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Oncogenesis Through Stem Cells

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Abstract. The hypothesis indicating the existence of tumoral stem cells and the process of oncogenesis refreshed the scientific world. The stem cells are able to proliferate symmetrically (by forming two stem cells) and asymmetrically. The existence of cancerous stem cells has been proved not only in carcinogenesis, but also in the evolution of various human tumor types (breast cancer, prostatic cancer). Furthermore, the frequent bad results following to anti-cancerous therapies seem to be the consequence of the great resistance of cancerous stem cells to many drugs. In fact it is known the resistance of normal stem cells to hostile or toxic environment. By having mentioned aspects there has been elaborated a new hypothesis regarding carcinogenesis. The initiation of the neoplastic process seems to happen in stem cells that suffer transformation (initiation), becoming in fact cancerous stem cells. These modified cells represent also the first stage of carcinogenesis, which later are involved in tumoral promotion and progression. This hypothesis based on cancerous stem cells, opened the perspective of some new researches directed against stem tumoral cells.

Key words: stem cell, carcinogenesis, oncogenesis, cancer

”The study of stem cells is one of the most
fascinate scientific adventures of the humanity”
Axel KHAN

The stem cells are the cells that undergo differentiation by generating all the organism’s cells, and have a great and unique plasticity.

A short chronological remember bring back few previous data to the actual knowledge:

- in 1950 have been notified into the bone marrow some cells capable to regenerate all sanguine cells;
- in 1958 it was realized the first graft of bone marrow;
- in 1970 Leroy STEVENS (USA) discover embryonic stem cells in rats;
- in 1981 Martin J. EVANS (UK) discover the origin of embryonic stem cells from “internal cellular mass” of blastocyst, and the possibility to preserve them in cultures;
- in 1998 THOMSON (USA) find stem cells in human embryo;
- in 2000 REUBINOFF (Israel) transform embryonic stem cells in neurons; Leroy STEVENS proves that embryonic stem cells derived from rat and implanted in uterus leads to teratoma, introducing also the term pluripotent embryonic stem cells for these cells (CHAMBON et al., 2006).

The stem cells is the only cell having the capacity to renew, to have unlimited multiplication, and to differentiate into a specialized cell. The stem cells having mentioned properties originate from embryonic and fetal cells. During a period of time the researchers

have been fascinated by the possibilities of the genetic, marginalizing the cell that is the base of the life into its complexity. Also, the return to the study of the cell it is not a simple event. In older books of histology are described strain cells or stem cells from bone marrow, which is later identified as multipotent cells that differentiate to red blood cells, granulocytes, and megakaryocytes.

Embryonic stem cells have been discovered in 1981 by isolating cells form a rat embryo, and their cultivation *in vitro* lead to the formation of several cell types encountered normally in adult rats. In 1994, A. BONGO succeeds to provoke the development of supernumerary embryos obtained by *in vitro* fecundation, until to the blastocyst stage of development (five days embryo). In this stage of embryo development, differentiate a group of peripheral cells that represents the origin of placenta, and a group of cells forming the central mass, respectively embryonic button. The author isolated and seed some cells from embryonic button, and notice that some of them undergo differentiation during some others are dying after a few days. THOMSON, in 1995, isolates and seeds embryonic stem cells from primates. Three years later, the authors succeed to induce *in vitro* proliferation of human stem cells derived from an embryo in the stage of blastocyst.

Depending on the capacity of multiplication and specialization, stem cells are classified in:

- unipotent cells, which are able to produce a unique type of differentiated cells; the best example are the stem cells of the skin utilized in autografts as a consequence of extended burn of the skin;
- multipotent cells that generate a limited number of cell types, such as bone marrow stem cells from which originate red blood cells, white cells and platelets;
- pluripotent stem cells are able to produce all cells of the body, excepting placental cells; these can be found in embryonic button of a blastocyst;
- totipotent stem cells have a great ability to generate a complete body, and are found in a embryo of 2-8 cells, respectively at 3 days following to oocyte fecundation by spermatozoa.

The adult body has only unipotent and multipotent stem cells.

Actually are known the following characteristics of stem cells:

- are able to survive indefinitely in adequate environment;
- produce differentiated cells;
- during evolution can establish cellular ”societies” by forming tissues and organs;
- following its division generates two cell types: a stem cell and a differentiated one.

Stem cells have a unique capacity to form by division a stem cell (self renew cell) and a differentiated cell. The proliferative capacity of the stem cells combined with the great ability to undergo specialization, indicates a unique structure of the body; this cells derive from embryonic and fetal tissue.

In 1998, THOMSON et al, isolated for the first time pluripotent stem cells from human embryo; later had been proved the ability of these cells to differentiate, and the regenerative potential of pluripotent stem cells when are placed into a tissue or organ.

At the beginning of this millennium the researchers established the existence of three stem cell types, with different morphofunctional characteristics: **adult stem cells, fetal** and **embryonic stem cells**.

Adult stem cells are undifferentiated cells capable to differentiate in some cell types that are characteristic for various tissues; hematopoietic adult stem cells from bone marrow are capable to form sanguine cells and immune cells, but in some other conditions are able to transform in neuronal cells (cells having some neuronal characteristics).

Adult stem cells are capable of self renew, and do not replicate indefinitely in cell cultures. Some sources of adult stem cells are: bone marrow, cornea, retina, bone, skeletal

muscle, dental pulp, skin, gastrointestinal mucosa, and pancreas. In addition, have been isolated adult stem cells in hippocampus from brain (memorizing region).

Plasticity represents the ability of the adult stem cells to regenerate and form differentiated cell types located in another tissue. Also, in experimental conditions, adult stem cells from bone marrow generate cells having some characteristics of neurons, and another cellular type that is able to accommodate in nervous tissue. The concept of plasticity has to be further investigated; in special conditions stem cells have the capacity of ***genetic reprogramming*** by forming cells specialized for various tissues.

Experimentally has been proved that adult stem cells, by their plasticity, have the capacity to take over the control of a tissue which had lost the function.

Fetal stem cells, progenitor or precursor cells originate from fetal or adult tissue; these cells have partial specialization and by division form two specialized cells that are not capable of self-replication. In time these cells are dying.

Primordial cells have been isolated from fetal gonadal tissue after 5 until to 10 weeks post-fertilization. In fact these cells are primordial cells for oocytes and spermatozoa. From primordial germinal cells have been developed *pluripotent stem cell lines*, which have the capacity of replication for a long period of time. In addition, are able to form numerous cell types and even human tissues. Human embryonic germinal cells and human embryonic stem cells are not similar genetically and molecularly. The two cell types are also different by proliferation potential and differentiation.

Embryonic stem cells derive from internal mass of the blastocyst in the status of pre-implantation (at about 5 days post-fertilization). Human embryonic stem cells originate from primordial fetal germinal cells at about 5 to 10 weeks post-fertilization.

IMPORTANCE OF THE STEM CELLS FOR PATHOLOGY

The studies and experiments involving stem cells have the target to evaluate the potential benefits in the treatment of some disorders during aging. According to this, there is the tendency to prolong the survival period due to wear and tear of the organism by using stem cells. In the same time, the researchers showed the possibility to induce some diseases, such as cancer initiation and progression by using stem cells. The hypothesis indicating the existence of tumoral stem cells and the process of oncogenesis refreshed the scientific world. The stem cells are able to proliferate symmetrically (by forming two stem cells) and asymmetrically. In symmetric division one of daughter cell preserves the embryonic character of a stem cell during the other one (progenitor cell) is able to initiate division in the process of differentiation. The progenitor cells, in both fibroblastic and epithelial cells, have a limited number of divisions (Hayflick limit). A terminal differentiated cell can't undergo some other divisions (red blood cells, the cells from crystalline, etc.). Also, there is a new hypothesis regarding the process of carcinogenesis originating from tumoral stem cells, the neoplasia being one of the most often encountered diseases in animals and humans.

By synthesizing the data regarding carcinogenesis Trosco (2009) have two hypotheses regarding the origin of cancer:

1. The initiation of the carcinogenesis using stem cells;

2. Reprogramming of a de-differentiated somatic cell to gain some properties that are specific for cancerous cells.

The epigenetic changes at cellular level are realized by local no-mutagenous events promoting also tumoral transformation. The changes of oxidative status and gene expression in cells are features that are happening during tumoral transformation. Mentioned aspects cannot occur only by mutation. The epigenetic alterations of the expression of some genes can occur during transcription, translation or post-transcription.

Concluding, the both genetic and epigenetic mechanisms are involved in carcinogenesis.

The concept of multistage development of cancer by initiation, promotion, and progression includes the involvement of both epigenetic mutation and suppressor oncogenes.

The origin of an initiated cell, which is later capable to induce tumoral development, could be a stem cell or a differentiated somatic cell. Also, it is not clear the role of stem cells in carcinogenesis (TROSCO).

V. R. POTTER consider the adult stem cells involved in cancer origin, mentioning: *oncology is a partially blocked ontogenesis*.

The toxicology of carcinogenesis supports the origin of cancer by mutations of oncogenes and suppressor genes. Epigenetic changes at cellular level are realized by toxic non-mutagens that promote tumoral transformation. The changes in oxidative status and also in genes expression of the cell occur during tumoral transforming. Mentioned modifications cannot be explained in random mutations (TROSCO).

According to TROSCO (2009) the multistage theory of carcinogenesis confirms the three stages evolution of cancer onset, the author bringing completions and scientific support for this theory.

The first stage involves a single cell, respectively premalignant or primary tumoral cell. It has to be proved if the first premalignant cell originate form a stem cell or from a differentiated somatic cell. This indicates a dedifferentiation of a differentiated cell gaining as well embryonic character and unlimited proliferative potential, but the dedifferentiated cell is unable to undergo back terminal differentiation.

The second stage of promotion it is characterized by clonal divisions of initiated cell and/or apoptosis inhibition. In this stage, by mitosis and apoptosis inhibition, a fast numerical growth of tumoral cells occurs.

In **the third stage of progression,** a cell that passed through initiation and promotion receive all the characteristics of a cancerous cell. In the stage of promotion, by using some epigenetic mechanisms, initiated cell is stolen from genetic and tissular regulating factors. According to this, initiated cell undergo clonal division processes.

The promoting factors may have specificity for specie, sex and organ, and have to act systematically for a long period of time. It must react on initiated cell in the absence of agents that could prevent reorganization of both gap junctions or cellular receptors of stem cells. On the other hand, the non-adaptative alterations of intercellular signals can lead to the interruptions of the signals that control the normal evolution of the cell. In order to complete the promotion it is necessary to correlate a sum of factors that act successively as promoting factors, in the same time with absence and inactivation of inhibiting factors. There have been differentiated several stages:

- the first it is realized by inhibiting abnormal division of a normal cell, leading to hyperplasia;
- induction of some anomalies in the division of stem cells (teratogens from the group of retinol and thalidomide that act during embryonic or fetal period);
- the third stage is represented by the induction of abnormal apoptosis, similar with that encountered in hair follicles and intestine following to irradiation.

The hypothesis of carcinogenesis originated in stem cells indicates that all the organs and tissues should have adult stem cells. These stem cells should not express gap junctions or connection genes, because the mentioned structures are necessary for differentiation and development (TROSCO).

”The initiation” of cells is represented by accumulation of some characteristics and properties that make it immortal. Also, a somatic cell has to be re-programmed to regain the properties of embryonic stem cells. Comparing to a stem cell that is able to divide by both

ways (symmetric and asymmetric), initiated cell is able to divide only symmetrically in order to produce two initiated cells after mitogen stimulus. Tumoral promoters are able to increase the number of initiated cells, and in the same time prevent apoptosis in initiated cells.

The **theory of carcinogenesis originating from somatic cells** indicates that in every tissue exist multipotent stem cells derived from pluripotent ones. These stem cells seem to be immortal; it ends the cell cycle once with differentiation and apoptosis.

In the case of **stemal origin of cancer**, the initiation prevents dead of adult stem cells more than induction of unlimited proliferation of somatic cells. Also, an initiated stem cell is able to have only symmetric divisions.

We have to mention again the immortality of stem cells, and the necessity of re-programming of somatic cells to gain immortality. In the case of stem cells it isn't induced this ability, but is blocked the differentiation in various cellular types.

The cancerous process could be the consequence of viral action that blocks the dead of adult cells in a tissue. This may explain the association between some tumourigenic viruses, such as papilloma virus, hepatitis virus and herpes virus, with human cancer. If the associated viruses affect adult stem cells, it may indicate the initiation of these cells without becoming cancerous cells. Also can be explained, probably, the great reduction of the cervical cancer risk by using vaccines against papilloma virus.

The adult stem cells have been isolated from mammary parenchyma, being proved the lack of functional gap junctions or any other connexions in these cells.

The fundamental problem it is to demonstrate the capacity to dedifferentiate (until to the embryonic state) of some differentiated somatic cells. Some experiments demonstrate the ability of fibroblastic cells from adult rat, monkey, and from human skin to undergo dedifferentiation until to embryonic stage, generating also pluripotent stem cells. According to this, it can be suggested that a normal differentiated cell can be re-programmed to go back to the initial embryonic state.

Conceptus of cancerous stem cell has been utilized to explain why the current anti-cancerous therapy is inefficient. This hypothesis based on cancerous stem cells, opened the perspective of some new researches directed against stem tumoral cells.

Numerous studies noticed the presence of cancerous stem cells in various tumours: breast cancer, prostatic cancer, etc. The presence of tumoral stem cells has been proved by adequate techniques. There are no therapies directed against stem cells.

Causes of non-satisfying therapies:

- some treatments disintegrate the DNA, induce mutations and chemoresistance in surviving cells;

- the stem cells are naturally more resistant to some drugs; logically, the stem cells have to be more resistant to some toxic tissular environments.

The stem cells don't express functional gap junctions or connexion genes, but manifest resistance to therapies by some genes that are resistant to toxic agents.

There is the possibility to exist in some tissues of precancerous stem cells, and cancerous cell lines.

Malign cancerous cells that do not control the growth and, in addition, do not have the ability of terminal differentiation or apoptosis, do not express functional GJIC (gap junction inhibitors). This has been observed in stem cells too. Also, stem cells preserve the state of immortality and undifferentiation no matter of tissular messages.

In the synthesis article regarding the cancerous stem cells, TROSCO (2009) ends the approached subject with the following phrase: *the comparative study from human and veterinary medicine, by using similar molecular methods, could initiate new steps to understand, prevent, and treat the cancer*.

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