Histopathology

Lecture 3

Molecular Basis of Cancer

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CARCINOGENESIS

Overview: For a cell to change from a normal cell to a malignant cell, it must follow several steps.

1- Acquire self-sufficiency in growth signals and ignore growth inhibitory signals.
2- Evade apoptosis, since apoptosis is the body's mechanism to rid itself of cells with genetic damage so they cannot propagate that damage.
3- Acquire defects in DNA repair.
4- Acquire the ability to divide an unlimited number of times.
5- Promote angiogenesis.
6- Invade surrounding tissue, passing through the basement membrane and spreading to distant organs (i.e., metastasize).

Process of carcinogenesis

■ The cell acquires mutations, which are nonlethal, so the cell can survive to divide and thus propagate the mutations. Mutations are acquired through damage caused by initiators. Promoters cause cell growth through promotion of the cell cycle and thus cause the propagation of mutations induced by initiators. Neither an initiator nor a promoter acting on its own can cause neoplasia; both must act on the cells.

Genes most commonly affected during carcinogenesis

■ Proto-oncogenes: Proto-oncogenes are genes commonly used during normal growth and development; without control, they have the potential to produce neoplasms through their uncontrolled expression. Oncogenes are genes that have made the transition and are now capable of producing neoplasms. Most commonly, oncogenes cause unregulated cell growth through promotion of cellular division, which results in further mutations.

■ Tumor suppressor genes: Genes that function to help control cell growth; their loss thus results in uncontrolled cell growth through loss of regulation of division.

■ Apoptosis genes.

■ DNA repair genes.

Important points regarding genes involved with carcinogenesis

■ No one mutation will result in a malignant neoplasm; malignant neoplasms result from the survival of cells that have accumulated multiple mutations.

■ Conversion of one of the two allelic genes from a proto- oncogene to an oncogene is sufficient to promote neoplasia. However, it requires loss of both tumor suppressor genes to promote neoplasia, as one of the two genes is sufficient to produce enough product to inhibit neoplasia.

Methods of conversion of proto-oncogene to oncogene

■ Overexpression of the gene.

■ Amplification of the gene.

■ Point mutation in the gene.

■ Translocation of the gene to another region with resultant overexpression of the gene, or resultant production of protein with oncogenic activity.

Role of oncogenes

Overview: Once converted from proto-oncogenes, oncogenes function by synthesizing growth factors, growth factor receptors, signal-transducing proteins, and nuclear transcription factors, or by promoting loss of regulation of cyclins and cyclin- dependent kinases.

1. **Synthesize growth factors** to which the neoplastic cell is also responsive. For example, glioblastomas produce platelet -derived growth factor (PDGF).

2. **Synthesize growth factor receptors**. For example

- RET receptor for glial cell line-derived neurotrophic factor—in medullary and papillary thyroid carcinoma (multiple endocrine neoplasia MEN syndrome).
- ERB B1, an epidermal growth factor (EGF) receptor, is overexpressed in squamous cell carcinoma of the lung.
- ERB B2,an EGF receptor, is overexpressed in 25% of breast carcinomas.

Gene	*Associated Neoplasm(s)*
RET	*Medullary thyroid carcinoma, pheochromocytoma*

3. **Synthesize signal-transducing proteins**: An example of a specific gene is the RAS gene.

• Incidence of mutations in RAS gene: Mutations of the RAS gene are in 30% of all malignant neoplasms and in 90% of pancreatic adenocarcinomas.

• Role of normal RAS gene: The RAS gene codes for protein that is associated with a growth factor receptor.

- *The main members of the RAS gene family— KRAS, HRAS, and NRAS—encode proteins that have a pivotal role in cell signaling. When RAS genes are mutated, cells grow uncontrollably and evade death signals. RAS mutations also make cells resistant to most available cancer therapies.*
- *A GTPase is an enzyme that facilitates the conversion of guanosine triphosphate (GTP) to guanosine diphosphate (GDP). It plays a crucial role in regulating various cellular processes such as cell growth, differentiation, migration.*

• Effects of mutations in the RAS gene: The RAS protein loses its GTPase activity, so it remains activated, resulting in continual promotion of transcription.

4. **Synthesize nuclear transcription factors**: An example of a specific gene is the MYC gene.

• Neoplasms associated with mutations of the MYC gene: Burkitt lymphoma; also amplified in breast, lung, and colon cancers.

MYC gene *This gene is a proto-oncogene and encodes a nucle phosphoprotein that plays a role in cell cycle progression, apoptosis and cellular transformation.*

5. **Loss of regulation of cyclins and cyclin-dependent kinases**.

Mutations in tumor suppressor genes

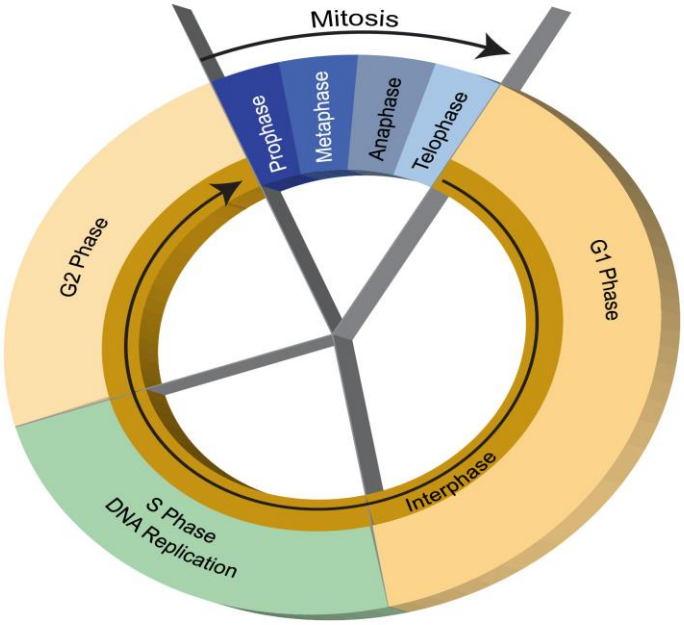
Important point: The two-hit hypothesis implies that with many hereditary neoplasms a tumor suppressor gene is involved. The protein product from one gene is enough to prevent neoplasms from developing; however, individuals born with a mutation of one gene are one step closer to the development of a neoplasm than those born with two normal genes.

Select tumor suppressor genes: Within neoplasms,the most common tumor suppressor genes with mutations are **retinoblastoma** and **p53**.

1. **Retinoblastoma (RB) gene**
   • **Associated neoplasms:** Familial retinoblastoma and osteosarcoma; breast cancer and small cell lung carcinoma.
   • **Role of normal RB gene**: Retinoblastoma binds E2F transcription factor, which is needed for the cell to move from the G1* phase of the cell cycle to the S* phase. When retinoblastoma is phosphorylated, the E2F is released and the cell moves through the cell cycle.
   • **Effect of mutations of RB gene:** Can affect retinoblastoma or the proteins that phosphorylate retinoblastoma, resulting in hyperphosphorylation of RB.
2. **p53 gene (Figure 1)**
   • **Incidence:** Mutations of the p53 gene are found in more than 70% of tumors.
   • **Role of normal p53 gene**
   - Activated by DNA damage.
   - p53 arrests the cell cycle by transcription of CDK1 (p21), which inhibits cyclin/CDK complexes and prevents phosphorylation of RB.
   - p53 promotes production of GADD45, which helps repair the cell.

-The BAX gene *(Bcl-2 Associated X-protein).*
*- **CDK1** Cyclin-dependent kinase1 :is involved in the control of events such as DNA replication and segregation, mRNA transcription, DNA repair.*
GADD45 *Growth Arrest and DNA Damage-inducible*

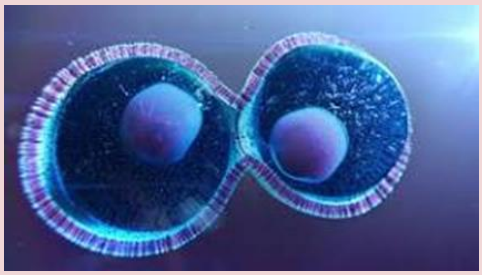
- If cellular damage is not repaired, p53 promotes induction of the Bax gene, which in turn promotes apoptosis.



*** Cell Cycle**

Cell Cycle:

*The cell cycle is a four-stage process in which the cell increases in size (**gap 1, or G1, stage**), copies its DNA (**synthesis, or S, stage**), prepares to divide (**gap 2, or G2, stage**), and divides (**mitosis, or M, stage**).*



BAX gene functions as an apoptotic activator
PUMA (p53 upregulated modulator of apoptosis).
The c-Myc gene serves as a "master regulator" of cellular metabolism and proliferation.
telomerase reverse transcriptase (TERT) act as a transcription co-factor to regulate gene expression.

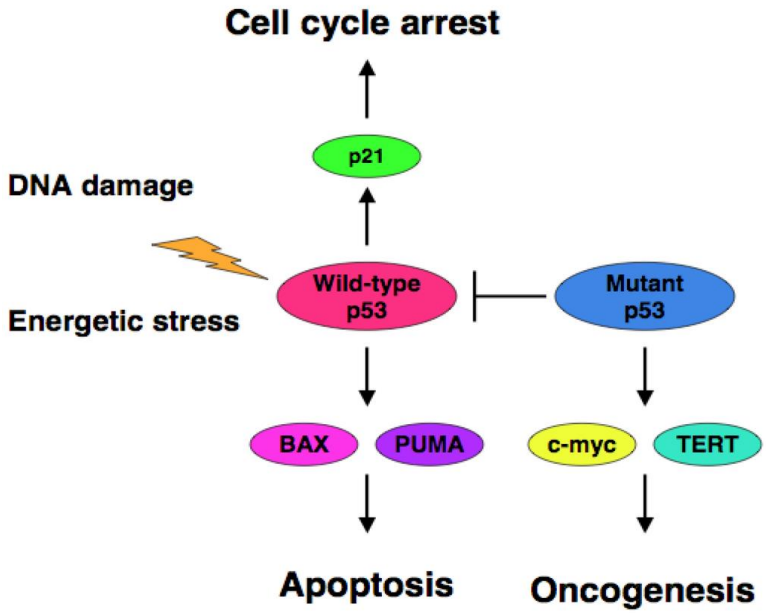


Figure 1. Dominant-negative effect of mutant p53 on wild-type p53. Pro-apoptotic function of p53 is significantly inhibited by certain p53 mutants which induce malignant transformation through up-regulation of c-myc and TERT.