

## 9.4 How Cancer Develops

Carcinogenesis is the development of cancer. **Cancer** is a genetic disease requiring a series of mutations, each propelling cells toward the development of a **tumor** [L. *tumor*, swelling], an abnormal mass of cells. The presence of a tumor indicates a failure in cell division control—a failure that is quite often due to a faulty *p53* gene. The *p53* gene ordinarily halts the cell cycle when DNA mutates and is in need of repair (Fig. 9.9). Why might DNA be in need of repair? DNA molecules are constantly acted on by physical and chemical agents that can cause mutations that lead to cancer. The best known mutagenic carcinogens are radiation, organic chemicals, and certain viruses. Radiation includes ultraviolet light, radon gas, X rays, and accidental emissions from nuclear power plants. Organic chemicals in tobacco smoke, certain foods, and pesticides and herbicides also bring about harmful changes in DNA molecules. A cell constantly monitors its DNA and if any agent has caused changes, repair enzymes set to work to correct the harm done. The *p53* protein (the product of the *p53* gene) is involved in mobilizing repair enzymes and stopping the cell cycle while repair is going on. Only if repair is possible does the cell cycle start up again. If repair of DNA is not possible, the *p53* protein promotes cell suicide, also called apoptosis. While ordinarily we think of cell death as a bad thing, it is obviously the best solution if cancer will develop otherwise.

The pivotal role of the *p53* gene is substantiated first by the observation that many different types of human cancers contain no or a faulty *p53* gene. Also, scientists have added the *p53* protein to rapidly dividing cancer cells in a petri dish. The cells stopped dividing and died.

The two cellular responses to activation of *p53* are either arrest of the cell cycle while DNA repair is going on or apoptosis.

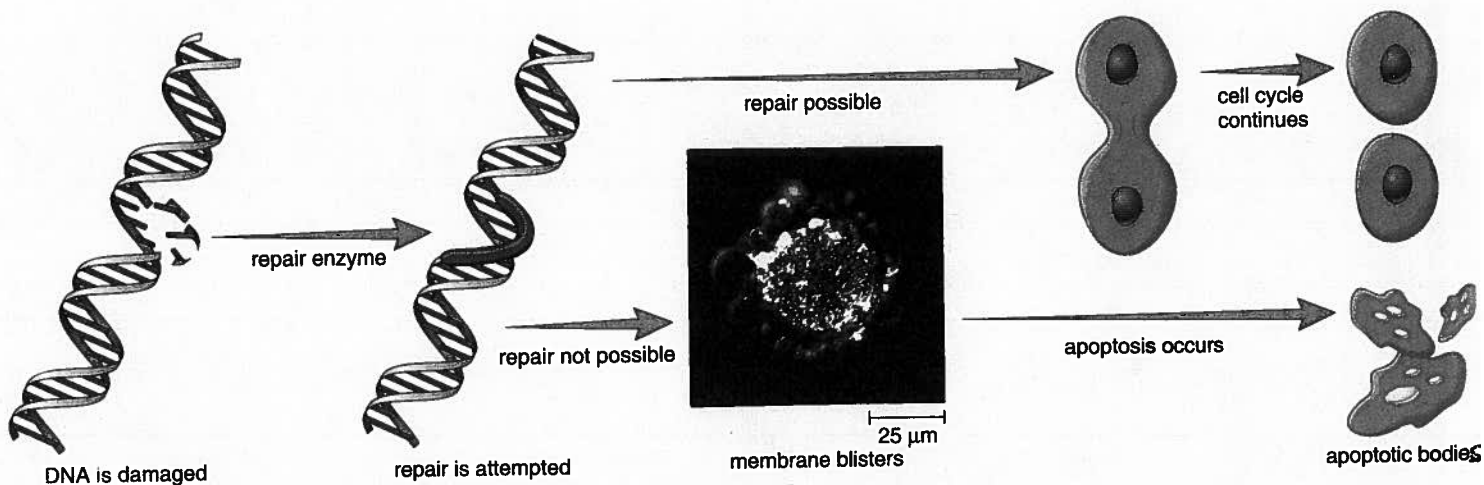
**Apoptosis** [Gk. *apo*, off, and *ptosis*, fall], defined as programmed cell death, is a set sequence of cellular changes involving shattering the nucleus, chopping up the chromosomes, digesting the cytoskeleton, and packaging the cellular remains into membrane-enclosed vesicles (apoptotic bodies) that can be engulfed by macrophages. The appearance of membrane blisters is a tip-off that a cell is undergoing apoptosis (Fig. 9.9).

A remarkable finding of the past few years is that cells routinely harbor the enzymes, now called caspases, that bring about apoptosis. The enzymes are ordinarily held in check by inhibitors but they can be unleashed in two ways. During human development, exterior signals cause certain cells to die, allowing paddles to be converted into fingers and toes, for example. In adults, cells that have DNA damaged beyond repair usually go ahead and kill themselves.

There are two sets of caspases. The first set are the "initiators" that receive the message to activate the "executioners," which then activate the enzymes that dismantle the cell. For example, there is an executioner that frees an endonuclease to enter the nucleus and start chopping DNA. Initiators, executioners, and dismantling enzymes all begin to work when they are clipped to make them shorter and ready for action.

Knowledge about apoptosis can possibly lead to new therapy regimens. Tumor cells, but not normal adult cells, contain high levels of a protein called survivin, which blocks apoptosis. If researchers can find a way to inactivate survivin, cancer cells might be more susceptible to radiation and chemotherapy. In Parkinson's disease and stroke, excess apoptosis may kill off brain cells. If so, inhibitors of apoptosis could be administered to keep brain cells alive.

The occurrence of apoptosis is usually essential for the good of the organism. A lack of apoptosis allows cancer to develop.



**Figure 9.9** Functions of *p53*.

If DNA is damaged by a mutagen, *p53* is instrumental in stopping the cell cycle and activating repair enzymes. If repair is impossible, the *p53* protein promotes apoptosis.

## Characteristics of Cancer Cells

Cancer cells exhibit characteristics that indicate they have experienced a severe failure in regulating the cell cycle.

### *Cancer Cells Lack Differentiation*

Most cells are specialized; they have a specific form and function that suits them to the role they play in the body. Cancer cells are nonspecialized and do not contribute to the functioning of a body part. A cancer cell does not look like a differentiated muscle, nervous, or connective tissue cell and instead has a shape and form that is distinctly abnormal (Fig. 9.10). Normal cells can enter the cell cycle for about 50 times, and then they die. Cancer cells can enter the cell cycle repeatedly, and in this way they are immortal. In cell tissue culture, they die only because they run out of nutrients or are killed by their own toxic waste products.

### *Cancer Cells Have Abnormal Nuclei*

The nuclei of cancer cells are enlarged, and there may be an abnormal number of chromosomes. The chromosomes have mutated; some parts may be duplicated and some may be deleted. In addition, gene amplification (extra copies of specific genes) is seen much more frequently than in normal cells.

### *Cancer Cells Form Tumors*

Normal cells anchor themselves to a substratum or adhere to their neighbors. They exhibit contact inhibition—when they come in contact with a neighbor, they stop dividing. In culture, normal cells form a single layer that covers the bottom of a petri dish. Cancer cells have lost all restraint; they pile on top of one another and grow in multiple layers. They have a reduced need for the growth factors that are needed by normal cells.

In the body, a cancer cell divides to produce a tumor which invades and destroys neighboring tissue. This new growth, termed neoplasia, is made of cells that are disorganized, a condition termed anaplasia. A benign tumor is a disorganized, usually encapsulated, mass that does not invade adjacent tissue.

### *Cancer Cells Undergo Angiogenesis and Metastasis*

Angiogenesis, the formation of new blood vessels, is required to bring nutrients and oxygen to a cancerous tumor whose growth is not contained within a capsule. Cancer cells release a growth factor that causes neighboring blood vessels to branch into the cancerous tissue. Some modes of cancer treatment are aimed at preventing angiogenesis from occurring.

Cancer in situ is found in its place of origin without any invasion of normal tissue. Malignancy is present when metastasis [Gk. *meta*, between, and L. *stasis*, standing, a position] establishes new tumors that are distant from the primary tumor. To accomplish metastasis, cancer cells must

first make their way across the extracellular matrix (substances including fibers secreted by the cell) and into a blood vessel or lymphatic vessel. It has been discovered that cancer cells have receptors that allow them to adhere to a component of the extracellular matrix; they also produce enzymes that degrade the matrix and allow them to invade underlying tissues. Cancer cells tend to be motile, have a disorganized internal cytoskeleton, and lack intact actin filament bundles. After traveling through the blood or lymph, cancer cells may then start tumors elsewhere in the body.

The patient's prognosis (probable outcome) is dependent on the degree to which the cancer has progressed: (1) whether the tumor has invaded surrounding tissues, (2) if so, whether there is any lymph node involvement, and (3) whether there are metastatic tumors in distant parts of the body. With each progressive step of the cancerous condition, the prognosis becomes less favorable.

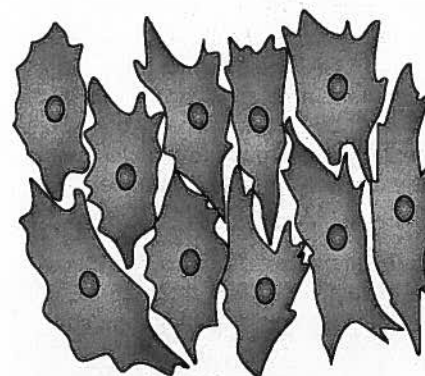
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**Cancer cells are nonspecialized, have abnormal chromosomes, and divide uncontrollably. Because they are not constrained by their neighbors, they form a tumor. Then they metastasize, forming new tumors wherever they relocate.**

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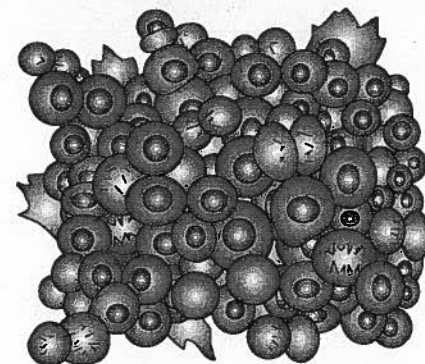
#### Normal Cells

Controlled growth  
Contact inhibition  
One organized layer  
Differentiated cells



#### Cancer Cells

Uncontrolled growth  
No contact inhibition  
Disorganized, multilayered  
Nondifferentiated cells  
Abnormal nuclei



**Figure 9.10** Cancer cells. Cancer cells differ from normal cells in the ways noted.