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Revisiting Terminology and Characteristics of Stem Cells

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Abstract

The majority of populations of differentiated cells are subject to renewal. Progenitor cells (cells-predecessors) and differentiated cells, having started the differentiation pathway or having finished it, can divide a limited number of times and are not capable of ensuring tissue regeneration during the whole period of ontogenesis. Renewal of tissues over such a long period is impossible without the participation of a specialized system which is responsible for regeneration. The given system is represented by pluripotent stem cells. Pluripotent stem cells, which conduct regeneration of all body tissues during ontogeny, are formed during implementation of the development program of the fertilized ovum, along with the formation of tissues and organs of the new organism. Being a separate direction of differentiation of embryonic cells, pluripotent stem cells are not embryonic cells. The immune system takes part in the formation of tissue-specific receptors among pluripotent stem cells. The latter remain pluripotent until the formation of tissue-specific receptors in them, and become committed (tissue-specific stem cells) after the formation of such receptors. Committed stem cells (tissue-specific stem cells) that migrate through the extracellular matrix replenish the progenitor cells of all tissues. Mesenchymal stem cells are the precursors of fibroblasts, and they only create conditions in the extracellular matrix for the migration and differentiation of committed (tissue-specific) stem cells in the places of cell death.

Keywords: pluripotent stem cells, regeneration, immune system

Introduction

The majority of populations of differentiated cells are subject to renewal. Cell death take place over the course of all of ontogenesis as a manifestation of normal vital functions of the organism. Death and the breakdown of old cells with following regeneration are constantly taking place in the organism, which thereby ensures the organism's normal vital functioning. Several million new cells should be formed each second in order to support the organism

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in a normal state [1, 2]. Progenitor cells (cells-predecessors) and differentiated cells, having started the differentiation pathway or having finished it, can divide a limited number of times and are not capable of ensuring tissue regeneration during the whole period of ontogenesis [1, 2]. Renewal of tissues over such a long period is impossible without the participation of a specialized system which is responsible for regeneration. The given system is represented by pluripotent stem cells, which are capable of differentiating themselves into all types of somatic cells and into a line of genital cells, and are also capable of renewing themselves over the whole life-cycle of the organism [1, 2].

Pluripotent stem cells, which conduct regeneration of all body tissues during ontogeny [2], are formed during implementation of the development program of the fertilized ovum, along with the formation of tissues and organs of the new organism. Being a separate direction of differentiation of embryonic cells, pluripotent stem cells are not embryonic cells [1, 2]. The use of embryonic cells that implement the development program as stem cells can be accompanied by the formation of teratomas [1, 2, 3].

The Role of the Immune System in Forming Tissue-Specific Receptors among Pluripotent Stem Cells and in Developing their Unipotency

The directed migration of pluripotent stem cells is impossible without the formation of specific chemoreceptor [2, 4]. Their appearance should be preceded by a series of interim stages. Initially, in response to desialation and the appearance on the surface of old or intensively proliferating cells of glycoproteins with free end mannose, there is binding of antigen-presenting cells (macrophages and other) with tissue specific antigens. Antigen-presenting cells deliver tissue-specific antigens of old dead cells through lymph nodes or other lymphoid organs to T-helpers. After analyzing the received antigens, T-helpers use antigen-presenting cells as intermediaries (increasing the likelihood of a meeting between the constantly circulating cells) to activate the pluripotent stem cells/T-killer cells with formation on their surface of tissue-specific receptors that determine the place of their migration [1, 2, 4, 5, 6]. T-helper cells adhere to endothelial cells of postcapillary venules, squeeze between them, and then migrate to lymphatic vessels, through which they enter the lymph nodes. This path is repeated by T-killer cells [5], and pluripotent stem cells [2, 4]. The presentation of antigens of virus-infected cells or antigens of foreign tissues leads to activation of killer T-cells [5, 6], while the presentation of autoantigens of dead old cells leads to activation of pluripotent stem cells with their subsequent focus on the recovery of the respective tissues [2, 4]. Participation of T-helper cells in the process of tissue renewal [2, 4] determines the high prevalence of autologous antigens among the peptides presented to T-helper cells and analyzed by them: 90% of them are common to the majority of various cells in the organism, while 10% vary amongst each other and only 1% of the latter are made up of foreing antigens [5]. The presentation of 99% autoantigens to T-helper [5] testifies to the following formation of a significant share of complimentary receptors to precisely autoantigens [2, 4]. Accordingly, the management of regeneration processes is the leading function of the immune system [2, 4].

In accordance with the theory of clonal selection [1] each stem cell, which is committed to producing one certain antigen-specific chemoreceptor, should form a family of clone of cells which have identical antigen specificity, analogous to cells of immunological memory. For pluripotent stem cells this is a step towards unipotency. Following the formation of tissue-specific receptors, stem cells begin differentiation and stop being pluripotent [2]. Therefore, the term “pluripotent stem cells” should apply only to stem cells that do not yet have tissue-specific receptors. After the formation of tissue-specific receptors, stem cells should be considered “committed” or “tissue-specific stem cells”.

Cells of various tissues have tissue-specific receptors that allow them to communicate with other cells or with the extracellular matrix. The combination of tissue-specific receptors and the corresponding antigens of cells and the extracellular matrix are determined by the morphogenetic code that determines the organization of cells in tissues [1]. The

superfamily of tissue-specific receptors (integrins) is divided into groups, represented, in particular, by the family of tissue-specific receptors on the surface of lymphocytes, macrophages [1] and committed (tissue-specific) stem cells [2], as well as by the family of receptors of fibroblasts [1]. The presence of these groups of receptors indicates that in response to the death of old cells, or the cells of damaged tissues at pluripotent stem cells (with participation of the immune system) tissue-specific receptors are formed to the antigens of the dead cells (MHC I class), as well as receptors to antigens of dead fibroblasts (MHC I class) of fibronectin of the basal membrane, as well on collagen fibrils of the extracellular matrix, which determine their direction of migration to sites of cell death. Under the influence of the cell environment and the extracellular matrix, migrated committed stem cells with tissue-specific receptors to antigens of dead cells differentiate into cells similar to the dead cells, and those with receptors to the antigens of fibroblasts of the extracellular matrix differentiate into fibroblasts [2]. Fibroblasts form components of the extracellular matrix that attract committed (tissue-specific) stem cells, which determine the direction of their differentiation, as well as create the necessary conditions for their migration. Committed stem cells (tissue-specific stem cells) migrate through the extracellular matrix and basal membrane and become the poorly differentiated progenitor cells under the influence of an original "morphogenetic code" of cell growth factors on fibronectin and laminin of the basal membrane, as well on collagen fibrils of the extracellular matrix [1, 2, 4].

The Meaning of Mesenchymal Stem Cells in Regeneration

Fibroblasts, being part of connective tissue, are distributed throughout the body. The precursors of fibroblasts – immature fibroblasts, called mesenchymal stem cells – can turn into all kinds of connective tissue cells, represented along with fibroblasts of fat, smooth muscle, cartilage and bone cells. The mutually reversible transformations of connective tissue cells are regulated by the extracellular matrix, hormones and growth factors [1]. Considering that fibroblasts and their precursors (mesenchymal stem cells) have receptors to the tissue-specific antigens of dead fibroblasts (MHC I class) of fibronectin of the basal membrane, as well on collagen fibrils of the extracellular matrix [1], the mesenchymal stem cells (fibroblast precursors) do not migrate from their places of local administration, unlike pluripotent stem cells. The multipotency effect observed during local administration of mesenchymal stem cells (precursors of fibroblasts), is due to the formation of extracellular matrix components, which attract committed stem cells, and which determine the direction of their differentiation, while creating optimal conditions for their migration. That said, these mesenchymal stem cells (fibroblast precursors) are not multipotent themselves, because they are only able to differentiate into connective tissue cells.

The Significance of Cell Growth Factors in Differentiation of Tissue-Specific Stem Cells

During cell death of old cells, and the simultaneous macrophage inflammation, as well as the surrounding epithelial and endothelial cells, the stromal cells form colony-stimulating and cell growth factors, interleukins [5, 6]. Colony-stimulating factors induce proliferation of pluripotent stem cells for their subsequent admission to poorly differentiated progenitor epithelial cells and progenitor cells of other tissues or directly to the place of cell death of old cells. Cell growth factors, acting in various combinations, selectively stimulate the proliferation and differentiation of progenitor cells of an epithelium and other tissues [2, 4].

The specificity of regulation of differentiation made by the cell environment in the strict sequence of local formation of cell growth factors and the same strict regulation of the sequence of receptors on the committed (tissue-specific) stem cells and progenitor cells of an epithelium and other tissues which determined by the according part of the development program [1, 2, 4]. Each cell of a multicellular organism contains a certain set of surface receptors which give it the possibility to react in a specific way to the complementary set of signal molecules, and which allow the cell to connect with in a certain way with other cells and with the extracellular matrix [2, 3,

7]. The given set of receptors represents a "morphogenetic code" which determines the organization of cells in tissues. The strict sequence of the appearance of expression of receptors to cell growth factors, a similarly strict regulation of the formation (autocrinally or paracrinally) of cell growth factors and a binding of an extracellular matrix (including a basic membrane) strict collection of cell growth factors direct the differentiation of cells [1, 2]. An example of such is the alternation of expression of receptors to various growth factors when differentiating T- and B-lymphocytes, as shown in the work by Roitt I. et al. (2000) [6].

Thus, committed stem cells (tissue-specific stem cells) migrate to tissue specific antigens of proteoglycans of fibronectin (part of the basal membrane, converts to the extracellular matrix) that are complementary to their receptors. The basal membrane does not prevent the migration of a macrophages and committed stem cells which support regeneration. After passing through the basal membrane, committed (tissue-specific) stem cells bind their tissue-specific receptors bind to their complementary antigens of proteoglycans of laminin (part of the basic membrane, converted to the epithelial layer), and are retained in the epithelial layer. Committed (tissue-specific) stem cells keep their connection with the basal membrane also keep contact with the underlying connective tissue, which executes control over differentiation of epithelial cells. The direction of differentiation of migrated committed stem cells is determined by the specific set (corresponding to the morphogenetic code) of cell growth factors on fibronectin and laminin of the basal membrane, as well on collagen fibrils of the extracellular matrix [1, 2, 4].

Formation of Chimerism as an Alternative to the Use of Induced Pluripotent Stem Cells

The induced pluripotent stem cells were created because of the fear of using allogeneic pluripotent stem cells due to their possible rejection by the recipient's immune system, as well as the desire to facilitate the application of cellular technologies, making it unnecessary to conduct sampling of cellular material in the patient. The formation of induced stem cells from somatic cells is unnatural, since it forces the cells to go in a backwards direction on the differentiation path that they already covered. The use of these cells in clinical practice is dangerous because of the risk of their malignant transformation [1, 2, 4].

Any attempts at reproducing the effects of regulatory factors "in vitro" for separate embryonic cells look to be unpromising considering the extreme difficulty at repeating the sequence of actions of regulatory factors of the development program [1, 2]. Outside the macroorganism, without the presence of the organism's constantly-changing regulatory factors, pluripotent stem cells are subject to death, which is proven by significant difficulties that arise when cultivating stem cells "in vitro". From these positions one can state that the creation of constant lines of embryonic stem cells, which aren't subject to aging in the culture in the absence of the regulating influence of the macroorganism, and which have lost their connection to the macroorganism, is apparently related to certain genetic changes which bring the given cells closer to malignant ones. The use of such cells in clinical practice can be accompanied by an increase in the risk of development of carcinogenesis [1, 2].

The chimerism effect opens a safe way to restore the pool of pluripotent stem cells and restoring renewal of tissues (regeneration) in aging people. Inhabitation of the thymus by stem cells is necessary not only for the subsequent formation of T-cells, but also for renewal of old cells of cortical and medullary substances of the thymus, including epithelial-reticular cells, in ontogenesis [1, 2, 4, 5, 6]. Epithelial-reticular cells of the thymus make up a microenvironment for developing thymocytes and serve as sources of signals which are generated under direct cell contacts. Epithelial-reticular cells of the thymus transfer information to T-lymphocytes on antigens of their own tissues during the process of the given contacts, as well as form for them the type of response to the presented antigens [5, 6]. The latter is more important when separating antigens of a cell damaged by a virus or of foreign tissue (with activation of T-killers to a greater degree) from autoantigens of dead, old cells (with the subsequent activation of pluripotent stem cells with the formation

of tissue-specific receptors for directed migration and renewal of tissues) [2, 4].

Allogenic pluripotent stem cells transfusion contained in the mononuclear fraction of peripheral blood form colonies in the bone marrow and leads to formation of a chimeric individual [2, 4, 8] as transplantation of cells of the embryo [1, 3]. The chimeric individual, in particular, have two types of pluripotent stem cells with two various genotypes. The subsequent migration of stem cells of these two types into the thymus and the renewal of its own epithelial-reticular cells lead to formation of T-lymphocytes which view both antigens of their own organism and those of the donor as "their own" [2, 4, 8].

Artificial formation of a chimeric individual through transfusion of allogeneic mononuclear fraction of peripheral blood taken from young donors 18-23 old of one with them blood types and a sex containing pluripotent stem cells (RF patent number 2350340) can be used to maintain the normal population of the pool of pluripotent stem cells, to reinstate regeneration, to reverse the development of mitotic activity disorders in people over 40-50 years old, and can also be seen as a promising way to reduce biological age, while providing a significant prolongation of life and the ability to work (while maintaining a high quality of life) [2, 4, 8].

Conclusion

The immune system takes part in the formation of tissue-specific receptors among pluripotent stem cells. The latter remain pluripotent until the formation of tissue-specific receptors in them, and become committed (tissue-specific stem cells) after the formation of such receptors. Committed stem cells (tissue-specific stem cells) that migrate through the extracellular matrix replenish the progenitor cells of all tissues. Mesenchymal stem cells are the precursors of fibroblasts, and they only create conditions in the extracellular matrix for the migration and differentiation of committed stem cells in the places of cell death.

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