7.4: Mutations and Cancer

What would happen if this cycle proceeds at will? Your cells may grow and divide without performing their necessary functions, or without fully replicating their DNA, or without copying their organelles. Probably not much good could come of that. So the cell cycle needs to be highly regulated and tightly controlled. And it is.

Control of the Cell Cycle

How does the cell know when to divide? How does the cell know when to replicate its DNA? How does the cell know when to proceed into mitosis or cytokinesis? The answers to these questions have to do with the control of the cell cycle. But how is the cell cycle controlled or regulated? Regulation of the cell cycle involves processes crucial to the survival of a cell. These include the detection and repair of damage to DNA, as well as the prevention of uncontrolled...
cell division. Uncontrolled cell division can be deadly to an organism; its prevention is critical for survival.

Cyclins and Kinases

The cell cycle is controlled by a number of protein-controlled feedback processes. Two types of proteins involved in the control of the cell cycle are kinases and cyclins. Cyclins activate kinases by binding to them, specifically they activate cyclin-dependent kinases (CDK). Kinases are enzymes that catalyze the transfer of a phosphate group from ATP to another molecule in a cell. They function as a control switch in many cellular functions, turning a function on or off, and regulating other cellular processes. Many times they are involved in activating a cascade of reactions. Cyclins comprise a group of proteins that are rapidly produced at key stages in the cell cycle. Once activated by a cyclin, CDK enzymes activate or inactivate other target molecules through phosphorylation. It is this precise regulation of proteins that triggers advancement through the cell cycle. Leland H. Hartwell, R. Timothy Hunt, and Paul M. Nurse won the 2001 Nobel Prize in Physiology or Medicine for their discovery of these critical proteins.

What makes a Cell Cancerous?

Cancer is a disease characterized by a population of cells that grow and divide without respect to normal limits. These cancerous cells invade and destroy adjacent tissues, and they may spread throughout the body. The process by which normal cells are transformed into cancer cells is known as carcinogenesis. This process is also known as oncogenesis or tumorigenesis. Nearly all cancers are caused by mutations in the DNA of the abnormal cells. These mutations may be due to the effects of carcinogens, cancer-causing agents such as tobacco smoke, radiation, chemicals, or infectious agents. These carcinogens may act as an environmental “trigger,” stimulating the onset of cancer in certain individuals and not others. Do all people who smoke get cancer? No. Can secondhand smoke increase a nonsmoking person's chance of developing lung cancer? Yes. It also increases a nonsmoking person's chance of developing heart disease. Complex interactions between carcinogens and an individual’s genome may explain why only some people develop cancer after exposure to an environmental trigger and others do not. Do all cancers need an environmental trigger to develop? No. Cancer-causing mutations may also result from errors incorporated into the DNA during replication, or they may be inherited. Inherited mutations are present in all cells of the organism.

Oncogenes and Tumor Suppressor Genes

Mutations found in the DNA of cancer cells typically affect two general classes of genes: oncogenes and tumor suppressor genes. In “normal,” non-cancerous cells, the products of proto-oncogenes promote cell growth and mitosis prior to cell division; thus, proto-oncogenes encode proteins needed for normal cellular functions. Mutations in proto-oncogenes can modify their expression and the function of the gene product, increasing the amount of activity of the product protein. When this happens, they become oncogenes; thus, the cells have a higher chance of dividing excessively and uncontrollably. Cancer-promoting oncogenes are often activated in cancer cells, giving those cells abnormal properties. The products of these genes result in uncontrolled cell growth and division, protection against programmed cell death, loss of respect for normal tissue boundaries, and the ability to become established in diverse tissue environments. Proto-oncogenes cannot be removed from the genome, as they are critical for growth, repair, and...
homeostasis. It is only when they become mutated that the signals for growth become excessive.

In "normal" cells, the products of **tumor suppressor genes** temporarily discourage cell growth and division to allow cells to finish routine functions, especially DNA repair. Tumor suppressors are generally **transcription factors**, activated by cellular stress or DNA damage. The function of such genes is to stop the cell cycle in order to carry out DNA repair, preventing mutations from being passed on to daughter cells. However, if the tumor suppressor genes are inactivated, DNA repair cannot occur. Tumor suppressor genes can be inactivated by a mutation that either affects the gene directly or that affects the pathway that activates the gene. The consequence of the lack of DNA repair is that DNA damage accumulates, is not repaired, and inevitably leads to detrimental phenotypes, such as cancer.

Table 1: over or underactivation of the normal cellular functioning may cause cancer.

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth factors, or mitogens</td>
<td>c-Sis epidermal growth factor receptor (EGFR), platelet-derived growth factor receptor (PDGFR), vascular endothelial growth factor receptor (VEGFR), HER2/neu</td>
<td>Usually secreted by specialized cells to induce cell proliferation in the cell, nearby cells, or distant cells. An oncogene may cause a cell to secrete growth factors that would normally not be secreted. The oncogene will thereby induce its own uncontrolled proliferation, as well as the proliferation of neighboring cells. It may also cause the production of growth hormones in other parts of the body.</td>
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<tr>
<td>Receptor tyrosine kinases</td>
<td>Src-family, Syk-ZAP-70 family, and BTK family of tyrosine kinases, the Abl gene in CML - Philadelphia chromosome</td>
<td>Receptor tyrosine kinases add phosphate groups to other proteins to activate or inactivate them. Receptor kinases add phosphate groups to receptor proteins at the surface of the cell. These receptor proteins receive signals from outside the cell and initiate a signal transduction process inside the cell. Tyrosine kinases add phosphate groups to tyrosine residues in the target protein. They can cause cancer by turning the receptor permanently on (constitutively), even without signals from outside the cell.</td>
</tr>
<tr>
<td>Cytoplasmic tyrosine kinases</td>
<td>Raf kinase, and cyclin-dependent kinases.</td>
<td>Cytoplasmic tyrosine kinases are similar to receptor tyrosine kinases, except that they are located within the cell. They, in turn, phosphorylate tyrosine residues of target proteins, initiating a cascade of intracellular processes.</td>
</tr>
<tr>
<td>Cytoplasmic serine/threonine kinases and their regulatory subunits</td>
<td>Ras protein</td>
<td>Cytoplasmic serine/threonine kinases are similar to cytoplasmic tyrosine kinases, except that serine or threonine residues are phosphorylated.</td>
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<tr>
<td>Regulatory GTPases</td>
<td>Ras protein</td>
<td>Ras is a small GTPase that hydrolyzes GTP into GDP and phosphate. Ras is activated by growth factor signaling and activates or inactivates growth signaling pathways. Downstream effectors of Ras include Raf, MEK, MEKK, MAPK, ERK, most of which in turn regulate genes that mediate cell proliferation.</td>
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### Oncogenes

Categories of oncogenes are described in the Table above. Oncogenes may be growth factors, protein kinases, GTPases or transcription factors. **Growth factors** are naturally occurring substances, usually a protein or steroid hormone, capable of stimulating cellular growth, proliferation, and differentiation. They are important for regulating a variety of cellular processes. Usually, they must bind to an extracellular or intracellular receptor to initiate a cellular reaction.

#### Several Mutations to Cause Cancer

Typically, a series of several mutations that constitutively activate oncogenes and inactivate tumor suppressor genes is required to transform a normal cell into a cancer cell (**Figure 7.4.2**). Cells have developed a number of control mechanisms to overcome mutations in proto-oncogenes. Therefore, a cell needs multiple mutations to transform into a cancerous cell. A mutation in one proto-oncogene would not cause cancer, as the effects of the mutation would be masked by the normal control of the cell cycle and the actions of tumor suppressor genes. Similarly, a mutation in one tumor suppressor gene would not cause cancer either, due to the presence of many "backup" genes that duplicate its functions. It is only when enough proto-oncogenes have mutated into oncogenes and enough tumor suppressor genes have been deactivated that the cancerous transformation can begin. Signals for cell growth overwhelm the signals for growth regulation, and the cell quickly spirals out of control. Often, because many of these genes regulate the processes that prevent most damage to the genes themselves, DNA damage accumulates as one ages.
Figure (PagIndex(2)): Cancers are caused by a series of mutations. (public domain; National Cancer Institute via Wikimedia.org).

Usually, oncogenes are dominant alleles, as they contain gain-of-function mutations. The actions of the mutant allele gene product, many times resulting in a constitutively activated protein, are dominant to the gene product produced by the "normal" allele. Meanwhile, mutated tumor suppressors are generally recessive alleles, as they contain loss-of-function mutations. A proto-oncogene needs only a mutation in one copy of the gene to generate an oncogene; a tumor suppressor gene needs a mutation in both copies of the gene to render both products defective. There are instances when, however, one mutated allele of a tumor suppressor gene can render the other copy non-functional. These instances result in what is known as a dominant negative effect.

Summary

- The cell cycle is controlled through feedback mechanisms involving cyclin and CDK proteins.
- Nearly all cancers are caused by mutations in the DNA of the abnormal cells.
- In non-cancerous cells, proto-oncogenes promote cell growth and mitosis prior to cell division; thus, proto-oncogenes encode proteins needed for normal cellular functions.
- In non-cancerous cells, tumor suppressor genes temporarily discourage cell growth and division to allow cells to finish routine functions, especially DNA repair.
- Mutations in proto-oncogenes and tumor suppressor genes may lead to cancer.
• Usually, mutations in multiple genes are necessary to develop cancer.

Review

1. Define cancer.
2. What are cyclin-dependent kinases? What is their role?
3. Discuss the role of oncogenes and tumor suppressor genes in carcinogenesis.
4. Why are multiple mutations required for transformation into a cancerous cell?
5. Identify all the categories of oncogenes and describe two categories.