Genetics of Cancer

PRINCIPAL POINTS

- Progression through the cell cycle is tightly controlled by the activities of many genes. Checkpoints at key points determine whether a cell has DNA damage or has problems with its cell-cycle machinery and only permits normal cells to continue. The key molecules used at these checkpoints are cyclins and cyclin-dependent kinases (Cdks). In addition, healthy cells grow and divide only when the balance of stimulatory and inhibitory signals received from outside the cell favor cell proliferation. A cancerous cell does not respond to the usual signals and divides without constraints.

- Mutant forms of three classes of genes—proto-oncogenes, tumor suppressor genes, and mutator genes—have the potential to contribute to the transformation of a cell to a cancerous state. The products of proto-oncogenes normally stimulate cell proliferation, the products of tumor suppressor genes normally inhibit cell proliferation, and the products of mutator genes are involved in DNA replication and repair.

- Some DNA viruses and RNA viruses cause cancers. All RNA tumor-causing viruses are retroviruses—viruses that replicate via a DNA intermediate—but not all retroviruses cause cancer. When a retrovirus infects a cell, the RNA genome is released from the viral particle, and through the action of reverse transcriptase a cDNA copy of the genome, called the proviral DNA, is synthesized. The proviral DNA integrates into the genome of the host cell. Then, using host transcriptional machinery, viral genes are transcribed, and full-length viral RNAs are produced. Progeny viruses are assembled and exit the cell, where they can infect other cells.

- Tumor induction can occur after retrovirus infection because of the activity of a viral oncogene encoded in that retroviral genome. Retroviruses carrying an oncogene are known as transducing retroviruses.

- Normal animal cells contain genes with DNA sequences that are similar to those of the viral oncogenes. These cellular genes are proto-oncogenes. When a proto-oncogene is mutated to produce a cellular oncogene (c-onc), it induces tumor formation.

- The two-hit mutation model for cancer states that two mutational events are necessary for cancer to develop, one in each allele of a cancer-causing gene. In familial
During development, specific tissues and organs arise by genetically programmed cell division and differentiation.

- Sometimes cells deviate, giving rise to tumors or neoplasms (new growth).

Transformation is the process by which a cell loses its ability to remain constrained in its growth properties. (Not like uptake of DNA)

Benign means if transformed cells stay in a single mass (tumor), normally not life threatening. Brain tumors, however, will damage other cells.

Malignant means cells of tumor can invade and disrupt surrounding tissues. 
- Called a cancer
- Spreading of malignant cells throughout the body called metastasis
Example of Tumor

A mammogram showing the presence of a tumor.
Metastasized Tumor in the human liver

Light micrograph of human liver, showing a metastasized tumor, in this case a melanosarcoma (in red).

\[
\text{Melanosarcoma} \quad \Rightarrow \quad \text{Malignant Neoplasm derived from tissue of mesodermal origin}
\]

Malignancy:
Result in death because of damage to critical organs, starvation, secondary infection, metabolic problems, secondary malignancies, and/or hemorrhage.
Relationship of the Cell Cycle to Cancer.

After a series of divisions (cell cycles), the progeny cells begin to express genes that are specific for the tissue.

* = cell differentiation *

Fully functional cell in a tissue—can no longer divide—are known as terminally differentiated cells (eventually replaced).

Derived from stem cells => small fraction of cells in the tissue that are capable of self-renewal.

*Malignant neoplasm fail to express fully the genetic programs that regulate terminal differentiation*
General events for regulation of cell division in normal cells. (a) When a growth factor binds to its cell membrane receptor, it acts as a signal to stimulate cell growth. To do that, the signal is transduced into the cell and relayed to the nucleus, activating the expression of a gene or genes that encode a protein or proteins required for the stimulation of cell division. (b) When a growth-inhibiting factor binds to its cell membrane receptor, it acts as a signal to inhibit cell growth. In this case the signal is transduced into the cell and relayed to the nucleus, activating the expression of a gene or genes that encode a protein or proteins required for the inhibition of cell division.

### a) Growth factor–induced stimulation of cell division

- Growth factors
- Receptor
- Cell membrane
- Signal transduced into cell and relayed to nucleus
- Transcription factor
- DNA
- mRNA
- Protein that stimulates cell division

### b) Growth-inhibiting factor–induced inhibition of cell division

- Growth-inhibiting factors
- Receptor
- Signal transduced into cell and relayed to nucleus
- Transcription factor
- DNA
- mRNA
- Protein that inhibits cell division

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**Figure 10.5**

Control of a normal cell through the cell cycle.
The two-hit mutation Model for Cancer

Current understanding of Cancer results from an accumulation of mutations in a particular class of genes over a period of time.

Two general types of Cancers

Familial (hereditary) cancers => run in families

Sporadic (nonhereditary) cancers => not inherited

More frequent than hereditary cancer.

Two-hit model => relationship of mutations to cancer.

Study of retinoblastoma: (birth to age 4)

Most common eye tumor in children => 90% destroyed if discovered early enough.

Two forms

Sporadic retinoblastoma

60%

No history

Unilateral tumor

One eye

Hereditary retinoblastoma

40%

Inherited

Multiple tumors involving both eyes

... Figure 18.1...

An eye tumor in a patient with retinoblastoma.
Knudson's two-hit mutational model—among a few cancers where one gene is critical for its development.

**Most cancers develop in a multistep process.**

Knudson’s two-hit mutation model to explain (a) sporadic retinoblastoma by two independent mutations of the retinoblastoma (RB) gene and (b) hereditary retinoblastoma by a single mutation of the wild-type retinoblastoma gene in retinal cells in which a mutant RB was inherited through the germ line.

- **Sporadic retinoblastoma**
  - Normal cell
  - RB+/RB+ — normal cell growth
  - RB/RB — loss of growth control
  - Eye tumor

- **Hereditary retinoblastoma**
  - Retina cell at birth
  - RB/RB+ — inherited RB mutation; normal cell growth
  - RB/RB — loss of growth control
  - Eye tumor

**Occurrence of a single higher than the occurrence of a mutation in each gene locus**

In sporadic, retinoblastoma will have mostly unilateral tumors. Although tumors will be late onset.

**Early onset & multiple bilateral tumors**
Genes and Cancer

Three classes of genes have a high frequency of mutations

Oncogenes $\rightarrow$ products normally stimulate cell proliferation

Tumor suppressor genes $\rightarrow$ products normally inhibit cell proliferation

Mutator genes $\rightarrow$ products needed for fidelity of replication and maintenance of genome integrity
Oncogenes

Transformation of cells into neoplastic state can result from infection with tumor viruses \( \Rightarrow \) (RNA or DNA) \( \Rightarrow \) found widely in animal cells

RNA Tumor virus \( \Rightarrow \) different mechanism for causing cancer

DNA Tumor virus

RNA Tumor virus \( \Rightarrow \) transform cells because of the property of a gene in their viral genome \( \Rightarrow \) cell

Gene called an oncogene - promotes cell proliferation
Retroviruses & Oncogene

Retroviruses = RNA tumor virus

*Oncogenes are altered forms of the host cell's genes.*

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**Figure 12.4**
Stylized drawing of a retrovirus.

- Single-stranded RNA genome (two copies)
- Viral envelope
- Viral glycoproteins
- Icosahedral viral core
- Protein
- 10kb

Rous Sarcoma virus (RSV)
HIV
Life cycle of non-oncogenic Retrovirus

Direct their own life cycle, but do not change growth properties of the host cell

Figure 18.7

Life cycle of a nononcogenic retrovirus.
The Rous sarcoma virus (RSV) RNA genome and a suggested mechanism for the integration of the proviral DNA into the host (chicken) chromosome. (a) RSV genome RNA. (b) RSV proviral DNA produced by reverse transcriptase. (c) Circularization of the proviral DNA. (d) Staggered nicks are made in viral and cellular DNAs. (e) By recombination, the viral ends become joined to the ends of the cell’s DNA. (f) The single-stranded gaps are filled in, and a complete, double-stranded, integrated RSV provirus results.

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**a)** RSV genome RNA

**b)** RSV proviral DNA

**c)** Circular proviral DNA

**d)** Integration of viral DNA begins

**e)** Viral ends become joined to the ends of the cell’s DNA by recombination

**f)** Integration of viral DNA completed
Retroviruses do not cause cancer.

Figure 1:

(a) Schematic drawing of a cross-section through an HIV particle. Note that the capsid of this particular retrovirus is "bullet" shaped. (b) Organization of the HIV genome.

Through normal viral replication, HIV causes death of cell.

Decrease in helper T-cell population, loss of macrophages and causes the loss of a functional immune system.
RSV-oncogene has complete compliment of genes necessary for viral replication and transducing viruses retroviruses (Transduce to other cells) lack a complete compliment of viral replication genes.

**Figure 18.1**

Structures of four defective transducing viruses (not to scale). (a) Avian myeloblastosis virus (AMV) contains the v-myc oncogene, which replaces the 3' end of pol and most of env. (b) Avian defective leukemia virus (DLV) contains the v-myc oncogene, which replaces the 3' end of gag, all of pol, and the 5' end of env. (c) Feline sarcoma virus (FeSV) contains the v-fes oncogene, which replaces the 3' end of gag and all of pol and env. (d) Abelson murine leukemia virus (AbMLV) contains the v-abl oncogene, which replaces the 3' end of gag and all of pol and env.

a) Avian myeloblastosis virus (AMV) genomic RNA

- LTR
- gag (part)
- pol (part)
- myc
- env (part)

b) Avian defective leukemia virus (DLV) genomic RNA

- LTR
- gag (part)
- myc
- env (part)

3' end of pol missing
5' end of env missing

3' end of gag missing
5' end of env missing

3' end of gag missing

4) Feline sarcoma virus (FeSV) genomic RNA

- LTR
- gag (part)
- fes
- LTR

3' end of gag missing

5) Abelson murine leukemia virus (AbMLV) genomic RNA

- LTR
- gag (part)
- abl
- LTR

3' end of gag missing

*That the product of a single gene was necessary and sufficient for tumor induction and formation was a significant discovery.*
**Viral oncogene** $V$-$\text{oic}$ => cause many different cancers

$V =$ Virus gene

$\text{oic} =$ name of oncogene

$V$-$\text{oic}$ gene for RSU is $V$-src

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Transducing Retroviruses => picked up an oncogene from the genome of the cell & transferred it to another cell.

### Table 12.2 Some Transducing Retroviruses and Their Viral Oncogenes

<table>
<thead>
<tr>
<th>Oncogene</th>
<th>Retrovirus Isolate</th>
<th>$v$-$\text{oic}$ Origin</th>
<th>$v$-$\text{oic}$ Protein</th>
<th>Type of Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>src</td>
<td>Rous sarcoma virus</td>
<td>Chicken</td>
<td>pp60src</td>
<td>Sarcoma</td>
</tr>
<tr>
<td>abl</td>
<td>Abelson murine leukemia virus</td>
<td>Mouse</td>
<td>P90-P160src-abl</td>
<td>Pre-B cell leukemia</td>
</tr>
<tr>
<td>erbA</td>
<td>Avian erythroblastosis virus</td>
<td>Chicken</td>
<td>P75src-abl</td>
<td>Erythroblastosis and sarcoma</td>
</tr>
<tr>
<td>erbB</td>
<td>Avian erythroblastosis virus</td>
<td>Chicken</td>
<td>gp65src</td>
<td>Erythroblastosis and sarcoma</td>
</tr>
<tr>
<td>fms</td>
<td>McDonough (SM)-FeSV</td>
<td>Cat</td>
<td>gp180src-abl</td>
<td>Sarcoma</td>
</tr>
<tr>
<td>fos</td>
<td>FBJ (Finkel-Biskis-inkins)-MSV</td>
<td>Mouse</td>
<td>pp55src</td>
<td>Osteosarcoma</td>
</tr>
<tr>
<td>myc</td>
<td>MC29</td>
<td>Chicken</td>
<td>P100src-myc</td>
<td>Sarcoma, carcinoma, and myelocytoma</td>
</tr>
<tr>
<td>myb</td>
<td>Avian myeloblastosis virus (AMV)</td>
<td>Chicken</td>
<td>p45myb</td>
<td>Myeloblastosis</td>
</tr>
<tr>
<td></td>
<td>AMV-E26</td>
<td>Chicken</td>
<td>P135src-Myb-en</td>
<td>Myeloblastosis and erythroblastosis</td>
</tr>
<tr>
<td>raf</td>
<td>3611-MSV</td>
<td>Mouse</td>
<td>P75src-rf</td>
<td>Sarcoma</td>
</tr>
<tr>
<td>H-ras</td>
<td>Harvey MSV</td>
<td>Rat</td>
<td>pp21ras</td>
<td>Sarcoma and erythroblastosis</td>
</tr>
<tr>
<td>K-ras</td>
<td>Kirsten MSV</td>
<td>Rat</td>
<td>P29src-ras</td>
<td>Sarcoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>pp21ras</td>
<td>Sarcoma and erythroblastosis</td>
</tr>
</tbody>
</table>
Most transducing retroviruses lack replication proteins \( \Rightarrow \) need helper virus to replicate.

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**Figure 18.17**

Transformation of cells by viruses produced by a cell making a defective transforming virus and a helper virus. **Top:** When a cell is infected by both a defective transforming virus and a nondefective helper virus, the result is a transformed cell that produces both types of virus. **Middle:** When a cell is infected by only a defective transforming virus, transformed virus-nonproducer cells are generated. Transforming viruses can be rescued from these cells by infection with a helper virus. **Bottom:** When a cell is infected by only a helper virus, a nontransformed, virus-producing cell results.
Cellular proto-oncogenes

Most human & other animal oncogenes are mutant forms of normal cellular genes. The normal cellular genes are called proto-oncogenes.

Regulate cell division & differentiation. When mutated and cause tumor, they are called oncogenes.

If they reside in host chromosome they are called cellular oncogenes or c-ones.

So v-src for virus

C-src for cellular

If proto-oncogen converted to c-one, a normal cell can be transformed without infection of viruses.

Proto-oncogenes contain intron

v-one do not
### Table 1

Examples of the Functions of Oncogene Products

<table>
<thead>
<tr>
<th>Category</th>
<th>Gene</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth factors</td>
<td>sis</td>
<td>PDGF B-chain growth factor</td>
</tr>
<tr>
<td></td>
<td>int-2</td>
<td>FGF-related growth factor</td>
</tr>
<tr>
<td>Receptor and nonreceptor protein-tyrosine and</td>
<td>src</td>
<td>Membrane-associated nonreceptor protein-tyrosine kinase</td>
</tr>
<tr>
<td>protein-serine/threonine kinases</td>
<td>fgr</td>
<td>Membrane-associated nonreceptor protein-tyrosine kinase</td>
</tr>
<tr>
<td></td>
<td>fpr/es</td>
<td>Nonreceptor protein-tyrosine kinase</td>
</tr>
<tr>
<td></td>
<td>kit</td>
<td>Truncated stem cell receptor protein-tyrosine kinase</td>
</tr>
<tr>
<td></td>
<td>pim-1</td>
<td>Cytoplasmic protein-serine kinase</td>
</tr>
<tr>
<td></td>
<td>mos</td>
<td>Cytoplasmic protein-serine kinase (cytostatic factor)</td>
</tr>
<tr>
<td>Receptors lacking protein kinase activity</td>
<td>mas</td>
<td>Angiotensin receptor</td>
</tr>
<tr>
<td>Membrane-associated G proteins activated by</td>
<td>ras</td>
<td>Membrane-associated GTP-binding/GTPase</td>
</tr>
<tr>
<td>receptors</td>
<td>H</td>
<td>Membrane-associated GTP-binding/GTPase</td>
</tr>
<tr>
<td></td>
<td>K-ras</td>
<td>Membrane-associated GTP-binding/GTPase</td>
</tr>
<tr>
<td></td>
<td>gsp</td>
<td>Mutant-activated form of G α</td>
</tr>
<tr>
<td>Cytoplasmic regulators</td>
<td>crk</td>
<td>SH-2/3 protein that binds to (and regulates?) phosphotyrosine-containing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>proteins</td>
</tr>
<tr>
<td>Nuclear transcription factors (gene regulators)</td>
<td>myc</td>
<td>Sequence-specific DNA-binding protein</td>
</tr>
<tr>
<td></td>
<td>fos</td>
<td>Combines with c-jun product to form AP-1 transcription factor</td>
</tr>
<tr>
<td></td>
<td>jun</td>
<td>Sequence-specific DNA-binding protein; part of AP-1</td>
</tr>
<tr>
<td></td>
<td>erbA</td>
<td>Dominant negative mutant thyroxine (T3) receptor</td>
</tr>
<tr>
<td></td>
<td>ski</td>
<td>Transcription factor?</td>
</tr>
</tbody>
</table>
Changing Cellular proto-oncogenes into oncogenes

Normal cells ➔ expression of proto-oncogenes is tightly controlled

Proto-oncogene vs oncogene

Point mutation ➔ coding region ↑ activity or controlling sequences ↑ expression

Deletion ➔ coding region or controlling sequence

Gene Amplification ➔ Some tumor have multiples of proto-oncogenes (hundreds) ↑ expression

Chromosomal Translocation

Gene moved to the controls of a constitutive or strong promoter

Common & specific for certain tumor types
DNA Tumor Viruses

=> Oncogenic
=> Induce cell proliferation
=> Do not carry oncogenes like RNA tumor viruses

Different Mechanism of Transformation

Transform cells by the action of a gene or genes that are essential parts of the viral genome

- Hepatitis B viruses
- Herpes viruses
- Adenoviruses
- Pox viruses

Normally, => Virus infects cell
=> Produces protein to activate DNA replication and uses host proteins to replicate & transcribe its genome.
=> Produce large #s of viral particles and kills the cells

Sometimes DNA of virus not replicated and becomes integrated into host genome
If viral protein that activate DNA replication is expressed, cell is transformed
Tumor Suppressor Genes

Oncogenes ⇒ stimulate cell growth and division

Tumor Suppressor Genes ⇒ suppress uncontrolled cell proliferation characteristics of cancer cells

~ Figure 18.22

Comparison of the effects of tumor suppressor gene and proto-oncogene mutations. (a) Mutations in both alleles of a tumor suppressor gene are needed for the cell to lose growth control. (b) A mutation in only one allele of a proto-oncogene, converting it to an oncogene, is needed for the cell to lose growth control.

a) Tumor suppressor gene mutations

<table>
<thead>
<tr>
<th>Tumor suppressor gene</th>
<th>Normal growth control</th>
<th>Mutated tumor suppressor gene</th>
<th>Normal growth control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal gene</td>
<td></td>
<td>Mutated tumor suppressor gene</td>
<td></td>
</tr>
<tr>
<td>Both tumor suppressor genes mutated</td>
<td>Loss of growth control</td>
<td>Both tumor suppressor genes mutated</td>
<td>Loss of growth control</td>
</tr>
</tbody>
</table>

b) Proto-oncogene mutation

<table>
<thead>
<tr>
<th>Proto-oncogene</th>
<th>Normal growth control</th>
<th>Proto-oncogene mutated to oncogene</th>
<th>Normal growth control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal growth control</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mutation in one allele is needed for loss of control

2 mutations for loss of control
## Table 3

### Some Known or Candidate Tumor Suppressor Genes

<table>
<thead>
<tr>
<th>GENE</th>
<th>CANCER TYPE</th>
<th>PRODUCT LOCATION</th>
<th>MODE OF ACTION</th>
<th>HEREDITARY SYNDROME</th>
<th>CHROMOSOME LOCATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>APC</td>
<td>Colon carcinoma</td>
<td>Cytoplasm?</td>
<td>Cell adhesion molecule</td>
<td>Hereditary adenomatous polyposis</td>
<td>5q21–q22</td>
</tr>
<tr>
<td>BRCA1</td>
<td>Breast cancer</td>
<td>Nucleus</td>
<td>Transcription factor</td>
<td>Breast cancer and ovarian cancer</td>
<td>17q21</td>
</tr>
<tr>
<td>BRCA2</td>
<td>Breast cancer</td>
<td>Nucleus</td>
<td>Transcription factor?</td>
<td>Breast cancer</td>
<td>13q12–q13</td>
</tr>
<tr>
<td>DCC</td>
<td>Colon carcinoma</td>
<td>Membrane</td>
<td>Cell adhesion molecule</td>
<td>Involved in colorectal cancer</td>
<td>18q21.3</td>
</tr>
<tr>
<td>NF1</td>
<td>Neurofibromas</td>
<td>Cytoplasm</td>
<td>GTPase-activator</td>
<td>Neurofibromatosis type 1</td>
<td>17q11.2</td>
</tr>
<tr>
<td>NF2</td>
<td>Schwannomas and meningiomas</td>
<td>Inner membrane?</td>
<td>Links membrane to skeleton?</td>
<td>Neurofibromatosis type 2</td>
<td>22q12.2</td>
</tr>
<tr>
<td>p16</td>
<td>Melanoma</td>
<td>Nucleus</td>
<td>Transcription factor</td>
<td>Melanoma</td>
<td>9p21</td>
</tr>
<tr>
<td>p53</td>
<td>Colon cancer; many others</td>
<td>Nucleus</td>
<td>Transcription factor</td>
<td>Li-Fraumeni syndrome</td>
<td>17p13.1</td>
</tr>
<tr>
<td>RB</td>
<td>Retinoblastoma</td>
<td>Nucleus</td>
<td>Transcription factor</td>
<td>Retinoblastoma</td>
<td>13q14.1–q14.2</td>
</tr>
<tr>
<td>VHL</td>
<td>Kidney carcinoma</td>
<td>Membrane?</td>
<td>Transcription elongation factor</td>
<td>von Hippel-Lindau disease</td>
<td>3p26–p25</td>
</tr>
<tr>
<td>WT1</td>
<td>Nephroblastoma</td>
<td>Nucleus</td>
<td>Transcription factor</td>
<td>Wilms tumor</td>
<td>11p13</td>
</tr>
</tbody>
</table>

Role of pRB in regulating the passage of cells from G1 to S. (a) In a normal cell unphosphorylated pRB is in a complex with the E2F/DP1 transcription factors. When pRB becomes phosphorylated, that binding is blocked, and the transcription factors activate specific genes involved in the G1 to S transition. (b) A cell with two mutant RB alleles produces a shortened or unstable pRB that does not bind to E2F/DP1, allowing the transcription factors to activate genes for G1 to S transition. This leads to unprogrammed cell division. (c) In cells infected with certain DNA tumor viruses, viral proteins bind to pRB, blocking its ability to bind to E2F/DP1 and allowing these factors to activate genes for G1 to S transition. This leads to viral-induced cell division.

- **a) Normal cell**
  - Phosphorylation of pRB by cyclin/Cdk
  - Released E2F/DP1 activates genes controlled by E2F
  - Protein products made that are needed for entry into S

- **b) Cell with two mutant RB alleles**
  - Truncated and unstable pRB cannot bind
  - E2F/DP1 activates genes controlled by E2F
  - Protein products made that are needed for entry into S

- **c) Cell infected with certain DNA tumor viruses**
  - Viral protein(s) bind to pRB and block its binding to E2F/DP1
  - E2F/DP1 activates genes controlled by E2F
  - Protein products made that are needed for entry into S
  - Viral-induced cell division
Demonstrates Complexity of p53 activity

Genomic Instability

Rad3/ATM

G2 arrest

 CHK1

14-3-3σ

Cdc25c

ARF/p19

MDM2

Increase in the amount or activity of p53

RAS/MAP kinase Pathway

Inhibition of mitosis
Spindle checkpoint
Centrosome duplication

IGF-BP3

BAX

Apoptosis

Genomic Instability

M-phase Progression

cdc2

Cyclin A

(potentiate)

Wee1

(potentiate)

DNA Repair
DNA Polymetization

Cyclin A, Cyclin B, CDK4/6

Cyclin D1

RB

E2F

RB + E2F → S-Phase progression

INK4a/p16

 Cyclin D1

CDK4/6

T-Ag

Rb

MDM2

094, p53

Cyclin A, cdc25, cyclin B, cdc2
Breast cancer  Tumor Suppressor genes
US ⇒ 185,000 new cases/year  31% of all new cancers in women
>46,000 women die/year

A woman has 1 to 10 chance of being diagnosed with Breast Cancer.

Average age is 55  Hereditary Early onset & Bilateral

5% hereditary ⇒ mutations in Tumor suppressor genes  BRCA1 + BRCA2

\[
\begin{align*}
\text{BRCA1} & \Rightarrow \text{Mutations} \Rightarrow \text{susceptible to ovarian cancer} \\
(17q21) & \text{Gene} \\
\frac{100\text{kb}}{190\text{KDa protein}} & \Rightarrow \text{uncertain function} \\
1863\text{aa} & \\
\text{BRCA2} & \Rightarrow \text{Mutations} \Rightarrow \text{no high risk of ovarian cancer} \\
(13q12-q13) & \text{Gene} \\
\frac{70\text{kb}}{3418\text{aa}} & \Rightarrow \text{uncertain function}
\end{align*}
\]
Mutator genes

Any gene that, when mutant, increases the spontaneous mutation frequencies of other genes

Normal DNA replication & DNA repair

Mutation in these gene can cause accumulations of mutations in other genes
Development of most cancers is a stepwise process involving the accumulation of mutations in a number of genes.

**Multistep Nature of Cancer**

**Figure 22.13**
A multistep molecular event model for the development of hereditary adenomatous polyposis (FAP), a colorectal cancer.

- **Normal colon cells**
- **APC gene loss**
- **Increased cell growth**
- **DNA hypomethylation**
- **Adenoma class I**
- **ras gene mutation**
- **Adenoma class II**
- **DCC gene loss**
- **Adenoma class III**
- **p53 gene loss**
- **Carcinoma**
- **Other gene losses**
- **Metastasis**

**Glandular Origin**

**Epithelial Origin**

**Sarcoma = mesodermal origin**
Chemical & Radiation as Carcinogens

Carcinogens = natural & artificial agents that increase frequency of cells becoming cancerous

Chemical Carcinogen  50-60% of Deaths  Smoking & Diet
Natural & synthetic

Two types

=> Direct-acting carcinogen => bind directly to DNA

=> procarcinogens => converted metabolically to active derivative called ultimate carcinogens

Mutagenesis of carcinogens tested by Ames Test

Radiation 2% of Deaths
Can avoid chemical but not Radiation
UV light