XIV. PROLIFERATION AND CELLULAR DIFFERENTIATION

XIV.1. CELLULAR PROLIFERATION

XIV.1.1. CELLULAR PROLIFERATION CONTROL MECHANISMS

The development of the human organism is the result of proliferation (cell proliferation) processes, massive cell growth and volume and cell differentiation (gaining functions and morphological structures specific to each cell type).

A fertilized human egg and a fertilized mouse egg are similar in size, but an adult human is much bigger than an adult mouse. This difference in body size reflects a difference in cell numbers: an adult human is constructed from many more cells (several million billion cells, 10^{17}) than an adult mouse. The conclusion is that it is a difference in the control of cell behavior in humans and mice that generates such different numbers of cells. Thus, cell proliferation, as well as cell differentiation, cell survival and cell death, must be regulated by signals from other cells in the body combined with programs intrinsic to the individual cell.

The human body is made up of an extremely large number of cells with a great variety of types in a dynamic process. According to cytology calculations, the human body is made up of several million billion cells, which can be classified by their morphological and functional character in approximately 200 different types. Billions of cells in the human body are continually multiplying day and night. In an adult, every 4 million cells divide each day, 350 million each day, and in one year the number of divisions exceeds 10^{14}. At such a number of time unit divisions, there is a risk that during the cycle of the cell cycle to make changes to DNA that lead to cell malignancy. However, a small percentage of the world's population suffers from cancer. Hence, the conclusion that the human organism possesses a remarkable division control mechanism to prevent the emergence of aberrant cells that could cause malignancy.

XIV.1.2. FACTORS THAT CONTROL PROLIFERATION - depend on signals from other cells, depend on cell cycle events (experiences have shown that the cytoplasm has a dominant effect on the nucleus during the cell cycle).

A) Signals from other cells. Unicellular organisms such as bacteria and yeasts tend to grow and divide as fast as they can, and their rate of proliferation depends on the availability of nutrients in the environment. The cells in a multicellular organism, are specialized members of a highly organized community, and their proliferation must be controlled so that an individual cell divides only when another cell is required by the organism- either to allow growth or to replace cell loss. So, for an human cell to proliferate, nutrients are not enough, cell must receive stimulatory chemical signals from other cells (neighbors cell).

B) Signals inside the cell meaning cell cycle components and events

1. The cell cycle is regulated by an oscillatory system of autonomic cytoplasmic factors. Recent research has enabled the identification and purification of a protein, called maturation acceleration factor (FAM). Its activity is oscillating, maximal in mitosis and absent in phase S. T At the same time, a second factor, called the cytostatic factor (FCS), has been identified that stops the cell cycle in metaphase. Its action is annihilated by Ca^2. The emphasis on autonomic cytoplasmic factors suggests the existence of a higher level of regulation of the cell cycle and proves the interdependence of the underlying reactions of cell proliferation.

It is known that the passage of interphase cells into mitosis involves chromatin condensation, nuclear membrane fragmentation, interphase cytoskeleton disintegration, and

mitotic spindle formation. In vitro, FAM has been shown to induce mitosis in somatic cells, causing chromatin condensation and nuclear membrane fragmentation. Experiences shown that FAM induces phosphorylation of laminin proteins, which causes disintegration of the nuclear lamina and subsequent breakdown of the nuclear membrane.

2. Cellular proliferation control during the cell cycle.

The cellular proliferation control occurs when Go / G1 cells pass into S phase. It is known that human lymphocytes stimulated by mitotic factors (phitohemaglutinine, cancavalin A) enter S phase only after a preparatory state of 26 hours. In this state (preparatory), a lot of biochemical processes occur: activation of ion flux, specific protein synthesis, expression of specific genes, etc. Recent research has shown that a few hours after the action of phytohemaglutinine on human lymphocytes, a 60 kd protein is synthesized in the cytoplasm and stimulates the entry of lymphocytes into the S phase.

3. The role of some nuclear proteins

A protein called cyclin (nuclear antigen of cell proliferation) has been identified in proliferative cells. In the nucleus of non-proliferative cells, a protein called statin was identified and appears in various types of aged or young non-proliferating cells in the Go / G1 phase located in the nuclear cisternae. Researches have shown that cyclin and statin are present alternately during the transition from the proliferative to the non-proliferative stage and reverse.

XIV.1.3. CLASSIFICATION OF CELL POPULATIONS

The human organism is made up of three different types of cell populations, classified according to their proliferative kinetics in:

a) Static cells populations - cells that are in an advanced stage of specialization and development. These cells limit or lose their proliferation capacity and gradually decrease as a number (neurons, muscle cells, oocytes)

b) Transient cells population - cells derived from precursor cell populations and have a well-defined, relatively short existence. Their life span is determined by the "suicide" process through maturation, during which cells lose their proliferation capacity before they are eliminated.

c) Stem cells or reserve cell stem- are not terminally differentiated and can divide without limit (or at least for the lifetime of the animal). When a stem cell divides, each daughter has one possibility – either it can remain a stem cell, or in can embark on a course leading irreversibly to terminal differentiation. So stem cell is not to carry out the specialized function of the differentiated cell but rather, to produce cells that will.

Cells identified as reserve stem cells may be thought of as G_0 cells that may be induced to reenter the cell cycle in response to injury of cells within the tissues of the body. Activation of these cells may occur in normal wound healing and in repopulation of the seminiferous epithelium after intense acute exposure of the testis to X-irradiation or during regeneration of an organ, such as the liver, after removal of a major portion. If damage is too severe, even the reserve stem cells die, and there is no potential for regeneration.

Stem cells have some characteristics: represent a minority population, react to radiation and drugs, have a special circadian rhythm and a biological cycle larger than transient cells. In a tissue, stem cells represent a minority population: 1-2% in the seminal epithelium, 0.4% in the bone marrow, below 10% in the epidermis where they always remain attached to the basal membrane. Stem cells also exist in tumor cell populations between 1-5%.

XIV.2. CELL DIFFERENTIATION

XIV.2.1. DEFINITION

Cell differentiation is the process by which stable differences arise between cells. All higher organisms develop from a single cell, the fertilized ovum, which gives rise to the various tissues and organs. The question of how an apparently structureless egg converts itself into a complex and highly organized embryo had interested scientists since the time of Aristotle 2000 years ago, and still remains one of the major unanswered questions of biology. The process of differentiation is not limited in time, it takes place throughout the individual's life, from conception to death. It comprises three important biological periods: ontogenesis; growth, development and maturity; aging and death.

Cell differentiation begins at the time of fertilization of the ovum. In most animal species females produce large unfertilized eggs that contain most of the materials and nutrients required to form an embryo. Development is triggered by fertilization. The sperm contributes a small, condensed nucleus (male pronucleus), which rapidly enlarges in the egg cytoplasm, fuses with the female pronucleus, and finally divides. Zygote and cells from the first two divisions are cells that by differentiation can generate any of the adult cell types. Because of this they are called pluripotent cells. They can generate any of the cell types because their entire set of genes is active. Any genetic message they receive can be accepted, so these cells can print any evolutionary path.

During embryogenesis, pluripotent cells are required to choose a particular evolutionary pathway, thus evolving towards a certain cellular type. This process takes place under the action of some factors called inductors, and the cells upon which these factors act are called determined cells. The fertilized egg then undergoes a series of very rapid cycles consisting of DNA synthesis followed by cell divisions. These divisions are called cleavage, because the cytoplasm is partitioned without growth. Then the cells form a hollow sphere (blastula) in which tissues are not yet evident. Some of the cells then invaginate in a series of cell movement as gastrulation, and the first signs or morphological differentiation appear. These complex changes take place in a comparatively short time.

In molecular terms, cell differentiation means variable gene activity in different cells of the same organism. Cell specialization involves the synthesis of some specific proteins (hemoglobin in erythrocytes, antibodies in plasma cells). Each eukaryotic cell expresses only a small percentage of the genes it contains, and cells of different tissues express different sets of genes. So will understand cell differentiation, when the mechanism of genes regulation in higher cell are clear and known. Also it is important to understand how the differentiated state is maintained in adult tissues. All nuclei in an early embryo are genetically equivalent, and thus the initial differences between cells must reside in the cytoplasm they inherit. In the cytoplasm off most eggs contains cytoplasmic determinants of development which at some point become unequally distributed among the cells of an embryo and subsequently change the activity of genes. The mechanism by which these determinants are segregated unequally in cleaving embryos is not known, and understanding this segregation will probably be as important as understanding how they modify gene activity.

XIV.2.2. TYPES OF CELL DIFFERENTIATION

a) intracellular differentiation

The action of the some factors which determined the process of differentiation (inductors) on the cell generate at some point successive structural changes that determine the appearance and the shape of the differentiated cell. For example, in spermatogenesis, a transformation takes place in the sense of adapting form to function, spermatids (round-oval cells) transforming into sperm cells (elongated cells with scarlet fever), the process is called spermiogenesis.

b) intercellular differentiation

A small group of cells, from a larger, uniform population, may undergo structural changes. Thus, intercellular differences occur between the original cell characters and the cell characters originating from the original cells. The process is explained by intracellular accumulation of specific, protein-specific substances with enzymatic functions. For example, erythrocyte accumulates hemoglobin, muscle cells contain a higher amount of actin and myosin than the rest of cell types.

XIV.2.3. TYPES OF INDUCTORS

- According to the place of action, there are two types of inductors:

a) Inductors acting locally within the cell or on which are in contact;

b) Inductors acting at a distance from where they were produced (hormones and growth factors act on target cells.

- According to the biochemically structure, inductors represent a heterogeneous category of factors. They are:

a) extracellular environmental factors;

b) cells that come together, come in contact, establish junctions (GAPs) through which they communicate;

c) cell's secretion products (hormones, polypeptides, growth factors, neurotransmitters).

The differences between cells in various tissues of a multicellular organism are stable and heritable. Differentiation may be induced in the embryo by a certain inductors, and this process will persist even in the absence of this initial inductor in the tissue culture.so the differentiation state is very stable and can persist throughout many cell generations. Examples, the neuron will persist as such throughout the lifetime of an individual, a cell committed to become a skin cell will gradually keratinize and eventually die. These persistent changes are very different from the type of regulation involved in enzyme induction.

XIV.2.4. GENERAL CHARACTERS OF DIFFERENTIATED CELLS

1. Specific function. The result of the differentiation is the appearance of some functions specific to each constituted cellular type. Examples the muscle cell is contractile, the sperm possesses locomotive capacity, the blood is capable of binding and transporting blood gases.

2. Shape and specific structure. The specialized cells have a characteristic shape and structure adapted to the function they perform. The erythrocyte has a biconcave discs which maximizes the cell's surface area n an important attribute in gas exchange and in order to store an optimal amount of hemoglobin, the neurons exhibit axonal extensions to mobilize the neurotransmitters away from their production site, the absorbent cells have an apical pole provided with microvilli in order to increase the absorption surface. On the other hand, structurally, although all cells (except for the red blood cells) contain all types of cytoplasmic organelles, the proportion of some cells is higher than others, according to the function of the cell type. For example, actin and myosin filaments are better represented in contractile cells (muscle

cells), lysosomes in phagocytic cells (PMN, monocytes), RE and the Golgi apparatus are in a larger number in the cells of synthesis and secretion.

3. Specific chemical composition. Cells accumulate specific proteins and specific enzymatic activity, so the chemical composition of cells differs from one cell type to another.

4. Substrate adhesion. This property is the basis for the formation of tissues and organs.

5. The junctions. Several membrane – associated structures provide adhesion and communication between cells. One of the most important feature of junctions is to maintain synchronous cell activity in a cell population.

6. Inhibition of division capacity. The higher degree of cell differentiation is, the lower capacity of division cells have. From this point of view, cells are classified into three categories:

a) high specialized cells: loss the division capacity- neuron, cardiac muscle cell, red blood cells;

b) differentiated cells: with varying capacity of division depending on need: hepatocytes.

c) young cells, incompletely differentiated cells: capable of self-sustaining division: enterocytes.

7. Inhibition of contact. When cell density in a tissue reaches the optimum level, cells are stopped from proliferation. The property is demonstrated "in vivo" by the phenomenon of scarring. The "in vitro" phenomenon is demonstrated by the proliferation of cells in culture on the support. As has been shown before, proliferation ceases when the cells come into contact with one another or with the walls of the vessel.

XIV.2.5. GENERAL CHARACTERS OF UNDIFFERENTIATED CVELLS

1. Absence of specific function. Undifferentiated cells have only one function, namely to give rise to specialized cells following successive determinations.

2. Absence of a specific structure and form. All undifferentiated cells resemble each other; have generally young cell characters: round or round-oval; large nucleus in comparison with cytoplasm; cytoplasm reached of free ribosomes; other organelles are reduced in number and poorly developed.

3. Absence of specific chemical composition.

4. Substrate adhesion. Undifferentiated cells have the ability to adhere to the substrate, to come in contact together and form tissues.

5. The junctions. Non-differentiated cells establish GAP junctions (communicating junction) with dynamic state, smaller in diameter than GAP junctions of differentiated cells.

6. Increased division capacity. Undifferentiated cells have a high mitotic index compared to differentiated cells.

7. Inhibition of contact. Non-differentiated cells possess the ability to migrate and inhibit contact. When cell density reaches a certain degree, both migration and cell division cease.

Alteration of the differentiation process

a) During embryogenesis, the very important feature of differentiation is the precise order of each inductor. Alteration of this order is responsible for the occurrence of congenital malformations.

b) In the adult body, the mechanism of differentiation is the same like in embryonic stage. There are no pluripotent cells in the adult body, all cells are differentiated or partially differentiated (stem cells). In adult differentiation, the major role is intercellular interactions and extracellular microclimate factors. Alteration of the succession of events in the process of

differentiation of the adult causes the appearance of tumors (neoplasms). It is known that tumor cells originated in partially differentiated cells (stem cells) from tissues. Transforming these cells into tumor cells occurs in two ways:

a) the inclusion of a viral RNA molecule, by which a new DNA which will cause cell structure, growth, division and function abnormalities;

b) the blockage of cellular interaction witch regulate the growth, division and functioning of a cell population due to the loss of GAP junctions.

Other alterations to the differentiation process are modulation, dedifferentiation and metaplasia.

Modulation is the phenomenon by which, under physiological or pathological conditions, mature cells suffer minimal and transient structural and functional changes that make them resemble the young cells from which they originated. For example, in cell cultures, due to environmental conditions, fibrocytes convert into fibroblasts. However, the transformation is reversible.

Dedifferentiation refers to the return of a differentiated cell to become a pluripotent cell again. In mammals, dedifferentiation is not possible.

Metaplasia is a pathological process in which a differentiated cell turns into a differentiated cell of another type. Metaplasia occurs exclusively in epithelial and connective tissues. For example, bone metaplasia of the uterine lining of the uterus, this occurs by transforming the connective tissue from the sub-epithelium of the uterine mucosa into another variety of connective tissue - spongy bone tissue.