

# Chapter 12 Outline and Notes

Biology Today: An Issues Approach, third edition

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## MULTICELLULAR ORGANISMS ARE ORGANIZED GROUPS OF CELLS AND TISSUES

### COMPARTMENTALIZATION

Multicellular organisms are subdivided into compartments called cells.

Structurally and functionally integrated groups of similar cells are called tissues.

As cells grow larger, they generally divide, thus maintaining the surface-to-volume ratio within certain limits.

### SPECIALIZATION

Cells in multicellular animals usually differentiate (i.e., become different from one another).

Differentiated cells are the basis for distinct tissues.

### COOPERATION AND HOMEOSTASIS

Cells cooperate to maintain a harmonious state of balance (homeostasis).

Control of cell division is important in maintaining homeostasis.

In certain cases, some cells may escape from the controls that maintain this homeostasis.

Cancers result from cell division that is out of control and from the consequent breakdown of homeostasis.

## CELL DIVISION IS CLOSELY REGULATED IN NORMAL CELLS

### THE CELL CYCLE

Cell division is part of a cell cycle. Two of the events in this cycle are mitosis and DNA synthesis. Between these two events are two "gap phases", called G1 and G2.

### REGULATION OF CELL DIVISION

Many groups of cells continue to divide until they reach a certain aggregate size, then the cells stop dividing.

One mechanism by which cell division is regulated is by contact inhibition, in which cells stop dividing when they fill the available space and are in contact with one another.

Another mechanism by which cell division is regulated is anchorage dependence, in which cells must be attached to a surface in order to divide.

Many cells receive information about their environment via external signaling molecules called cytokines. Cytokines attach to specific receptors on the cell surface, causing the activation of second messengers within the cytoplasm.

Some cytokines, called growth factors, initiate the cell cycle and thus stimulate cell division.

### REGULATION OF GENE EXPRESSION

Gene expression can be regulated at various levels:

1. By regulating transcription from DNA to RNA. RNA polymerase must bind to a promoter sequence in order to initiate transcription.
2. Posttranscription: mRNA can be chemically modified before it leaves the nucleus.
3. The rate of translation from mRNA to protein can be regulated.
4. The amino acid chain may be modified after translation.
5. The activity of the final protein can be altered by binding to effector molecules.

Cell division is regulated by control of the expression of genes that code for the proteins that initiate the cell cycle.

### LIMITS TO CELL DIVISION

Hayflick's experiments show that most cells cannot go on dividing indefinitely.

The maximum number of doublings that cells will undergo is called the doubling number. Different types of cells have different doubling numbers.

## DEVELOPMENT BEGINS WITH UNDIFFERENTIATED CELLS CALLED EMBRYONIC STEM CELLS

### CELLULAR DIFFERENTIATION AND TISSUE FORMATION

The potentiality of a cell includes all the possible cell types that it might be able to form.

Differentiation is a progressive (step by step) restriction of potentiality.

Once a cell has differentiated fully, its potential is completely determined (it can only form one type of cell).

The differentiation of cells can be induced by cytokines secreted by tissue regions called organizers.

Gurdon's experiment shows that differentiation does not affect the cell nucleus: transplanting a nucleus from a differentiated cell into an undifferentiated egg cell results in a cell that can grow into a complete, normal tadpole with all types of tissues present.

Cells in different tissues and in organisms of different ages still contain the full amount of DNA in most cases.

### STEM CELLS

Stem cells in embryos have the ability to keep dividing and to form various types of differentiated cells.

Some ability for differentiation must remain in adult tissues that constantly need repair. Cells that maintain the ability to differentiate in adulthood are called adult stem cells.

### CLONING

At the cell level, cloning is the repeated division of a cell and its cellular progeny. Cloned cells inherit their genetic characteristics from the cell that started the clone.

Therapeutic cloning is the production of cloned tissues and organs for therapeutic purposes, e.g., to repair damaged tissue or to make functional gene products. In some cases, the cell used to start the clone has the nucleus from a differentiated cell.

Reproductive cloning is the production of a new individual from cloned cells.

### ETHICAL AND SCIENTIFIC QUESTIONS

We are not sure how healthy cloned material will be, or how long it will live; some evidence suggests that it may suffer from reduced life span and possibly from ill health as well.

For this reason, many people object to all types of cloning.

Even more people object specifically to reproductive cloning, saying that we should not purposely create any organism whose health risks have been intentionally worsened.

### CANCER AT THE ORGANISMAL LEVEL

Tumors that are surrounded by a basement membrane are called benign.

Benign tumors can often be fully removed by surgery.

Tumors that invade surrounding tissues are called malignant.

Surgical removal of malignant tumors is usually incomplete; it leaves some cells behind.

The most dangerous tumors are those malignant tumors that metastasize.

In metastasis, transformed cells lose their attachments, break through the extracellular matrix, and spread via the blood or lymph to other areas of the body.

## CANCER RESULTS WHEN CELL DIVISION IS UNCONTROLLED

### PROPERTIES OF CANCER CELLS

Cancer cells do not obey any Hayflick limit and are therefore immortal.

The process by which cells become deregulated and immortal is called transformation.

Transformed cells lose their contact inhibition and anchorage dependence, undergo more frequent mutations, take up nutrients more rapidly, and yet have lower nutrient requirements than normal cells (Table 9.2).

Transformed cells grow in unorganized lumps called tumors.

### THE GENETIC BASIS OF CANCER

PROTO-ONCOGENES are normal genes in host cells that control growth promoters or other signals that tell a cell when to divide.

ONCOGENES are viral genes that cause host cells to become transformed. They are usually the mutated or altered versions of proto-oncogenes.

Gene sequences of oncogenes and proto-oncogenes are often very similar.

Burkitt's lymphoma is associated with changes in a gene called *myc*. Mutations in this gene can immortalize a cell, signaling it to divide continuously. In its normal location on chromosome 8, the proto-oncogene obeys normal cell controls. However, in transformed cancer cells infected with Epstein-Barr Virus, this gene has undergone a translocation to another chromosome, placing it near the genes that control antibody production in B-lymphocytes. When a second infection, such as malaria, occurs, the B lymphocytes are stimulated to produce antibodies, an act which also activates the *myc* gene, activating cell division and producing the cancer.

Cancers such as Burkitt's lymphoma have given rise to the two-hit theory, in which two separate genetic changes are required to produce transformation: One change is an immortalization which releases cells from their Hayflick limits, the other change is a loss of contact inhibition and/or anchorage dependence.

### TUMOR SUPPRESSOR GENES

Tumor suppressor genes are normal genes that govern DNA repair.

Mutations of these genes often result in failure of DNA repair, which may result in cancer. Cancers are thus associated with changes in tumor suppressor genes.

### ACCUMULATION OF MANY MUTATIONS

The study of diseases in populations is called epidemiology.

There are two general kinds of epidemiological studies:

Retrospective studies: People who are already sick are investigated to find out what influences they were exposed to that might have made them sick. These are the easiest studies to do (therefore the most frequent), but reliance on people's memories limits the reliability of such studies, especially if long time spans are involved. (For example, breast cancer patients can be asked about the fat in their diet, but what was the percentage of fat in your diet over the last ten years?)

Prospective studies are considered more reliable because they begin with a healthy group of people and monitor and record certain occurrences (diets, exposures to suspected carcinogens, etc.). After a certain time, the people who get the disease under investigation are compared to those who did not.

Epidemiological evidence suggests environmental causes for many cancers:

- \* rates for lung cancers have increased in populations that have not genetically changed.
- \* irregular patterns of incidence of many cancers in populations also suggest environmental causes, not genetic causes.

### PROGRESSION TO CANCER

There are many factors, most of them poorly understood, that govern the progression to cancer.

Suppression of the immune system from stress or other causes can increase the risk of progression to cancer.

## CANCERS HAVE COMPLEX CAUSES AND MULTIPLE RISK FACTORS

### INHERITED PREDISPOSITIONS FOR CANCERS:

Retinoblastoma, xeroderma pigmentosum (both very rare and both associated with errors in spell-checking proteins)

BRCA1 and BRCA2 genes predispose to premenopausal breast cancer

### INCREASING AGE:

The risks for most cancers increase with age, perhaps due to accumulated mutations, or perhaps to the accumulation of exposure to carcinogens.

### CANCERS ASSOCIATED WITH VIRUSES:

Viruses may cause cancers by inserting oncogenes into host DNA.

Examples of such viruses include:

- Human T-cell Leukemia Virus (HTLV)
- Rous Sarcoma Virus
- Epstein-Barr Virus (EBV) (associated with Burkitt's lymphoma)
- Human Papilloma Virus (associated with cervical cancer)

### PHYSICAL AND CHEMICAL CARCINOGENS:

Ultraviolet light, ionizing radiation (from radioactivity)

Many chemicals in cigarette smoke

Many industrial chemicals: vinyl chloride, formaldehyde, asbestos, nickel, arsenic, benzene, cadmium, polychlorinated biphenyls (PCBs), and others.

Many of the above agents act synergistically.

### SCREENING FOR CARCINOGENS:

MUTAGENS are chemicals or other agents that cause mutations.

The Ames test is a screening test that detects mutagens.

Many mutagens are tumor initiators because they cause permanent damage in the DNA; they are therefore carcinogenic.

Other chemicals, not necessarily mutagenic, promote cancer by serving as tumor promoters. (Transformation often needs a tumor promoter for its completion.) Alcohol, tobacco, asbestos, dioxin, and phenobarbital are all known to be tumor promoters.

### DIETARY FACTORS IN CANCER

High-fat, low-fiber diets are associated with cancers of the colon, rectum, pancreas, prostate gland, and postmenopausal breast cancer.

Stomach cancers are associated with consumption of very salty food and pickled vegetables.

### INTERNAL RESISTANCE TO CANCER

Your immune system protects you against many cancers, a process known as immune surveillance. This is why individuals with suppressed immune systems get cancer more easily; it also explains why cancers become more common as people's immune systems decline with advancing age.

Synthetic estrogens such as DES are associated with uterine cancer, and estrogen levels also influence the rates of breast cancer.

Many cancers are more common and more severe in people under stress.

Some otherwise rare cancers, such as Kaposi's sarcoma, occur more often in patients whose immune systems are suppressed or who are immunodeficient.

### SOCIAL AND ECONOMIC FACTORS

People who are reluctant to seek medical care or to follow doctor's orders often have higher mortality rates for many cancers.

This includes many poor people.

## WE CAN TREAT MANY CANCERS AND LOWER OUR RISKS FOR MANY MORE

### SURGERY, RADIATION, AND CHEMOTHERAPY

Surgery: removal of visible tumors is generally the first step

Cancer cells that remain behind must also be killed. The problem is killing the cancer cells without also killing large numbers of normal cells.

Radiation and chemotherapy both target rapidly dividing cells. This also kills rapidly dividing normal cells: those of the scalp (causing hair loss), of the intestinal lining (causing nausea and loss of appetite), and of the bone marrow (causing suppression of the immune system).

NEW CANCER TREATMENTS include:

- \* boosting the immune system as a whole,
- \* targeting the immune system against tumor-associated antigens,
- \* using antibodies to target anti-cancer drugs to attack cancer cells more exclusively,
- \* testing new and sometimes unconventional therapies for efficacy.

CANCER DETECTION AND PREDISPOSITION

Advances in diagnostic technology now allow us:

- \* to detect certain cancers much earlier, when they are still more easily treatable
- \* to detect certain genes that predispose people to higher rates for certain cancers

CANCER MANAGEMENT includes:

- \* developing drugs or strategies to reduce the side-effects of chemotherapy (example: cold-capping the scalp to avoid hair loss)
- \* support groups, which have proven effective in increasing survival rates in many cases.

CANCER PREVENTION— things you can do:

- \* avoid smoking, also avoid passive (second-hand) smoke;
- \* eat a balanced diet low in fats, high in fiber, and containing adequate vitamins;
- \* avoid exposure to radioactive substances, X-rays, and ultraviolet light;
- \* avoid occupational and other exposure to chemical carcinogens;
- \* get regular checkups and (if female) practice breast self-examination.

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