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Tumor Genetics

MGL-12

May 13th 2014

Cancer Genetics

- Types of Genetic Alterations in Cancer
- Evidence that Mutations Cause Cancer
- Multistage Model of Carcinogenesis
- Oncogenes, Tumor Suppressor Genes,

CELL GROWTH

Cancer is a Disease of the Cell Cycle

- Cells in the body are "programmed" to:
  - To develop
  - To grow
  - To differentiate
  - To die

  in response to a complex system of biochemical signals.
- Cancer results from the emergence of a clone of cells freed of these developmental programming constraints and capable of inappropriate proliferation

Response to the Environmental Signals

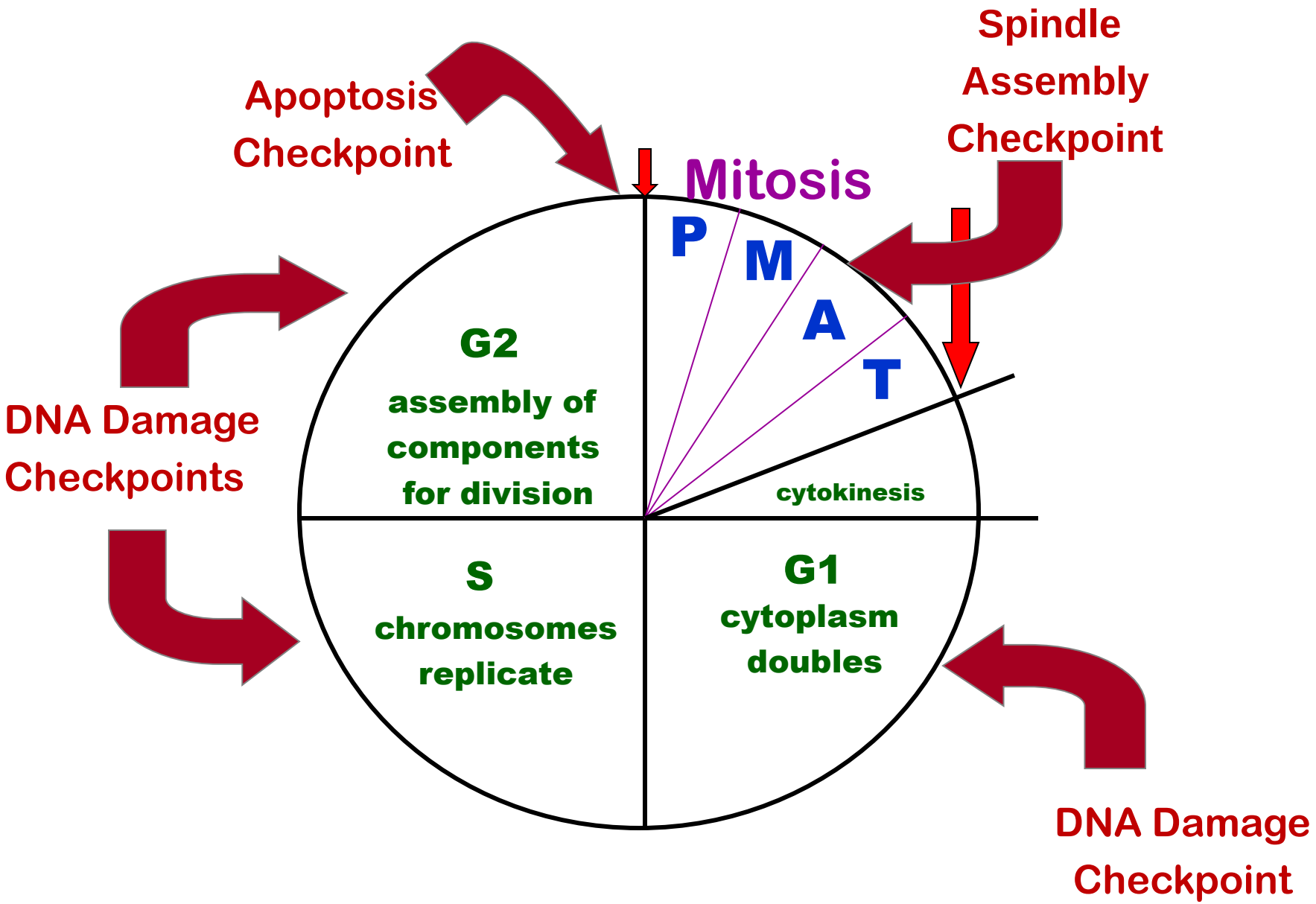
SIGNALS		RESPONSE
▪ Growth Factors	→	Differentiation
▪ Steroids	→	Growth and Death
▪ Cell to Cell Interaction	→	Mitosis

Control of the Cell Cycle

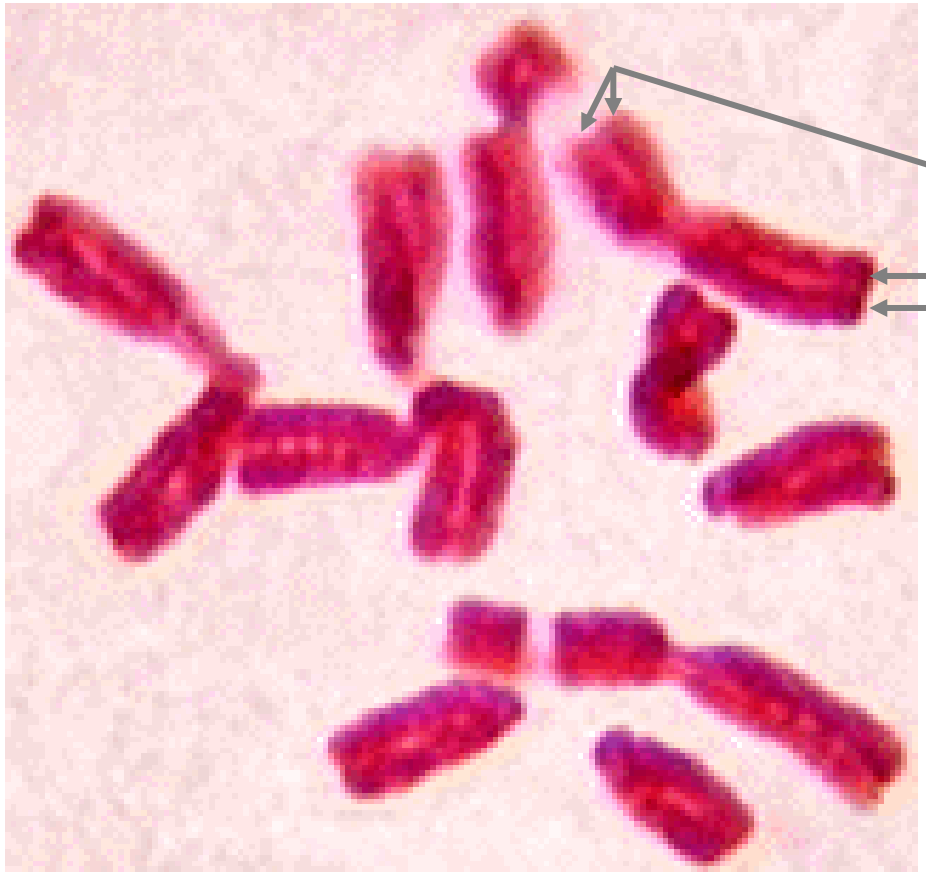
Mechanisms for controlling progress through the cell cycle:

- Transitions between different phases of the cell cycle **(G_1, S, G_2, and M)** are regulated at checkpoints.
- Checkpoints
- Length of Telomeres
- Chemical Signals from within and outside the cell

Cell Cycle Checkpoints



Length of Telomeres



Telomeres are structures at the ends of chromosomes that shorten with each cell division. After 50 divisions, the shortened length of telomeres causes mitosis to stop.

Chemical Signals that Control the Cell Cycle

1. **Cyclin and Kinase**
   - proteins that initiate mitosis
   - requires buildup of cyclin to pair with kinase
2. **Hormones**
   - chemical signals from specialized glands that stimulate mitosis
3. **Growth Factors**
   - chemical factors produced locally that stimulate mitosis

Cyclins and CDKs

- Important checkpoint proteins are the **cyclins** and the **cyclin-dependent kinases (CDKs);** complexes formed between cyclins and CDKs cause the cell cycle to advance.

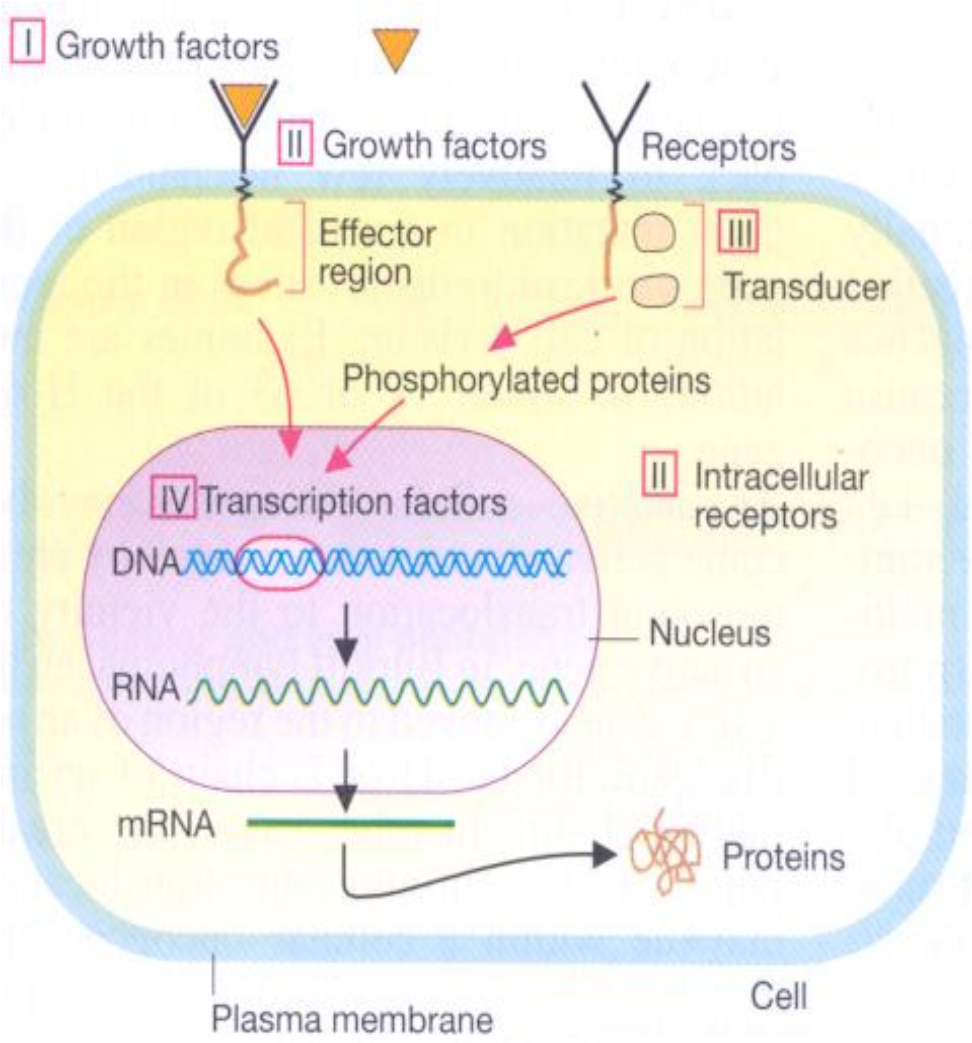
- The CDKs **phosphorylate** target proteins but are inactive unless they are associated with a cyclin protein.

- Cell cycling requires the alternate **formation and degradation** of cyclin/CDK complexes.

Signaling Molecules

- Growth Factors
- Receptors for Growth Factors and Hormones
- Intracellular Signal Transducers
- Nuclear Transcription Factors
- Cell-Cycle Control Proteins

Types of Growth Factors for Differentiation



Examples:

I. Growth factors
PDGF/*sis*

II. Growth factor receptors
EGF / *erb* B
PDGF

III. Transducer
Protein kinases / e.g., *src*
ras proteins / e.g., H-*ras*

IV. Nuclear transcription factors
e.g., *jun*
fos
myc
myb
N-*myc*
p53
RB

Cancer

- Cancers arise when critical genes are mutated, causing unregulated proliferation of cells.
- These rapidly dividing cells pile up on top of each other to form a tumor.
- When cells detach from the tumor and invade surrounding tissues, the tumor is **malignant** and may form secondary tumors at other locations in a process called **metastasis.**
- A tumor whose cells do not invade surrounding tissues is **benign.**

Cancer Cell Do Not Grow Faster Than Normal Cells

Rather, Their Growth is Just Uncontrolled

How do we define cancer?

Cancer is a group of disorders that causes cells to escape normal controls on cell division

- Cancer cells divide more frequently
- Cancer cells are not inhibited by contact with other cells and can form tumors
- Cancer cells can invade other tissues, a process called metastasis

Cancer: General Etiology and Pathogenesis

- **Etiologic agents:**
  - Environmental (chemical, physical, and biological)
  - Hereditary (familial cancer syndromes)
- **General mechanisms:**
  - Acquired capabilities (Self-maintained replication, longer survival, genetic instability, neoangiogenesis, invasion and metastasis)
  - Activation of oncogenes, inactivation of TSG, non-effective DNA repair
  - Caretaker and gatekeeper pathways

THE CAUSES OF GENOMIC CHANGES IN CANCER : Somatic Changes

Cause	Damage	Cancer Risk	Signals
Physical	UV	Skin Ca, Melanoma	P53 (CC-TT)
	Radiation	Thyroid Ca., Leucemia	Translokation
Chemical	Benzopren	Lung Ca.	p53 (G-T)
	Aflatoxin	Liver Ca.	p53 (249 G-T)
	Oxidative Stress	Geriatric Ca	P53 (C-T)
Biological	HBV	Liver Ca.	Virus DNA Integration

Exogenous Sequences

- Tumor viruses
  - contribute genes resulting in abnormal cell growth
- Cervical cancer
  - HPV (human papilloma viruses)
- Burkitt's lymphoma
  - EBV (Epstein-Barr virus)
- Hepatocellular carcinoma
  - hepatitis viruses

Genetic Mechanisms of Tumors

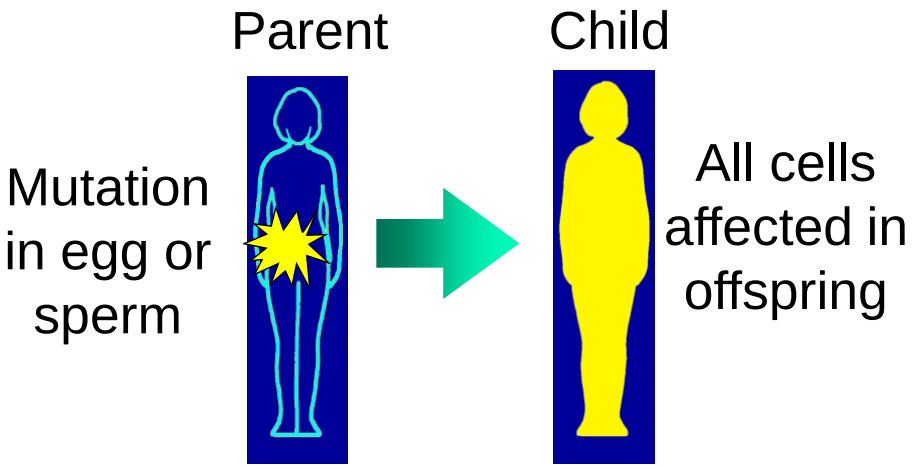
- Gene deletions / amplifications
- Mutations
  - Inserstional
  - Point Mutations
- Genetic Instability
  - Microsatellite Instability (MSI)
  - Chromosomal Instability (CIN)

Evidence that Mutations Cause Cancer

- Most carcinogens are mutagens
  - *Not all mutagens are human carcinogens*
- Some cancers segregate in families
  - *Genes cloned, mutations lead to cancer in animals*
- Oncogenes and Tumor Suppressor Genes
  - *Found in human tumors, enhance growth*
- Chromosomal instability
- Defects in DNA repair increase probability of cancer

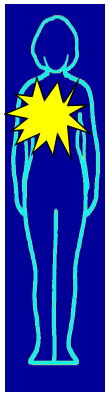
Cancer Arises From Gene Mutations

Germline mutations



- Present in egg or sperm
- Are heritable
- Cause cancer family syndromes

Somatic mutations



- Occur in nongermline tissues
- Are nonheritable

Types of Genetic Alterations in Cancer

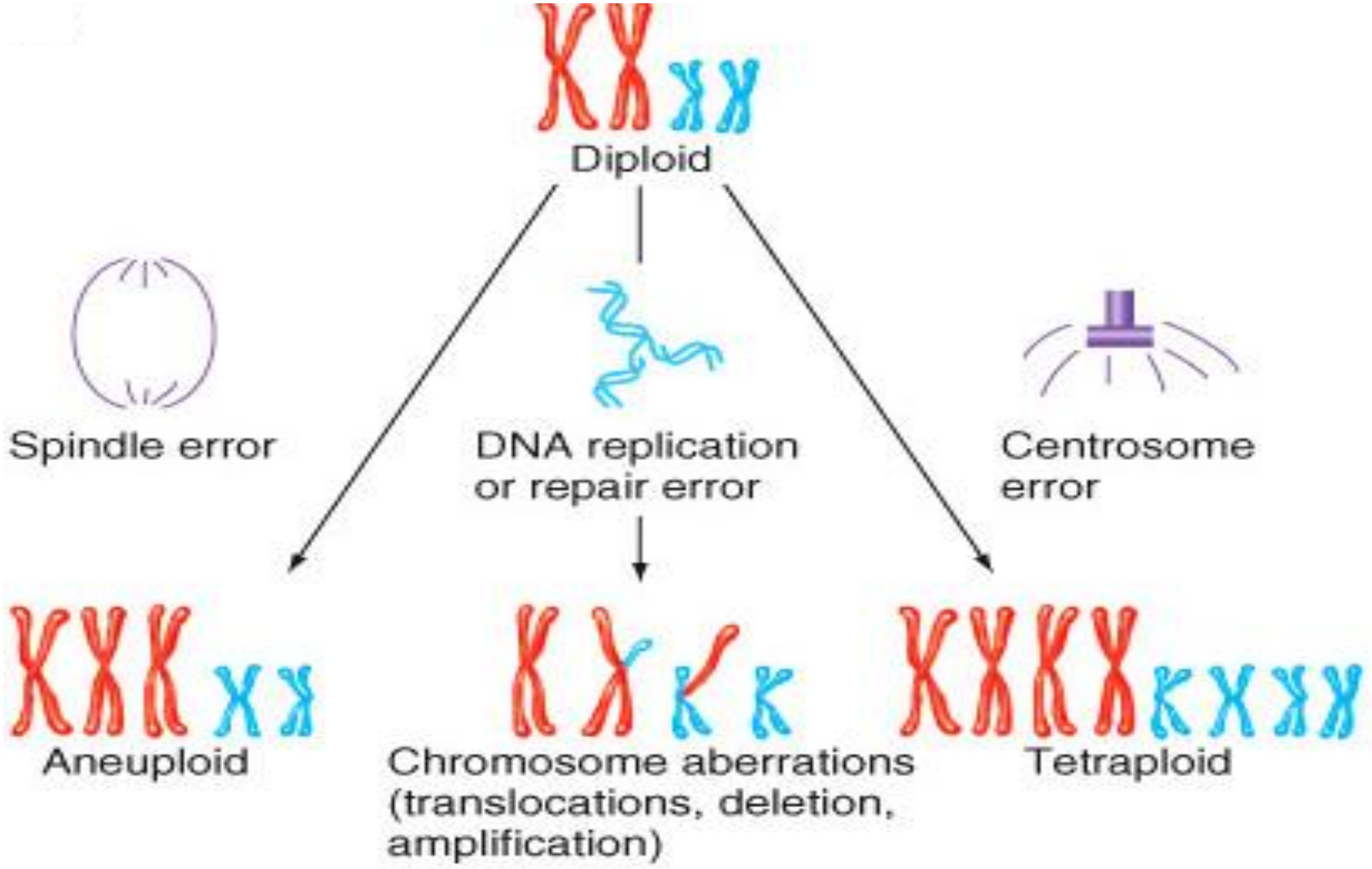
- Subtle alterations
- Chromosome number changes
- Chromosomal translocation
- Amplifications

Each type represents one of the mutations a cell can accumulate during its progression to malignancy

Subtle Alterations

- Small deletions
- Insertions
- Single base pair substitutions
  (Point mutations)

Three classes of error lead to aneuploidy in tumor cells



Changes in Chromosome Number and Structure Are Often Associated with Cancer

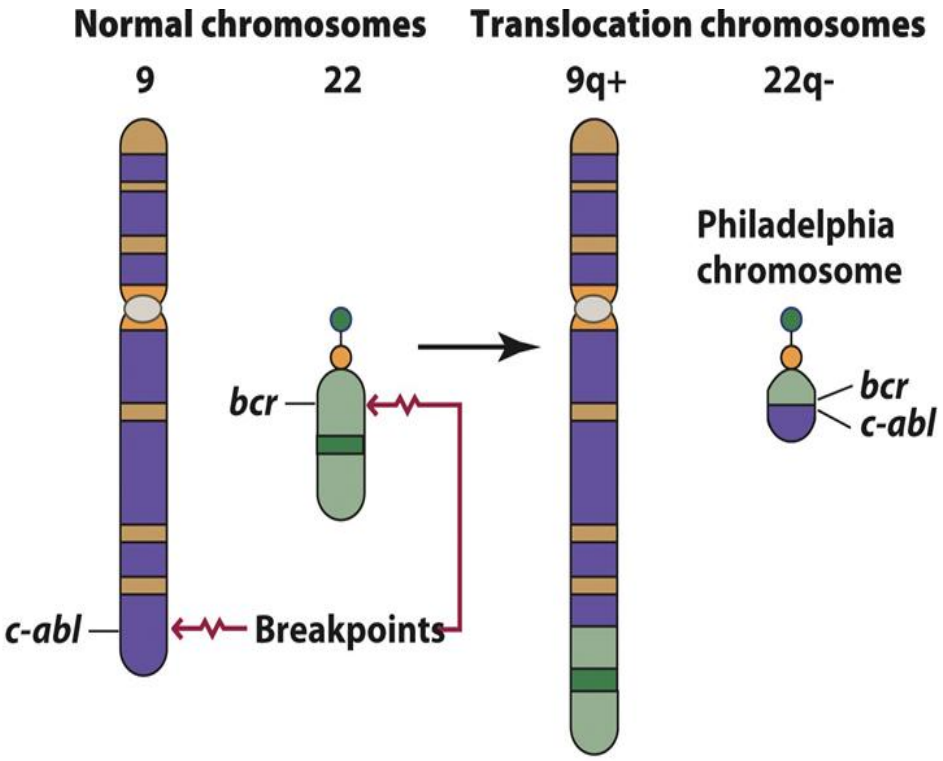
- Random translocations

  breast, colon, prostate (common epithelial tumors))

- **Non-random translocations**

  leukemia, lymphoma

  (reciprocal translocation between chromosome 9 and 22 causes chronic myelogenous leukemia)



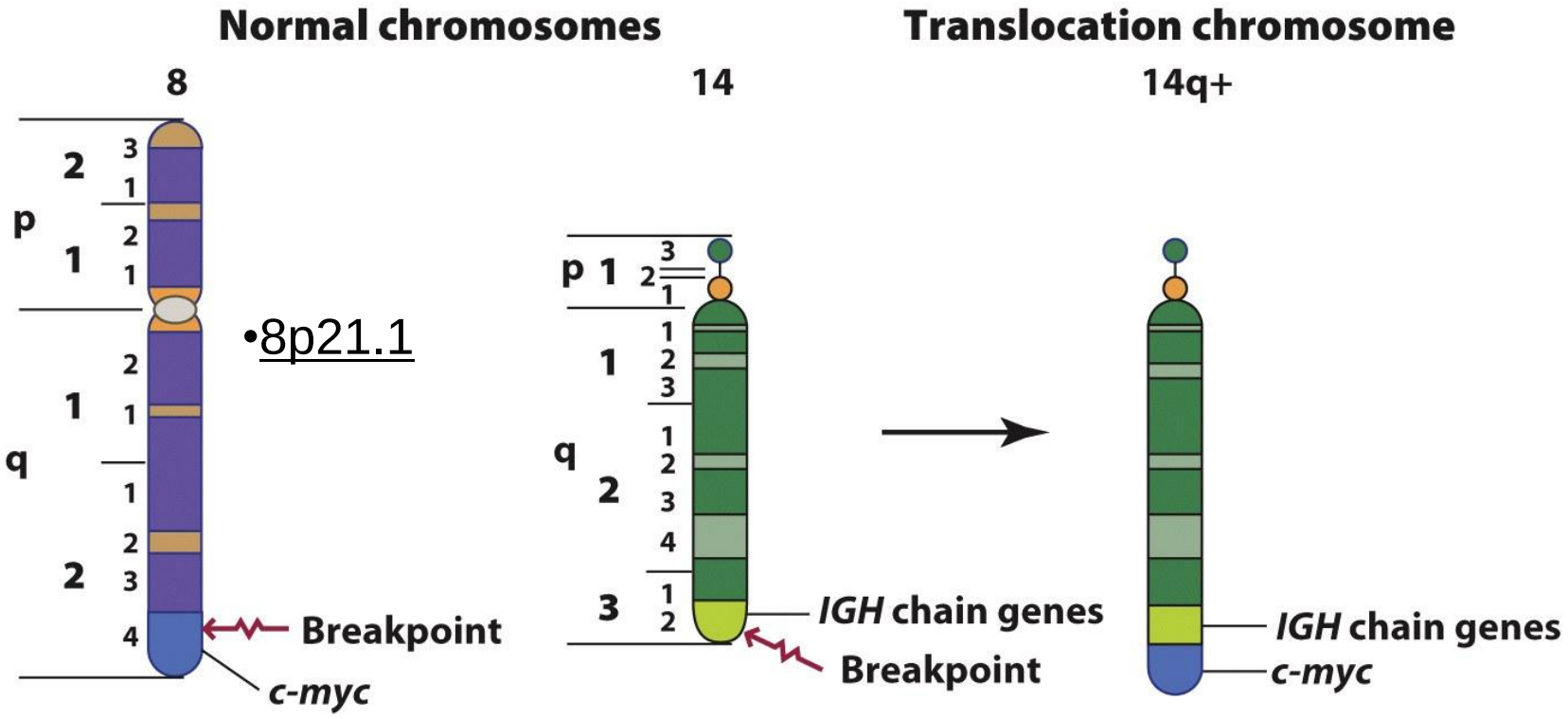
Chromosomal Rearrangements: Burkitt's Lymphoma

- Burkitt's lymphoma is associated with **reciprocal translocations** involving **chromosome 8** and a chromosome carrying an **immunoglobulin gene (2, 14, or 22)**.

- The translocations juxtapose *c-myc* to the genes for the immunoglobulin genes, causing overexpression of *c-myc* in B cells.

- The *c-myc* gene encodes a transcription factor that activates genes for cell division.

A Reciprocal Translocation Involved in Burkitt's Lymphoma



MOST FREQUENT CLONAL CHROMOSOME ABNORMALITIES IN HEMATOLOGIC MALIGNANCIES

DIAGNOSIS:	ABNORMALITY:
CML, ALL	t(9;22)(q34;q11.2)
AML	t(8;21)(q22;q22)
APL	t(15;17)(q22;q12~21)
AML with EO	inv(16)(p13q22)
MDS /AML	5q-, -7, 7q-,+8, 20q-
CLL	del(13q), +12
ALL	t(1;19)(q23;p13)
	t(4;11)(q21;q23)
Burkitt's Lymphoma	t(8;14)(q24;q32)
Follicular Lymphoma	t(14;18)(q32;q21)

Chromosomal Rearrangements or Translocations

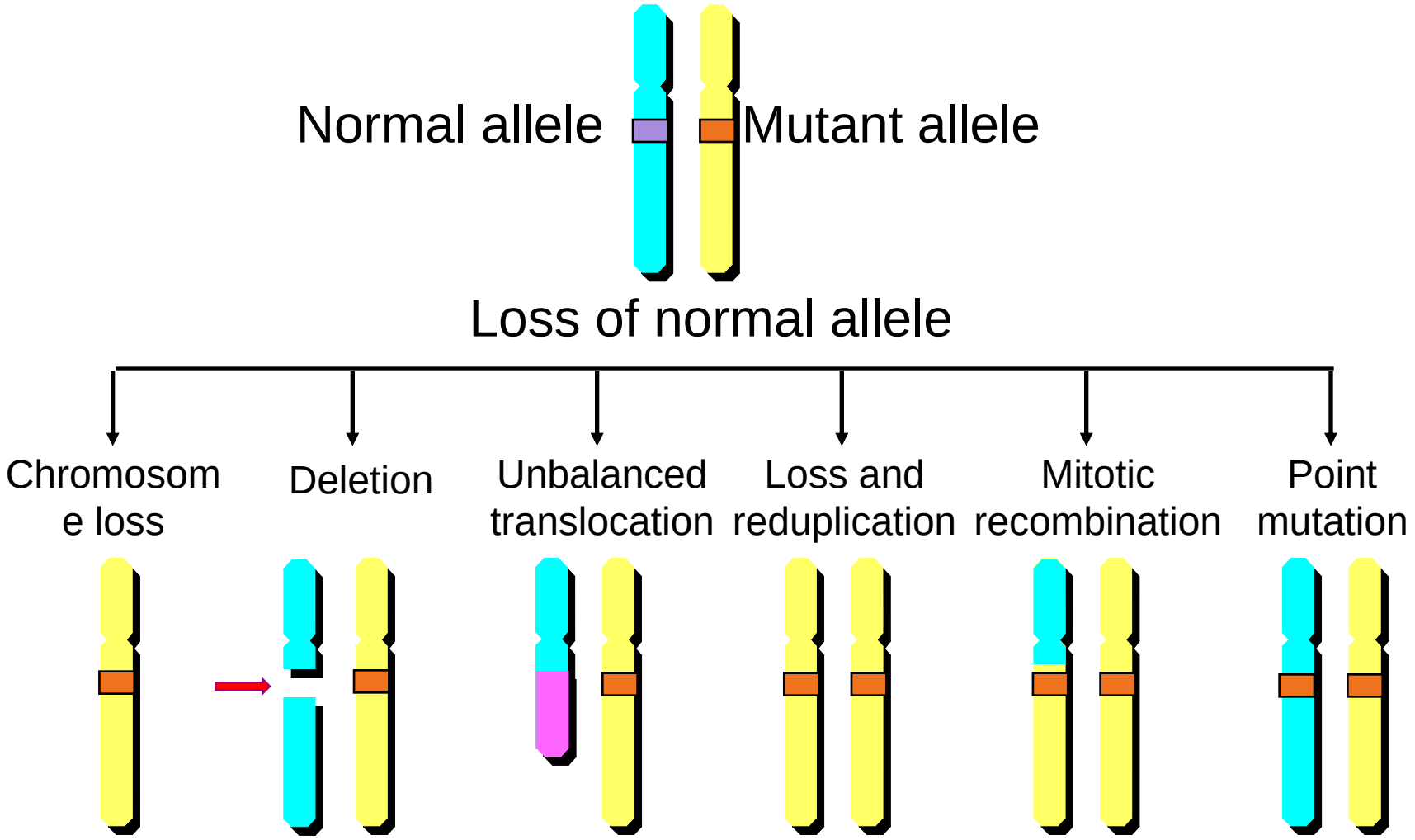
Neoplasm	Translocation	Proto-oncogene
Burkitt lymphoma	t(8;14) 80% of cases t(8;22) 15% of cases t(2;8) 5% of cases	c-myc[1]
Chronic myelogenous leukemia	t(9;22) 90-95% of cases	bcr-abl[2]
Acute lymphocytic leukemia	t(9;22) 10-15% of cases	bcr-abl[2]

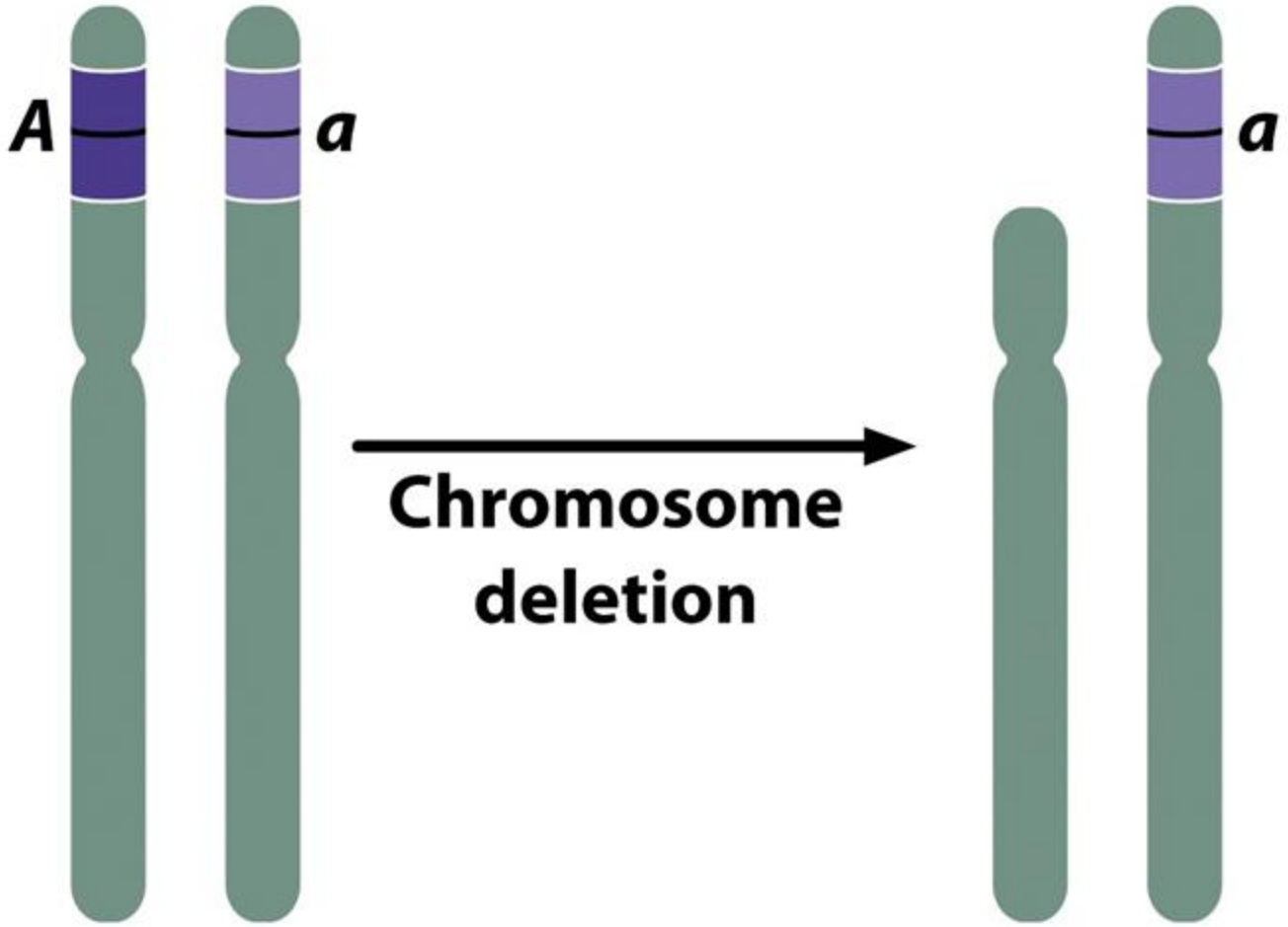
- [1]c-myc is translocated to the IgG locus, which results in its activated expression
- [2]bcr-abl fusion protein is produced, which results in a constitutively active abl kinase

Examples of Chromosomal Regions That Show Loss of Heterozygosity in Tumors

Chormosome Region	Disorder(s)	Associated TSG
lq	Breast carcinoma	Unknown
3p	Small~celllung carcinoma	Unknown
5q	Familial polyposis coli; colorectal carcinoma	MCC
11 p	Wilms tumor; rhabdomyosarcoma	WTl
13q	Retinoblastoma; breast carcinoma; osteosarcomas	RB 1
17p	Colorectal carcinoma; breast cancer	TP53
18q	Colorectal carcinoma	DCC
22	Neurofibromatosis, type 2	Unknown

Mechanisms Leading to Loss of Heterozygosity





Conclusion: People heterozygous for a tumor-suppressor gene are predisposed to cancer.

Amplifications

- Seen only in cancer cells
  - 5 to 100-fold multiplication of a small region of a chromosome
- “Amplicons”
  - contain one or more genes that enhance

Checkpoints in Tumor Cells

- In tumor cells, cell cycle checkpoints are often deregulated due to genetic defects in the machinery that **alternately raises and lowers the abundance of the cyclin/CDK complexes**.

- **These mutations may be:**
  - in the genes encoding the cyclins or CDKs,
  - in genes encoding the proteins that respond to specific cyclin/CDK complexes
  - in genes encoding proteins that regulate the abundance of these complexes.

Oncogenes and Tumor-Suppressor Genes

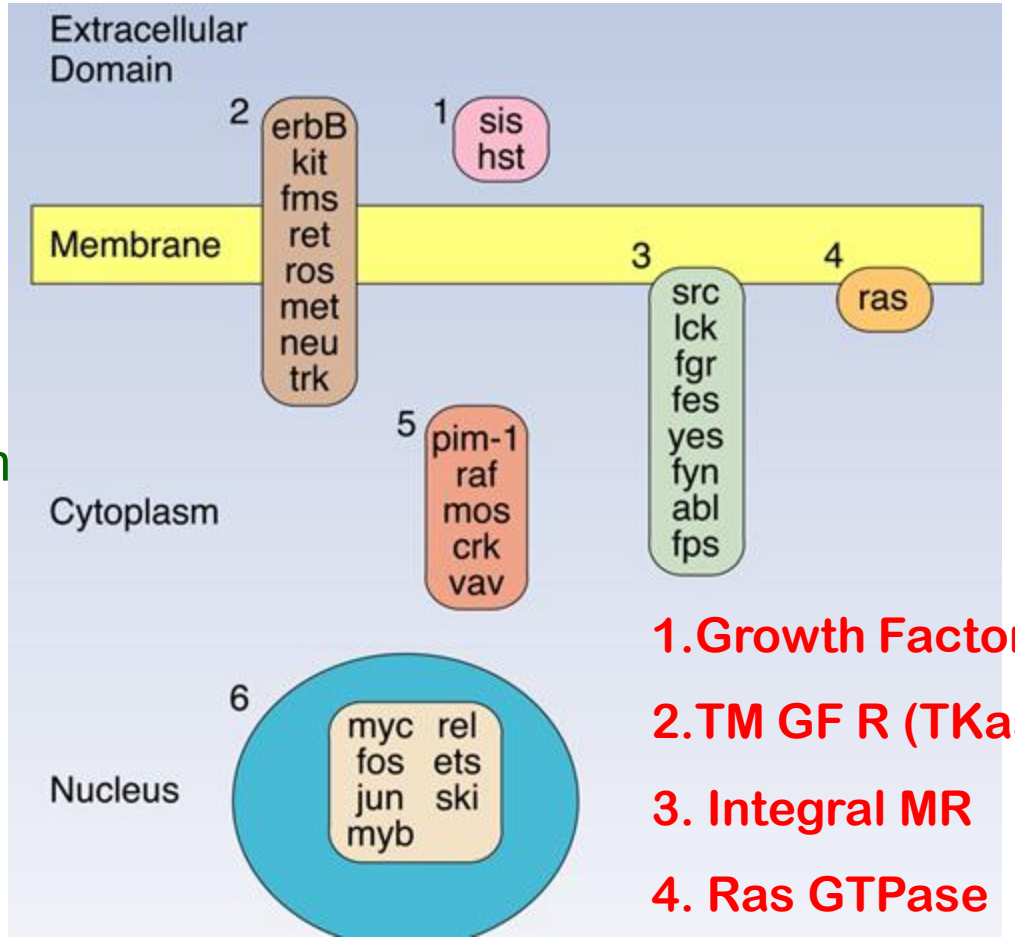
- **Oncogene:** dominant-acting stimulatory genes that cause cancer

- **Proto-oncogenes:** responsible for basic cellular functions in normal cells; when mutated, they become oncogenes.

- **Tumor-Suppressor Genes:** Inhibit cancer and recessive acting; when mutated, normal cells become cancerous.

Genetic Pathways to Cancer

Cancers develop through an accumulation of **somatic** (**not a single**) **mutations** in **proto-oncogenes** and **tumor suppressor genes.**

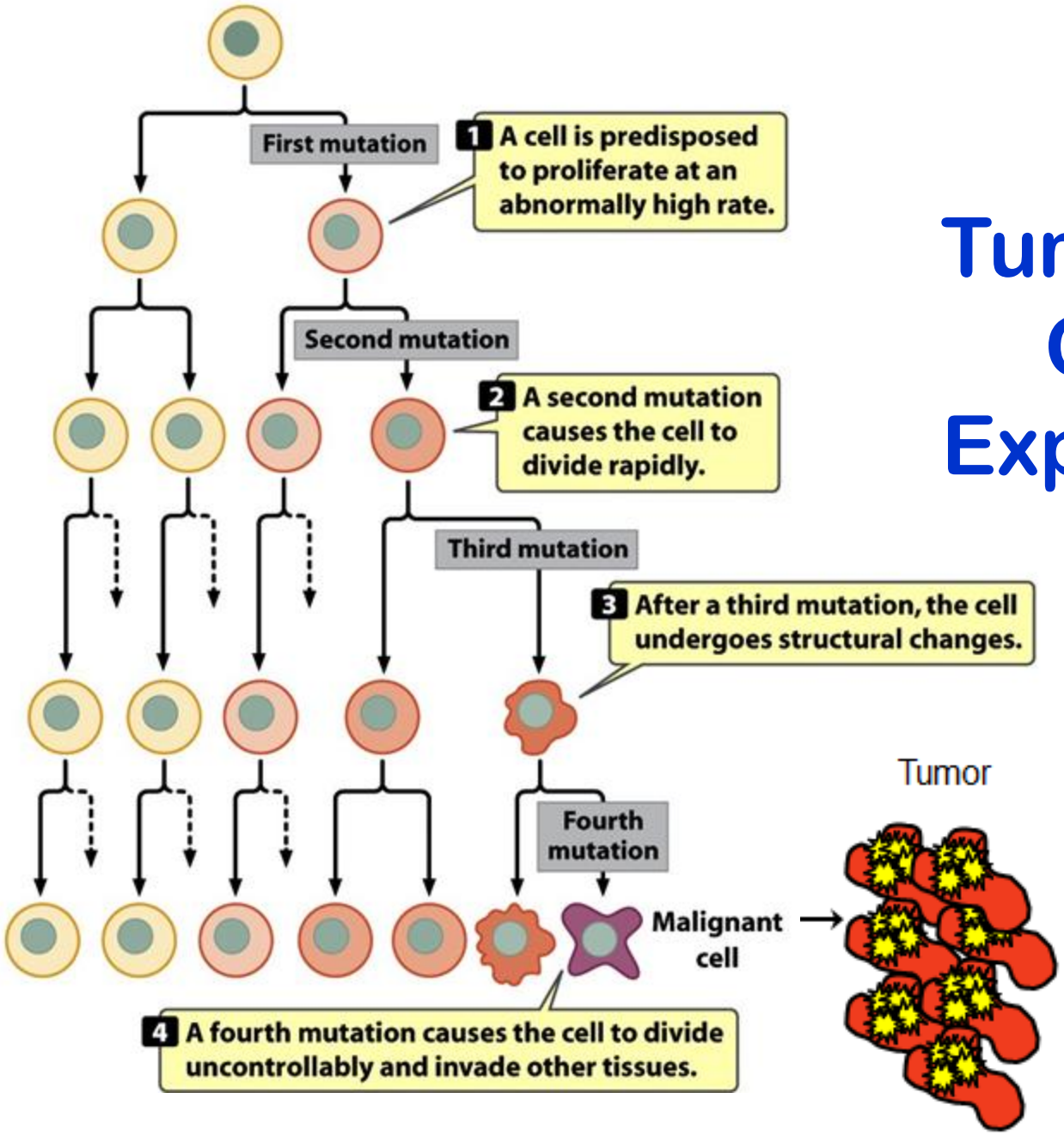


1. Growth Factors
2. TM GF R (TKase)
3. Integral MR
4. Ras GTPase
5. Cytoplasmic Oncogenes
6. Nuclear Oncogene

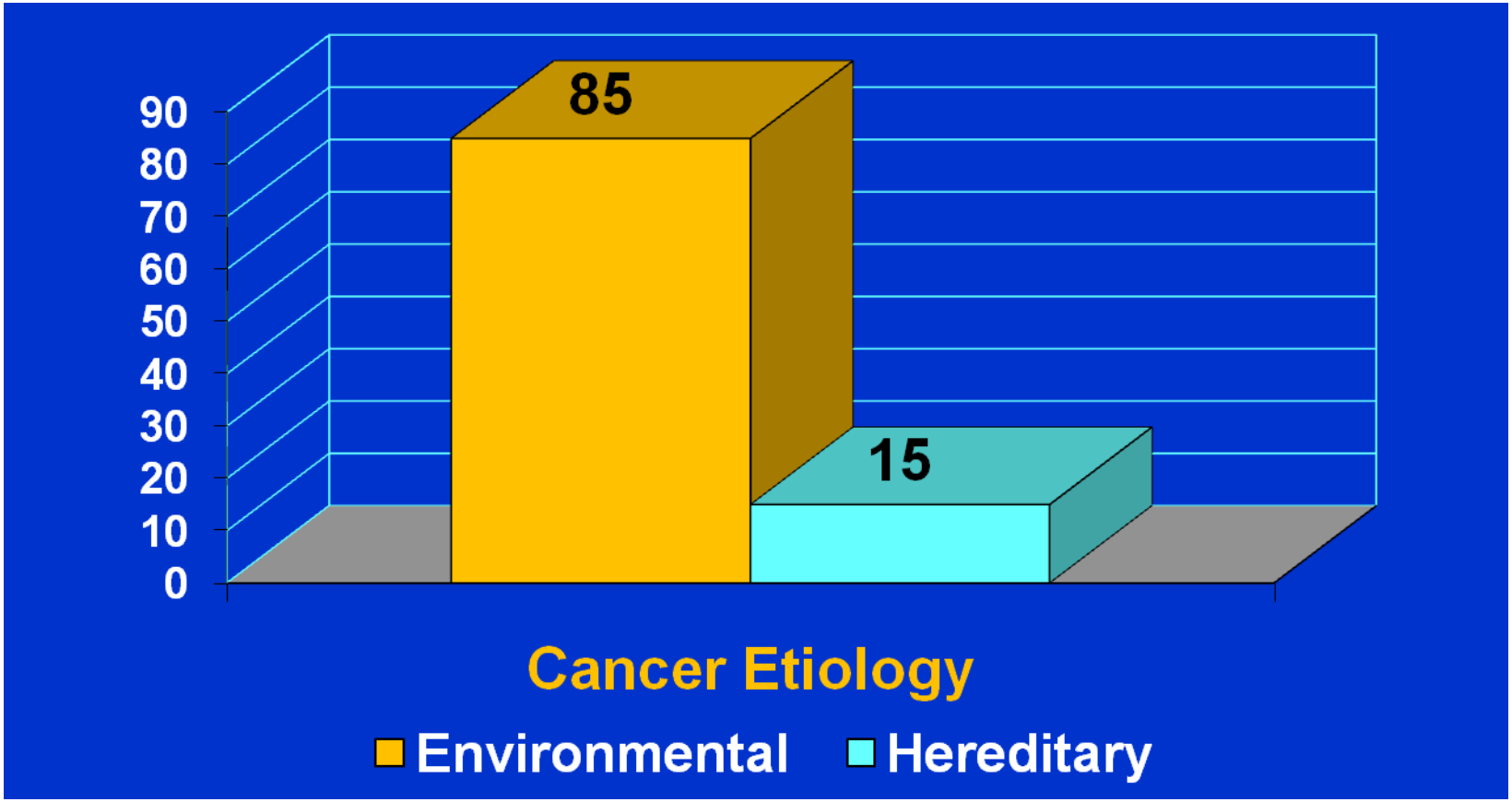
Multiple Mutations in Cancer

- Most malignant tumors cannot be attributed to mutation of a single gene.
- Tumor formation, growth, and metastasis depend on the accumulation of mutations in several different genes.
- The genetic pathways to cancer are diverse and complex.
- Changes in DNA Methylation Are Often Associated with Cancer

Tumors Are Clonal Expansions



Environmental *vs.* Hereditary Cancer



Familial Clustering of Cancer

- Epidemiological studies show an increased relative risk of cancer in individuals with a family history of cancer

- This is probably due to a mixture of rare highly penetrant genes, commoner lower penetrance genes and environmental effects

Inherited Cancer Genes

- Neurofibromatosis type-1
- P53 gene
- Familial Polyposis Gene (APC)
- Hereditary nonpolyposis colon cancer (HNCC)
- Breast Cancer Genes (BRCAI, BRCA2)
- P16 Familial Melanoma
- RET proto-oncogene and multiple endocrine neoplasia

SOLID TUMORS SARCOMAS

- In addition to leukemias and lymphomas some sarcomas also have specific chromosomal abnormalities

- One example is t(11;22) seen in Ewing's sarcoma in which the DNA binding domain of a transcription factor FLI1 is fused with the transactivation domain of EWSR1 gene

RECURRENT ABNORMALITIES EPITHELIAL TUMORS

- Small cell ca of the lung del(3)(p14-p24)
- Wilm's tumor del(11)(p13)
- Breast Her-2/neu amplification
- Mostly multiple abnormalities

Ovarian Cancer

- 2 cytogenetic pathways
  - 1: +7,+8q and +12
  - 2: 6q- and 1q-

- karyotypic evolution

- CGH reveal multiple changes in the malignant and fewer changes in borderline tumors

Uterine leiomyomas and leiomyosarcomas

- Benign tumors such as leiomyomas also show recurrent chromosomal abnormalities such as t(12;14) and deletion of 7q
- 40% of leiomyomas show abnormal karyotypes
- Leiomyosarcomas show complex chromosomal rearrangements

LOSS

- **13q (59%)**
- **10q(59%)**
- **2q(35%)**
- **16q(29%)**

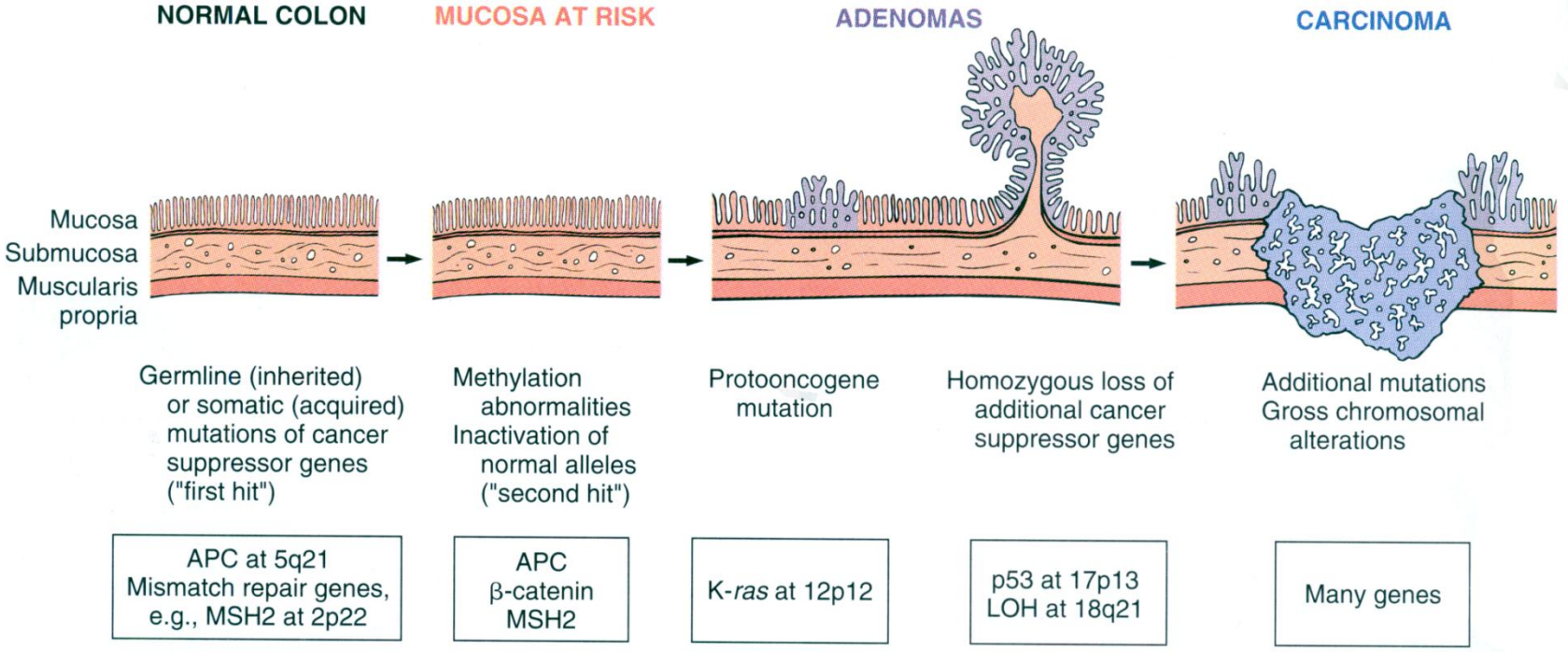
GAIN

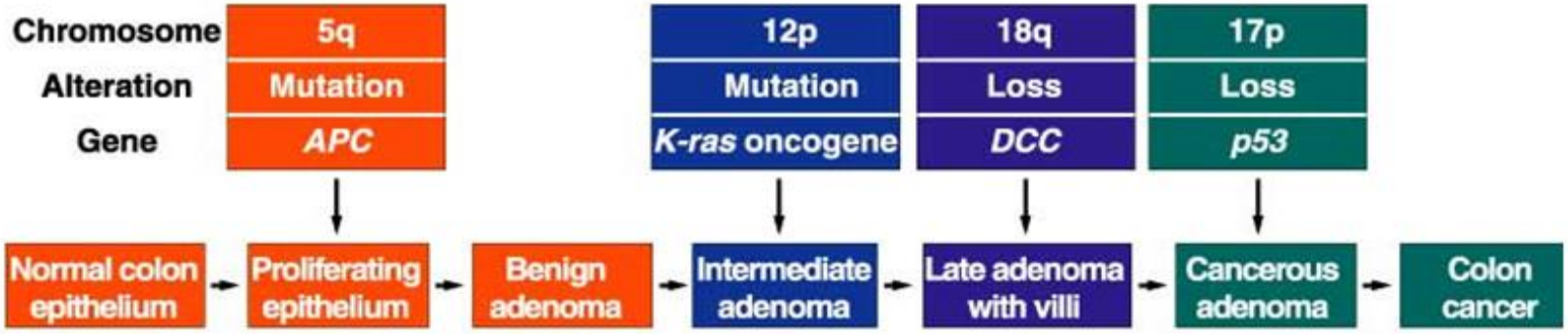
- **5p(35%)**
- **6p amplification**
- **17p amplification**

The Familial Polyposis Gene (A PC),

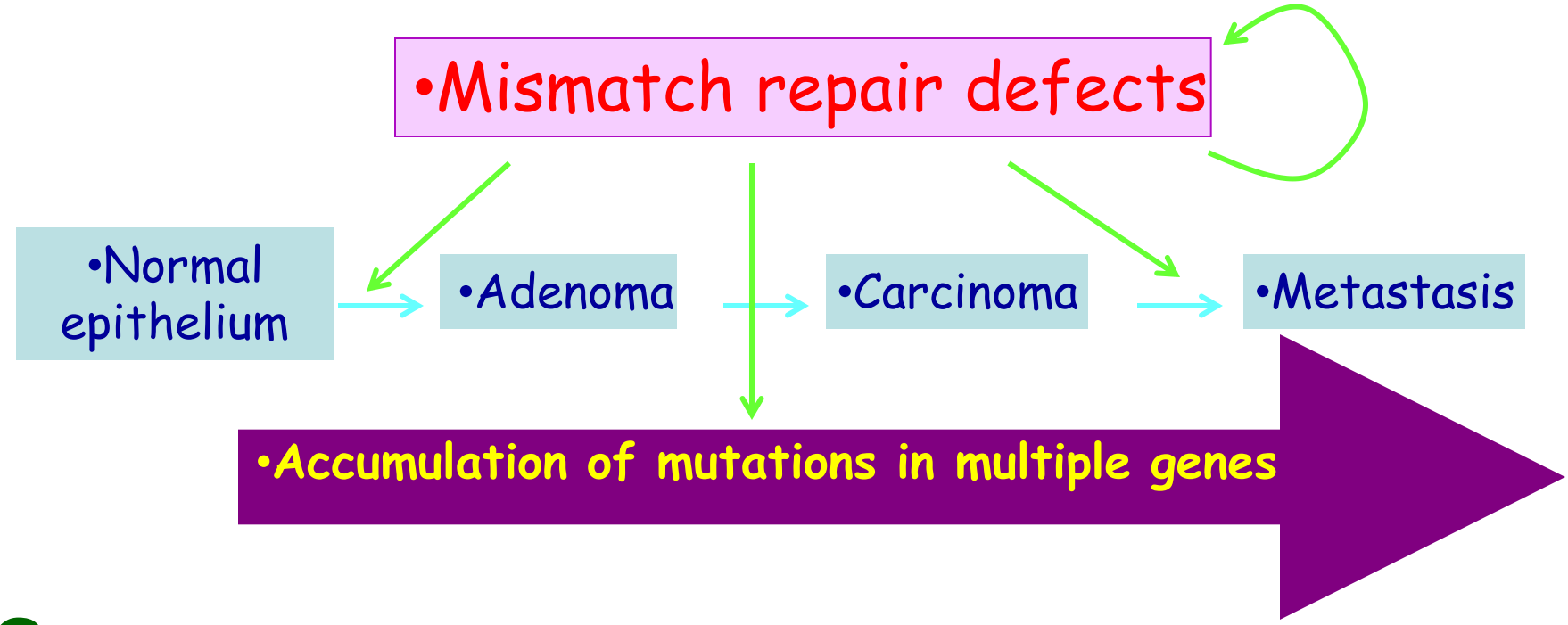
- The familial polyposis gene (APC), which strikingly predisposes to colon cancer, was ultimately identified by mutations in patients.
- The inherited gene is also involved in the great majority of sporadic cases of colon polyps and colon cancer.
- This tumor suppressor gene has been shown to function as a major regulator of the Wnt pathway, a signaling system that is well characterized both biochemically and developmentally

Morphological and Molecular Changes in Adenoma and Carcinoma Sequence





Cancer and repair: HNPCC



Oncogenes:

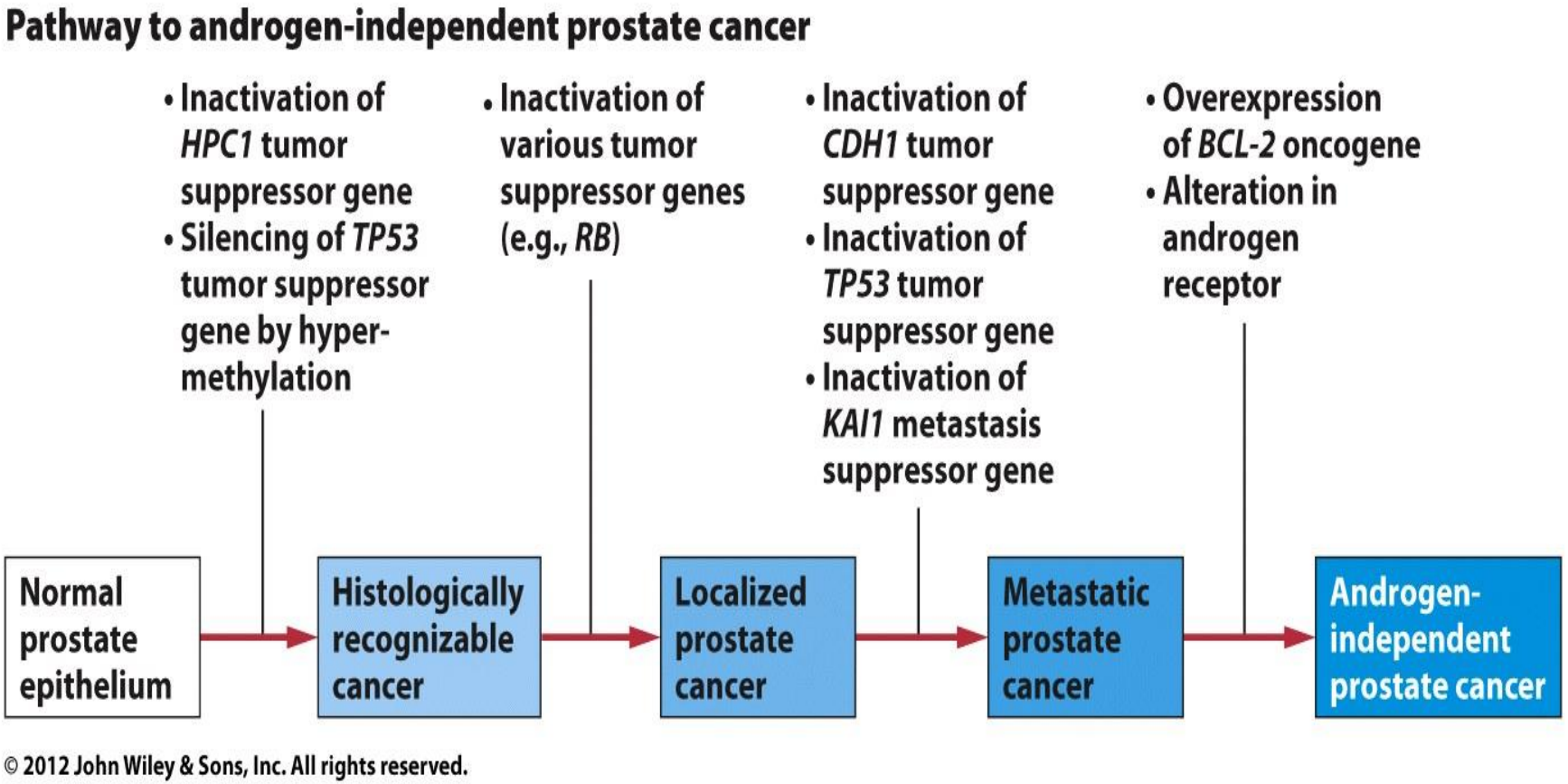
gain of function)

=increased proliferation, etc.

Tumor supressors:

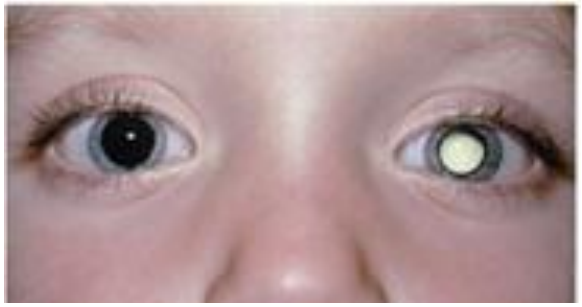
(loss of function)

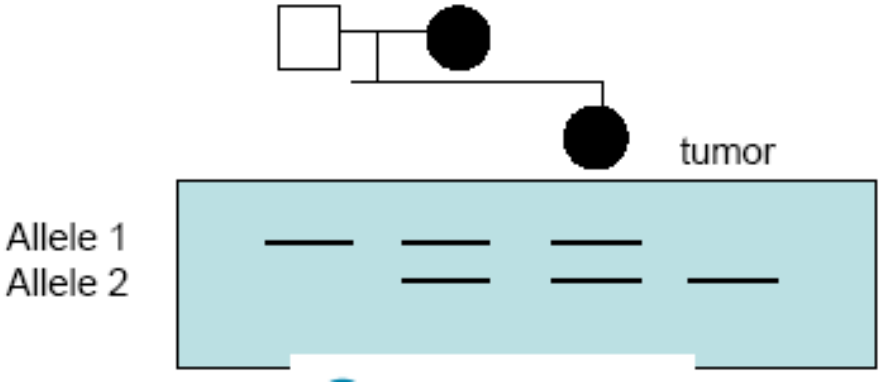
Pathway to Androgen-Independent Prostate Cancer



Retinoblastoma

- Deletions 13q14 or mutations of the RB1 gene
- Cell cycle regulatory protein that inhibits G1 to S phase transition
- 80% de novo mutations
- High rate of loss of heterozygosity in tumor tissue





The Development of Hereditary Cancer

In hereditary cancer, one damaged gene is inherited

Nonheritable vs Heritable Retinoblastoma

Feature	Nonheritable	Heritable
Tumor	Unilateral	Usually bilateral
Family history	None	20% of cases
Average age at dx	~2 years	<1 year
Increased risk of second primaries	No	Osteosarcoma, other sarcomas, melanoma, others

- Affects 1 in 20, 000 live-born infants
- Males and Females equally affected

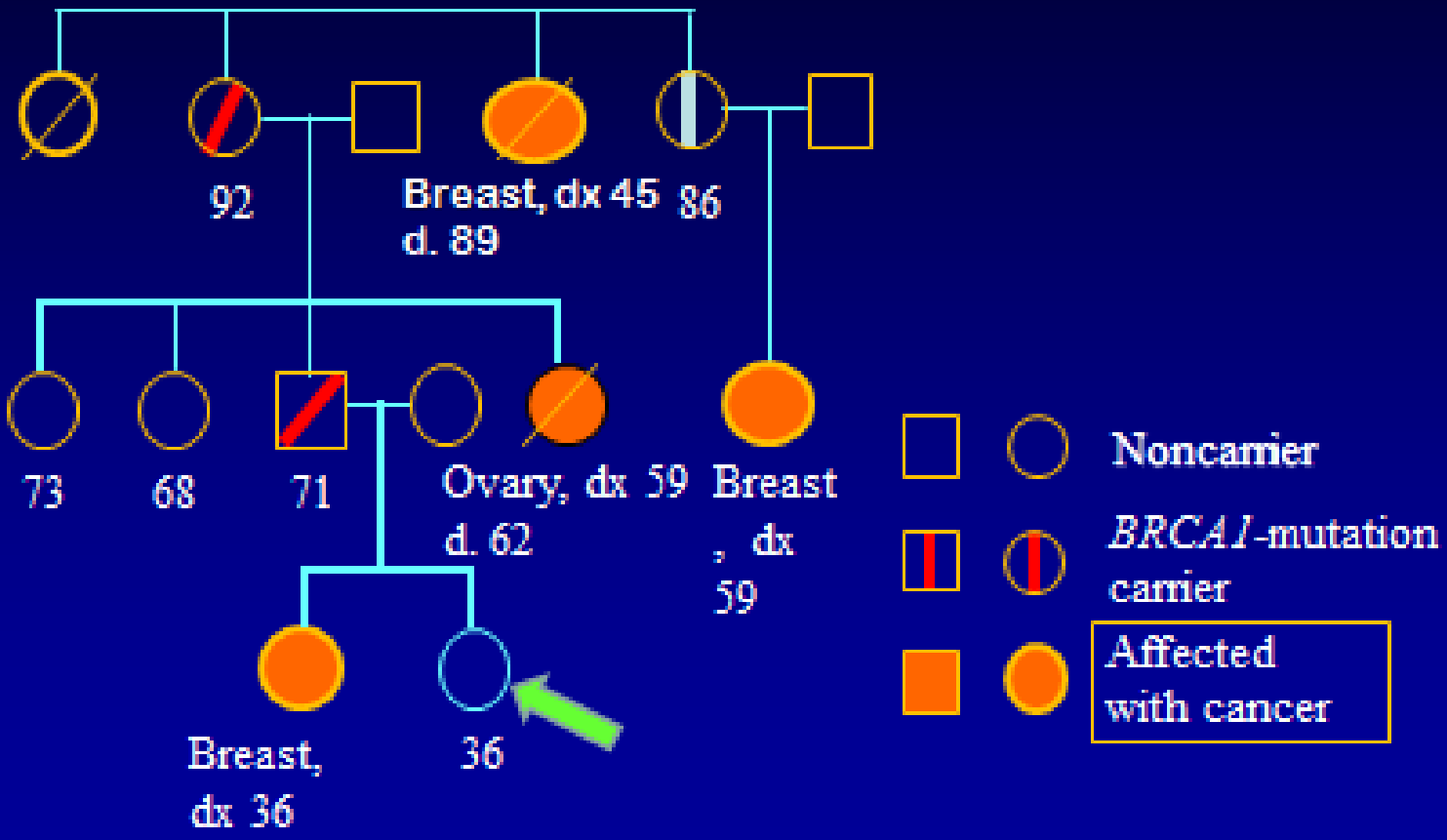
Breast Cancer
BRCA1 and BRCA2

- High (60-80%) lifetime risk of breast cancer, both genes.
- Increased ovarian cancer risk (BRCA1>BRCA2)
- Surveillance for both indicated; mammography, MRI, Ultrasound
- Consider prophylactic surgery

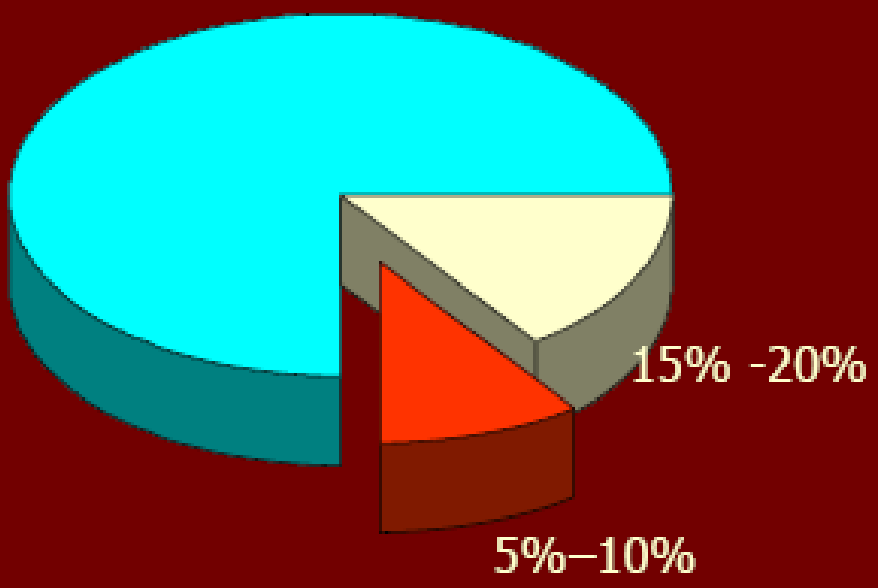
The Inherited Breast Cancer Genes: BRCA 1 and BRCA2

- Mutations in BRCA 1 and BRCA2 are responsible for a large proportion of inherited breast cancer cases.
- These mutations usually result in a truncated protein product and loss of function.
- The protein products of both of these genes interact with RAD51, a DNA repair protein.

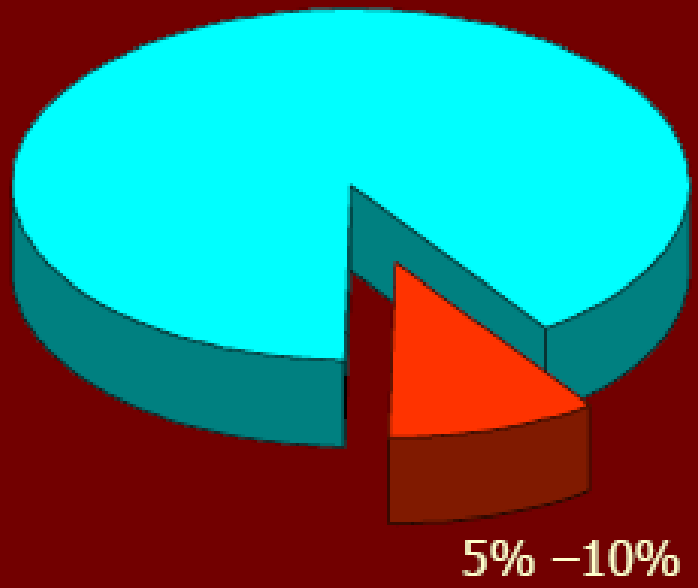
BRCA1-Linked Hereditary Breast and Ovarian Cancer



How much of breast cancer is hereditary?



Breast Cancer



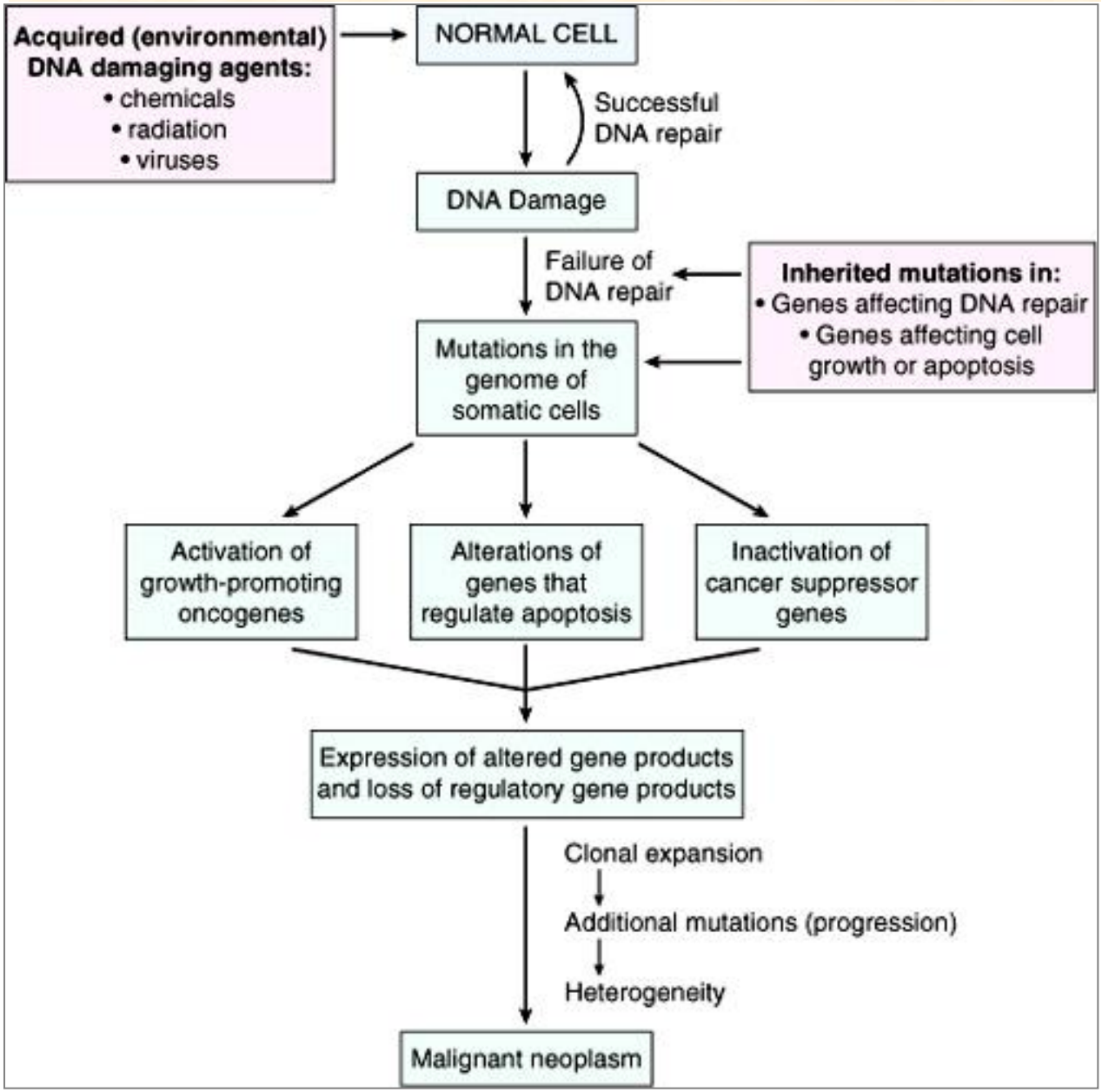
Ovarian Cancer

Sporadic

Family clusters

Hereditary

SUMMARY: General Etiology and Pathogenesis



Hallmarks of Pathways to Malignant Cancer

1. *Cancer cells acquire self-sufficiency in the signaling processes that stimulate division and growth.*

2. *Cancer cells are abnormally insensitive to signals that inhibit growth.*

3. *Cancer cells can evade programmed cell death (apoptosis).*

4. *Cancer cells acquire limitless replicate potential.*

5. *Cancer cells develop ways to grow themselves.*

6. *Cancer cells acquire the ability to invade other tissues and colonize them.*