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SAFETY IN USE OF STEM CELLS IN REGENERATIVE MEDICINE

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Premise

Today, more and more, we talk about stem cells and their possible use to regenerate tissues or organs. Even under physiological medicine, recently, treatments have been proposed based on cells defined by the generic term of stem cell (**liposowing**).

We should, in light of any legislative issues, to make a clarification in this scientific field. Indeed, the generalization of the term stem cell can lead to include useful treatments and therapies, without biological damage, including treatments that must be rightly adjusted and maintained in appropriate environment.

Attitudes towards the use of stem cells for research or medical care vary from country to country. In Germany, for example, the extraction of stem cells from human embryos is illegal. In Britain is perfectly legal, but laws are strict. In many countries there is still no explicit laws designed to regulate research on human stem cells.

Since the use of embryos is a matter of great controversy in ethical terms, scientists around the world are looking for other sources of stem cells. The type of stem cells found in bone marrow of adults seems to be a possibility. Today, the discovery of the high numbers of adult stem cells present in adipose tissue resulted in vogue the conservation of this cell type.

Moreover, scientists have begun to manipulate these adult stem cells so that instead of producing only one type of tissue, may give rise to other cell types.

Stem Cells

Stem cells are primitive cells non-specialized with the ability to become many other cell types of the body.

To be defined as a stem cell this must have both the capacity to perform an unlimited number of replication cycles, while maintaining the same level of differentiation, and the ability to give rise to one or more mobile species.

Depending on the capabilities we can distinguish four types of stem cells:

- The **totipotent stem** cells capable of developing into a complete organism.
- The **pluripotent stem** cells able to specialize in all types of cells that found in an individual.
- The **multipotent stem** cells able to specialize only in certain cell types.
- The **unipotent stem** cells that generate only one type of specialized cell.

Stem cells are also classified according to the source of derivation, as embryonic, fetal, amniotic, and adult.

The **pluripotent stem cells** are induced obtained in the laboratory to the regression of adult cells (already determined, for example, skin) in a state stem cell (pluripotent), using a pool of specific genes, placed via a viral vector. Therefore, in future these cells may be used to obtain adult stem cells already established, belonging to any tissue or organ.

The bulk of the regenerative work leading to the repair and/or to proliferation of tissues, is played by cells no-stem defined **progenitors** or **transit amplifying cells** (**TACs**), directly derived from stem cells, but partially differentiated and lack the ability to self-renewal . This replicative strategy, which limits the number of replication events that a stem cell can do, is based on the need to keep checking the number of stem cells and maintain the integrity of the genome of stem cells by reducing the risk of damage to DNA (i.e. mutations). Mutations in stem cells are extremely harmful and dangerous, because are transmitted to all generations of daughter cells derived from stem cells. Unlike, a mutation in a TAC affects only a single generation of cells, that after some time will be replaced. or may induce stem cells to develop into cancer, becoming a stem cell tumor, a type of cell that is probably responsible for the continuous supply of new cells that characterizes the development and especially the recurrence of cancer.

The transit amplifying cells

Adult stem cells or transit amplifying cells are unspecialized cells that reproduce daily to provide certain specific cells, e.g. red blood cells are generated daily in the body from hematopoietic stem cells. Until recently it was thought that each of these cells can produce only one type cell. Today there were evidence that adult stem cells can become many different forms: it is known that stem cells in the stroma of the bone marrow can become liver cells, neural, muscle, kidney, and follicular. Transform one type of stem cell into another is called **transdifferentiation**. Useful sources of adult stem cells are actually detectable in all organs of the body.

Cell differentiation

This is the process by which a less specialized cell becomes more specialized. Cell differentiation occurs during the development of a multicellular organism, but also common in adult stem cells during tissue repair and during normal cell turnover. The differentiation changes dramatically the size of shape cell the membrane potential, activities and metabolic response to signals.

The main types of molecular processes that control the cell differentiation, involve the cellular signals. Many of the signaling molecules used for transmit information from one cell to another are called **growth factors**. Typically, a ligand produced by a cell binds to a receptor of another cell, inducing a conformational change of the receptor. The receptor then catalyzes a cascade of phosphorylation reactions that eventually trigger a transcription factor or cytoskeleton proteins, activating the differentiation process of the target cell.
Other important mechanisms fall into the category of the **asymmetric cell divisions**, divisions which give rise to daughter cells with distinct developmental fates. Asymmetric division is a fundamental step for the development of the embryo and also for storage of stem cells. Normally when a cell divides, produces two identical daughter cells but in some cases the daughter cells have different properties. Scientists have found that for the occur of the asymmetric division , it is necessary that the *mitotic fuse* is positioned towards the rear of the cell (not centrally). This positioning of the *fuse* occurs through the interaction of the microtubules forming the *mitotic fuse* and the network of actin filaments adhering to the plasma membrane. This leads us to investigate the molecular interactions of cells with other cells based on the accession process

The cell adhesion

Accession is a system of communication between cells based on the interaction of pairs of receptors expressed by cells adhering to each other. This system is an alternative to communication related to the release of cellular soluble messengers (hormones, neurotransmitters, cytokines, etc.).. The cell adhesion is involved in a variety of physiological and pathological mechanisms. The adhesion between cells happens when a plasma membrane receptor form a bond with one molecule that is located in the extracellular matrix, or in the neighboring cell. The receptor binding then establishes a connection with the cell cytoskeleton.
From this, adult stem cells have a state of differentiation that implying cell junctions. These are a specialization of the membrane strip that enables and controls the processes of adhesion between cells. Among the various types of cell junctions, the junctions members provide to structural support to tissues using binding to actin filaments. We can differentiate groups of **adhesion and focal contacts**.
The adhesion contacts are links established, between a cell and other adjacent, thanks to cadherins. The focal contacts, however, are joints that connect the cell to the matrix, except that instead of cadherins they use integrins, associates with actin filaments via transmembrane proteins such as the alfa-actina, talina, vinculina and filamina
Therefore, this type of cells may express a regulation of inhibition contact with other cells following the accession which induces a block to the anarchic proliferation. In the normal process of contact inhibition is mainly the accumulation of p27Kip1

protein to trigger the inhibition of Cyclin E/CDK2 complex, which in turn inhibits the phosphorylation of Rb protein, leading to cell cycle block.
We can now reach the ultimate explanation and that the absence dl risk of neoplastic transformation of adult stem cells.

Carcinogenesis

Cancer is characterized by the uncontrolled reproduction of some body cells that stop responding to physiological mechanisms of cell control after damage to their genetic heritage.
For a cell becomes cancerous, it must accumulate a series of damage to its system of control of reproduction. To all cancer and precancerous cells have occurred changes, often very large, their chromosome structure (karyotype). Underlying the pathogenesis of cancer is therefore the mutation of certain genes

- proto-oncogenes,
- tumor suppressor genes,
- genes involved in DNA repair.

The latter are those that ensure genetic stability because if other genes are mutated by the carcinogens actions, these repair the DNA before the replication, which was before these changes become permanent.
Mutations necessary that a given cell must accumulate to give rise to cancer are as follows, and are common to all types of cancer:

1. acquisition of autonomy multiplicative for incapacity to submit to the regulatory mechanisms of cell proliferation;
2. absence of density-dependent inhibition (the normal cells multiply up to a certain cell density, reached by which they become quiescent);
3. reduced adhesion with other cells or tissue components;
4. absence of extracellular matrix (usually digested by proteases), which promotes the invasion of adjacent normal tissues;
5. angiogenesis: formation of new blood vessels to deliver oxygen and nutritional factors to cancer cells;
6. reduction or loss of ability to differentiate;
7. acquisition of the capacity for unlimited replication effect of the expression of telomerase;
8. reduction or loss of the possibility of getting programmed cell death (apoptosis).
9. loss of so-called contact inhibition.

These events require more than one mutation, in general, the most mutations of certain classes of genes. The loss of proliferation control will take place only in response to mutations in genes that control cell division, cell death and DNA repair processes.
Because the cells begin a uncontrollably division must be damaged the genes that regulate growth. The proto-oncogenes are genes that promote cell growth and

mitosis, that is the process of cell division, the tumor suppressor genes discourage cell growth or prevent cell division to allow DNA repair. Typically requires a series of several mutations in these genes before a normal cell turns into a cancer cell.
So, are required in various types of gene mutations because they form cancer. A mutation limited to one oncogene would be removed from the normal control processes of mitosis and tumor suppressor genes.
A mutation of a single tumor suppressor gene, would also be insufficient to cause cancer by the presence of numerous copies of "backup" genes that duplicate its function. It is only when a sufficient number of proto-oncogene is mutated in oncogenes and a sufficient quantity of tumor suppressor genes have been turned off that the signals to cell growth are superior to the inhibitors signals that this increases rapidly and out of control.

Conclusions

From the above and to confirm the safety of the Liposowing, we can conclude that the use of adult stem cells or transit amplifying cells derived adipose tissue is devoid of possible side effects and requires no adjustments control laws.

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