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Adult Stem Cells: Will Nature find a Way?

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Introduction

The stem cells and their abilities are resulting in a medical revolution called regenerative medicine. We are living in a very exciting era because we see medical paradigms everyday that will rebut, discuss and guide our practice for years to come. We are part of this great change and in a next few years medicine will radically change its precepts and we will not see the medicine we know today. The old conception of the cell as a small structure will become the cell as a complex individual, able to communicate, interact, adapt and function. All these changes lead us to know more, not only about Science, but also about philosophy and religion. Science currently provides detailed information about the life that extends the base for philosophical and religious reflections, making it impossible to separate them.

We firmly believe that the clinical use of adult stem cells has sufficient evidence supporting its clinical applications. The mechanism of action of these cells, their doses as well as their advantages is quite understood today and these cells carry null complications.

Different works described that stem cells, activated by specific chemokines present in the damaged tissues, initiate the migration (towards the injury site), adhesion, and differentiation of these cells in order to repair the injured tissues. Moreover, these also activate the resident stem cells, quiescent in specific tissue niches [1,2]. These cells are safe to use and do not cause tumors or autoimmune reactions, which are effective in causing changes in the clinical evolution of various diseases. The use of stem cells in medical treatments, from the knowledge of their immunological and regenerative capacities has many preclinical and clinical antecedents.

Antecedents

In 1984, Cesar Milstein shared the Nobel Prize in Physiology or Medicine with NielsKaj Jerne and Georges J. F. Köhler. In this work Milstein obtain the hybridome by fusing a specific antibody-producing B cell with a myeloma (B cell cancer) cell that is selected for its ability to grow in tissue. This was the first experience where the fusion of two different cells and the production of an immortal hybrid cell line were achieved. The hybridome causes the appearance of mono-clonal antibodies specific and it also earned them immortality to the authors.

In 1994, the Danish Academy of Sciences awarded the Nobel Prize for Medicine to professors Alfred G. Gilman and Martin Rodbell for their work regarding the role of the G protein and its part in cells signaling. This was a major step forward towards the molecular biology, which showed in detail how cells function and provided a new basis for reflection of nature. The way of working of the amplifying G protein signals that stimulate the specific cell receptors showed the way stem cells function. Multifaceted molecules, housed in the cell membrane, coordinate cellular responses to many external signals.

Both experience shows that stem cells can communicate, and cause changes that are points that deserve to be analyzed.

Cellular Communications and Mechanisms of Action

All cells in the human body emit signals, listen, obey and decide their fate, from undifferentiated stem cells to fully differentiated cells. Each individual cell is a true miniature as its core contains all the genetic information, and lives, as it was, its own life: gets nutrition from the outside, transforms, gets energy, eliminates wastes, manufactures components that body needs and exports them to the right place, is played by processes that doubles and divides the genetic material, may change jobs and has an exemplary degree of fellowship.

The functioning of a cell signal is enormously sophisticated but yet fully understood. It is safe to say that best example of this are the stem cells that show more plasticity and transforming power. Studies within the last few years have demonstrated the capacity of these adult stem cells to differentiate into cells of lineages such as hepatocytes, renal cells, pancreatic islets and even early astrocities [3-8].

Just like a human society organizations, cells depend on each other for their existence and operation. There is a set of specific processes by which cells act in a very specific way. It is a fascinating world that everything runs on "information". We can say unequivocally that the cells "think and talk" to each other using a specific chemical language and in this direction the scientists discovered other particles as the chemokines that are part of this multilingual process of cellular communication.

Adult stem cells receive signals from the environment that surrounds and influences differentiation. We know that the plasticity of stem cells and the differentiation mechanism is the same but the final result is different. The peripheral blood, bone marrow, placenta, umbilical cord, adipose tissue and menstrual blood stem cells have a predisposition, and a pathway, different differentiation, and this is functionally reasonable. The presence of different receptors and signals is cause of this particularity surely.

We believe that there is scientific evidence supporting the theory of cellular communication, not only as an in vitro experiment, but as a truth, with clinical demonstration in the real world.

In this regard, the work of Hussein et al. [9] was published in 2005 that obtained stem cells from male mice expressing the CRE-LoxO system with

green fluorescent protein and were injected into the female mice, which was lethally irradiated to stop secreting insulin. After 4 to 6 weeks, islets of Langerhans with Y chromosome marked with fluoresce in were observed in the pancreas of the female mice. This experiment was the first one to describe the cellular migration and its differentiation without evidence of cellular fusion. Sordi et al. [10] demonstrated that the cytokines involved in the migration of bone marrow stem cells and stimulation of cell differentiation towards β cells with secretion of insulin are CX3CL12 and CX3CL1. Various research teams corroborated the mechanisms. In addition, it has been demonstrated that pancreatic chemokines could promote the aggregation of bone marrow mononuclear and progenitor cells transplanted into the pancreatic circulation and these cells and their secreted growth factors provoked the activation of quiescent stem cells that differentiated into insulin-secreting pancreatic cells.

These two works are particularly important to us because they provide important information in a chronic, incurable disease that affects millions of people such as diabetes. Our team was strongly influenced by their results which are the basis of our pathophysiologic reasoning.

Cell Recruitment and Effective Number

It is also known that if the cells work together it is easier to achieve their global objectives. In this respect it was discovered that there are cellular mechanisms that allow them to coordinate work using a new capability, recently described in bacteria, called "quorum sensing". A study published by researchers at the University of Linköping, Sweden, describes how the human pathogen *P. Aeruginosa* and other bacteria communicate with each other through a process of self-inductance ("quorum sensing") that is important for growth, virulence, motility and biofilm formation.

This work demonstrated that after injury to the human body, a signal that causes bacteria to build up around the damaged tissue is issued. After the amount of bacteria is sufficient to act as if it were a multicellular organism, they are able to generate biofilms, dense structures capable of withstanding both, the antibiotics as well as the human immune system.

All these changes are initiated when the molecules responsible for the communication, short chain fatty acids called AHLs, join the multiple receivers within the bacterial cells. In low concentrations, white blood cells are more flexible and effective, but with more bacterial concentrations the opposite effect occurs, which weakens the immune system and leads to progressive infections and inflammations.

Almost the same happens in the intrinsic regenerative and reparative mechanisms of the human body. When tissue injury occurs, signals that cause stem cells to migrate and adhere to the injured tissue are issued. When the amount of cells is enough, they act as a multicellular organism. They are able to generate new functional tissues and structures identical to the injured one. At low cell concentrations or during major tissue damage, the damage is irreparable and the conversion or appearance of nonfunctioning scar tissue replaces normal cells with serious clinical implications which are studied extensively over the past few years.

The observed beneficial effects of adult stem cell transplantation have led to numerous human clinical trials in the past several years. Stem cell transplants in blood malignancies such as leukemia's demonstrated safety and efficacy [10,11]. The use of adult stem cells in myocardial infarction showed a significant improvement in ventricular function [12-16]. Similarly the use of bone marrow stem cells in osteoarthritis [17,18] and peripheral vascular diseases [19-22] showed new cartilage and angiogenesis, with significant benefits in suppressing the pain and improving functional capacity. In liver cirrhosis, the subject's condition was significantly improved and maintained stable after receiving human umbilical cord blood-derived mononuclear cell (CBMC) transplantation [23].

Different working group showed better clinical outcomes when patients receive large quantities of cells in the implants. This also demonstrates the low impact on clinical trials achieved where cell infusion is performed systemically. Herreros et al. [24] demonstrated that 70% of stem cells released into the venous circulation stopped in the lung and only a small amount of cells arrived to the heart, kidneys and liver.

Immunomodulatory Capacities of Mesenchymal Cells

Recently it was demonstrated that different types of stem cells, including mesenchymal stem cells, have properties allowing them to regulate the function of immune cells. The therapeutic use of mesenchymal stem cells in autoimmune diseases is being studied in different pre-clinical and clinical experiments in adults and children [25-31]. In addition, other studies showed that mesenchymal cells also secrete peptides that act as modulating factors for local micro-immunity [32-35]. We have many clinical antecedents about the capacity of this cell in decrease the acute reject in bone marrow transplant or in recently diagnosed type 1 diabetes mellitus. Voltarelli et al. reported significant increase in C-peptide or pancreatic function after adult stem cells transplantation combined with immunosuppressant [36,37] and we observed a reduction in anti-islet (ICA) and GAD antibodies in type 1 diabetics patients newly diagnosed, which remained during the follow-up at 12 months, and noted that the negative results for antibodies is associated with increased C peptide, decreased requirement for daily insulin dose, and decreased concentrations of glycosylated hemoglobin (HbA1c) [38]. In this way other diseases like multiple sclerosis or refractory systemic lupus erythematosus show same results [39,40].

This is a perfect example of team spirit that dominates the cells, which can cause changes in cells of different systems and an example of this is the ability of stem cells of the immune system to reset and disable activated T cells in autoimmune diseases. The molecules secreted by mesenchymal cells are predominantly anti-inflammatory in nature. Mesenchymal cells play a central role in immunologic homeostasis and several studies have shown that mesenchymal cells (MSCs) can secrete specific peptides, such as hepatocyte growth factor, that can contribute to the creation of a local immunosuppressive environment.

Similarly, transforming growth factor-1 is also involved in T cell suppression by working with hepatocyte growth factor in promoting the allo-escaping phenotype [41]. Di Nicola et al showed that neutralizing antibodies to hepatocyte growth factor and transforming growth factor-1 restored the proliferative response in mixed lymphocyte reactions [41]. Other suggested factors include interferon (INF), tumor necrosis factor, and interleukin (IL)-2 [42,43]. Interleukin-10 also seems to be constitutively expressed by MSCs and has a well documented role in T cell regulation and in the promotion of the suppressor phenotype by antagonizing the action of IL-12 during induction of the inflammatory immune responses.

The effects of these signals in the immune system are: reduction in the activation of T cells and monocytes, changes in lymphocyte proliferation, reduction of proinflammatory cytokines and inflammatory increased.

It has been demonstrated that adult stem cells remain undifferentiated and modify the microenvironment blocking, or preventing the activation of other cells called dendritic, that activate T lymphocytes.

Conclusion

Under this new magnifier we could say that diseases are actually cell disorders or the disorders of their microenvironments where the main factor is a cellular communication problem. Perhaps we can coin the term cell Deafness? Or maybe the problem is that there are few cells in critical locations? Cancers, heart diseases, vascular diseases and other

diseases where pharmacological treatments have failed to make an impact should be observed through the prism of regenerative medicine where the body is healing itself and not the drugs, and the radiations. We know the mechanism of action, have not serious adverse events in clinical research, we have safe indications, and what are we waiting?

Some persons will think that this process of unification of the function means a new triumph of reductionism, because it allows us to understand how life works through physical and chemical processes, without resorting to pipe dreams, souls or vital principles. The microphysical world that we discovered is so fantastic that it is difficult not to wonder beyond what science can discover in the future.

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