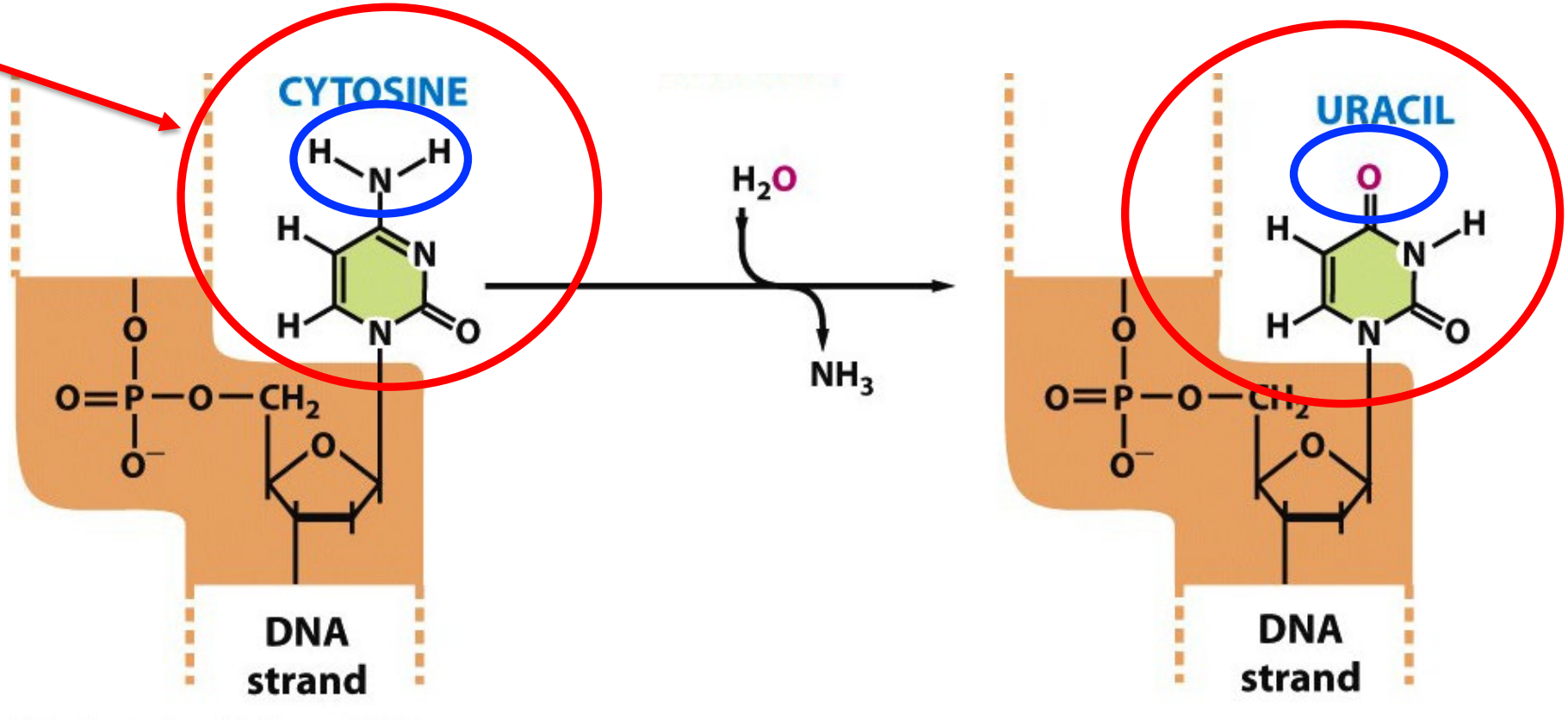
1. **Spontaneous (random)**
   - Alterations to DNA bases, replication errors
   - By products of normal cellular metabolism (e.g., free oxygen radicals)

2. **Environmental**
   - UV light, cigarette smoke, toxic chemicals, etc. that damage/alter DNA

DNA can spontaneously deaminate



DNA double helix



Occurs in 100 bases per cell per day!

Alberts, MBOC, 2002.

Mutations result when DNA machinery tries to replicate through damage

U instead of a **C**

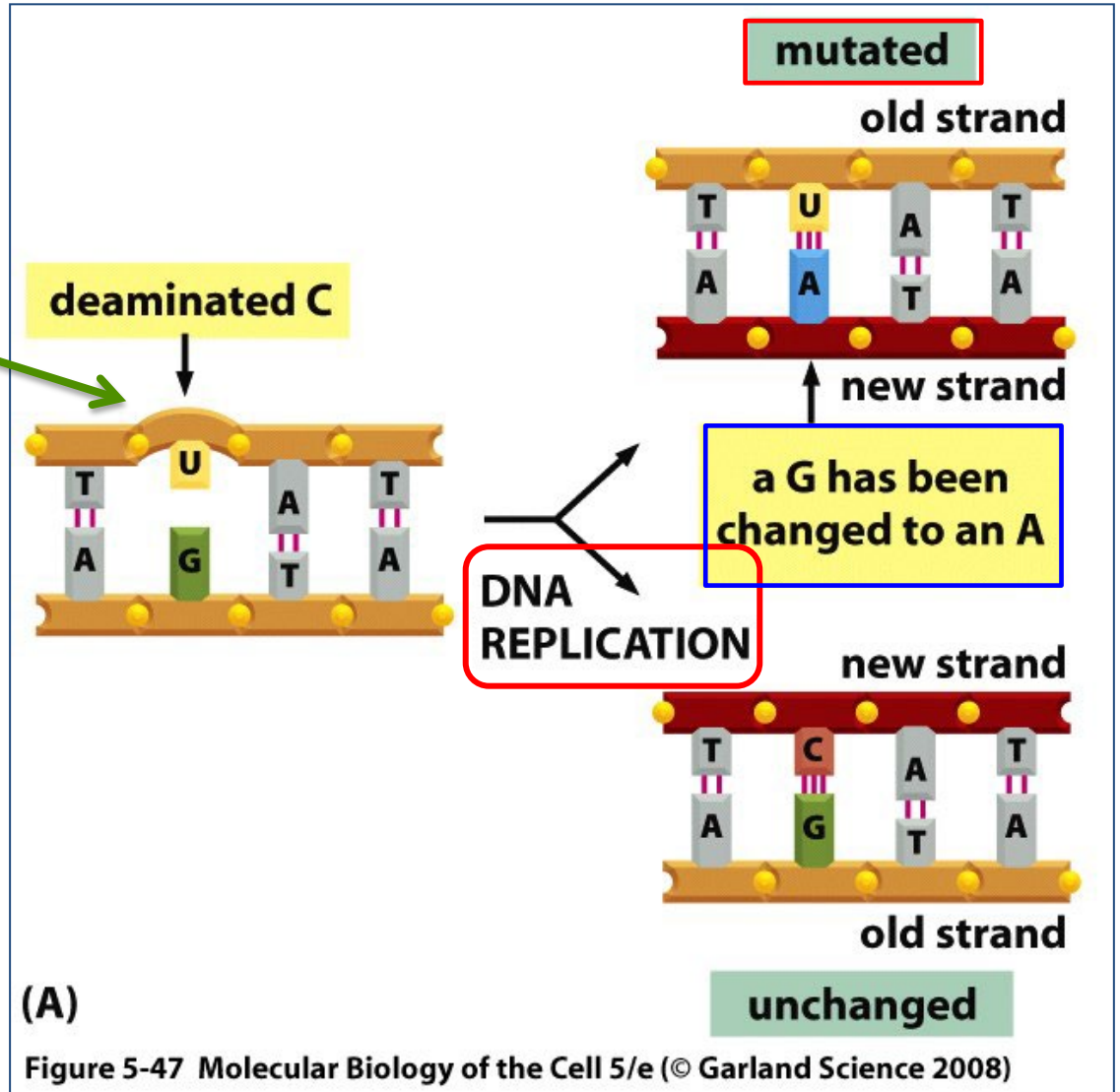
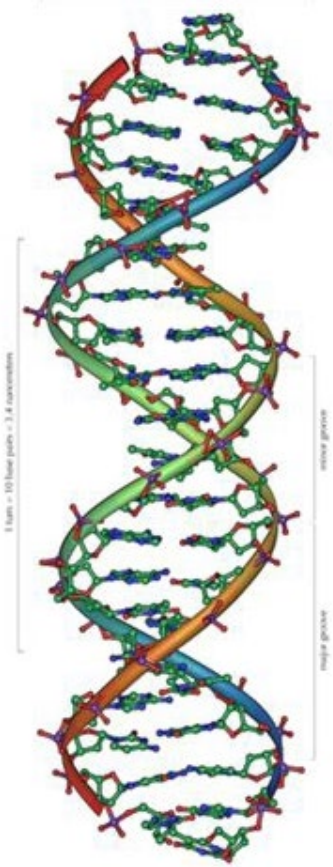


Figure 5-47 Molecular Biology of the Cell 5/e (© Garland Science 2008)

The newly replicated strand has an **A** instead of a **G**;
After the next round of replication, there will be an **A-T** instead of a **G-C**.

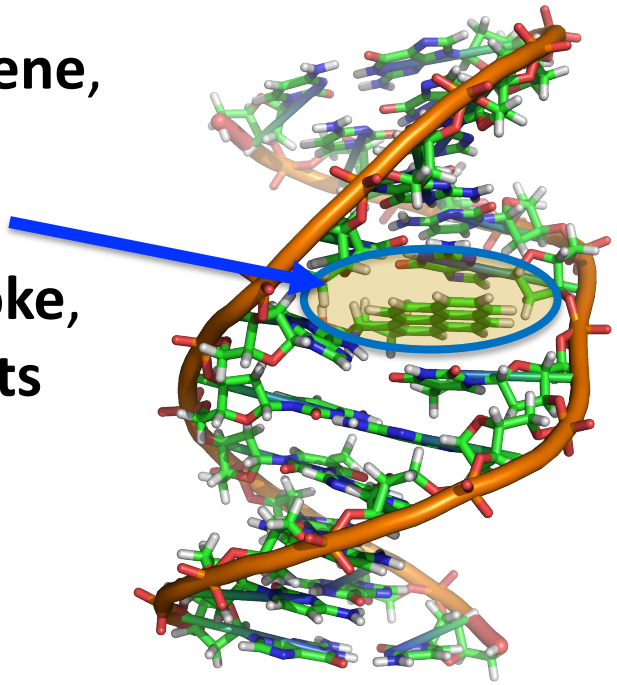
***Take home**:
If the altered base is not repaired, it leads to a **mutation** that is maintained in the DNA.

Chemicals (mutagens) from cigarette smoke can damage DNA



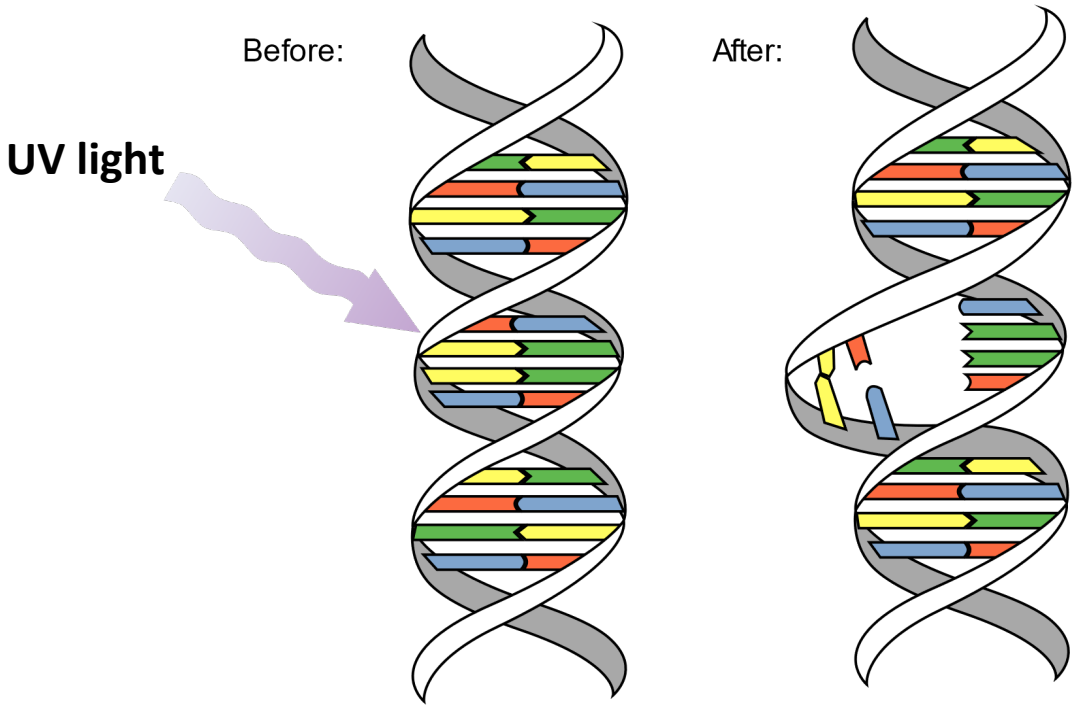
Undamaged DNA

Benzo(a)pyrene, the major mutagen in **tobacco smoke**, forms **adducts on DNA**



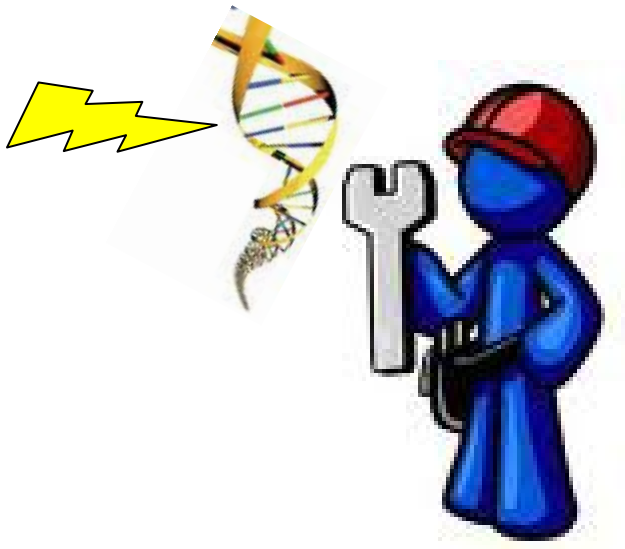
Zephyris, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=2268968

UV light can damage DNA



UV-induced pyrimidine dimer distorts the DNA helix

DNA repair mechanisms ensure the integrity of the genome

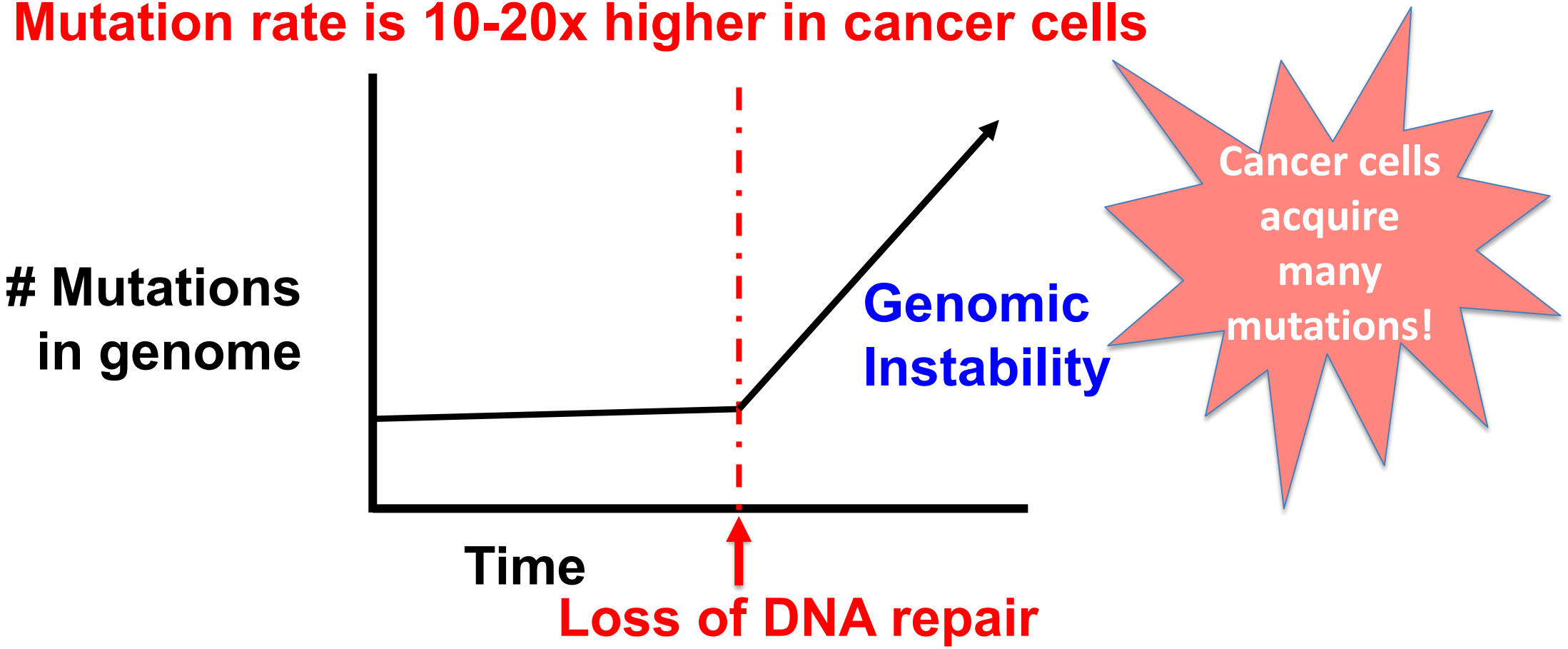


1. Base Excision Repair
2. Mismatch Repair
3. Nucleotide Excision Repair
4. Homologous Recombination Repair
5. Non-Homologous End Joining

DNA repair proteins are encoded by "Caretaker" Genes

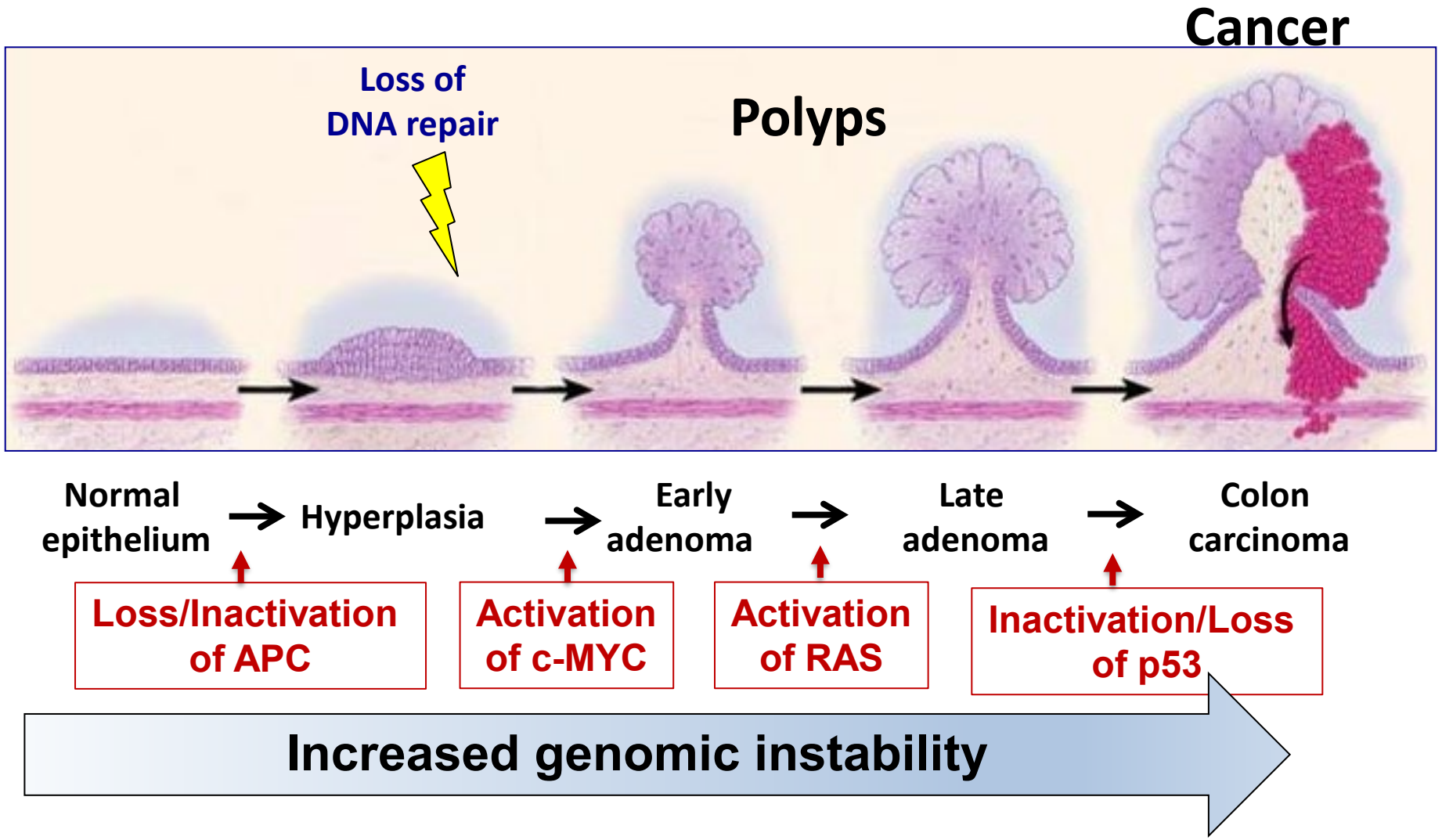
Loss of "Caretaker" genes causes DNA damage to accumulate

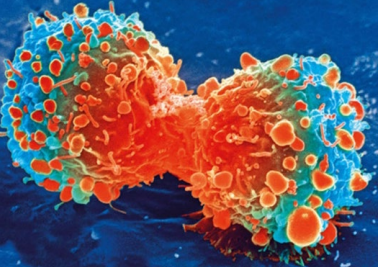
- Normally ~ 1 mutation per one hundred million bases/cell division
- **Mutation rate is 10-20x higher in cancer cells**



Alberts, MBOC, 2002.

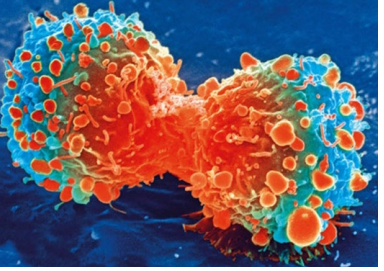
Genomic Instability is an early event in tumor progression





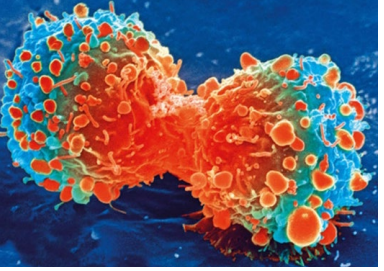
Summary Part 1

- Cancer results from genetic mutations that disrupt normal tissue homeostasis
- Tumors arise from:
  - Multi-step process of accumulation of mutations
  - Mutations in genes involved in control of cell proliferation, cell death and DNA repair
    - Inactivation/loss of tumor suppressor genes
    - Activation of oncogenes
- Cancers all share certain hallmark features



Summary part 2

- Random DNA damage is constantly occurring due to normal cellular processes and environmental factors
- Most DNA damage is repaired by specific repair mechanisms; unrepaired damage leads to mutations
- Loss of DNA repair leads to genomic instability and the potential to acquire cancer-promoting mutations
- Genomic instability is believed to be an early event in tumor progression



Why is it important to understand the molecular basis of cancer?

- More accurate diagnosis and prognosis
- Development of targeted cancer therapies
- More precise and individualized cancer treatment


Thank You!