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COMPARATIVE CHARACTERISTICS OF HUMAN STEM CELLS

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ABSTRACT. Stem cell therapy is one of the most perspective methods of clinical medicine; SC-containing products are actively investigated in clinical trials, while some of them are already officially approved for treatment in many countries worldwide. The purpose of this review is to perform comparative analysis of stem cell types, methods of their procurement and perspectives of their employment. Stem cells (SCs) could be divided into groups according to the age of the donor organism. Embryonic SCs are isolated from blastocyst, obtained as a result of extracorporeal fertilization, cloning, semicloning or parthenogenesis (androgenetic and gynogenetic SCs). Fetal SCs could be isolated from embryonic and fetal tissues before the birth or from miscarriages and abortion material (including ectopic pregnancy). Among fetal there is and especial group of perinatal extraembryonic SCs which are obtained from extraembryonic organs (umbilical cord, amnion, placenta) after the birth; among them hematopoietic, mesenchymal, epithelial and decidual cells are distinguished. Adult (somatic, tissue specific) SCs could be isolated from different tissues and organs of adult organism throughout the life; their properties depend on the place of their localization and age of the donor. Additionally, SCs could be created artificially from mature cells by modification of gene expression; they are united in the group of induced pluripotent SCs. Every group of SCs is not homogenous and has its advances and drawbacks are analyzed in this review. Also, application of exosomes, microvesicles and apoptotic bodies produced by stem cells as an alternative of cellular therapy is considered.
Key words: embryonic stem cells, perinatal extraembryonic stem cells, adult stem cells, induced pluripotent stem cells, extracellular vesicles.

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Introduction

Stem cells (SCs) like a double edged sword: on the one hand they provide physiological regeneration and growth, on the other hand they might give rise to cancer. Therefore, the desire to stimulate SC to rejuvenate and restore the body is limited by the risk of tumor development, and the desire to destroy the tumor is limited by the possibility of simultaneous reduction of the regenerative potential of the whole organism. Being the object of interest for two popular directions in medicine - regenerative medicine and oncology, SC are becoming more and more popular with the time. In 2021 in the "PubMed" database of medical literature on the search query "stem cells" 41,062 articles were published (Figure 1 shows the dynamics of this indicator over the past 20 years). Table 1 shows the number of clinical trials using different types of SCs worldwide, indicating a high probability of introducing new SC-based cellular products into practical medicine in the near future. Currently, the official healthcare authorities of most countries have approved for practical use only bone marrow SCs or umbilical cord blood SCs for a narrow range of diseases (mostly oncohematological). Thus, the list of Cellular and Gene Therapy Products approved by the US Food and Drug Administration's includes 22, most of which are related to umbilical cord blood cell transplantation in dis-

eases associated with hematopoietic disorders [1]. There is also a caution for patients, emphasizing the necessity of using only approved products included in this list, or only in officially registered clinical trials.

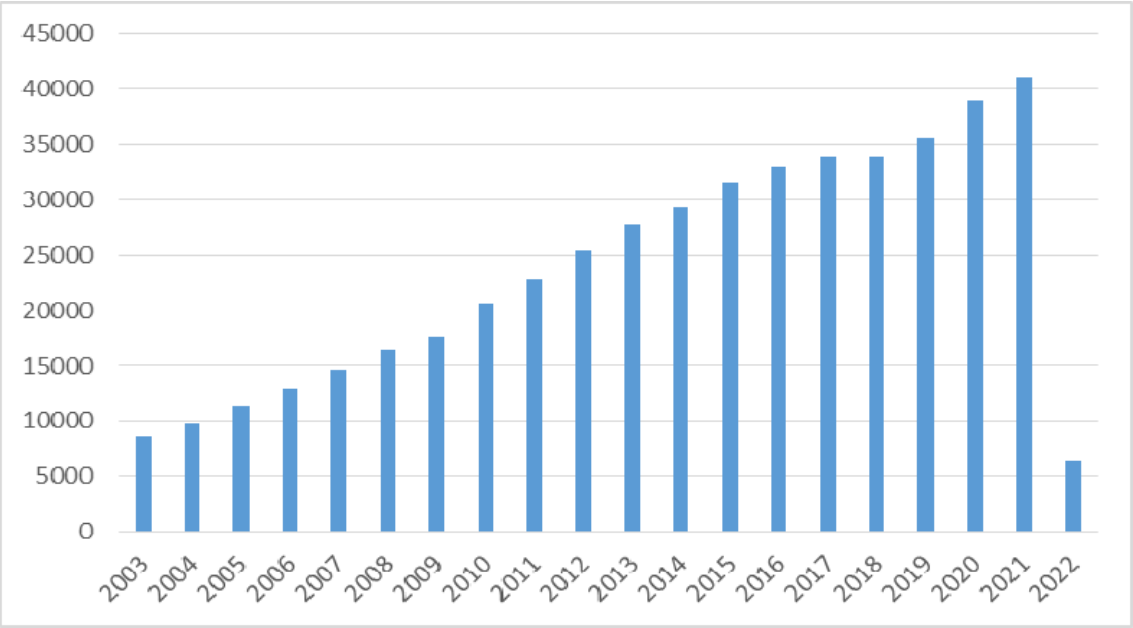

Fig. 1. Number of publications in PubMed with keywords "Stem cells" from 2003 to 2022.

Table 1

Quantitative distribution of clinical trials using SCs in different databases (taking into account the types of SCs)

	Stem cells (total number of trials)	Embryonic stem cells	Umbilical cord blood stem cells	Bone marrow stem cells	Adipode tissue stem cells	Mesenchymal stem /stromal cells	Induced pluripotent stem cells	Extracellular vesicles of stem cells
WHO http://apps.who.int/trialsearch/default.aspx	3278	35	373	648	402	1300	51	0
USA https://clinicaltrials.gov/ct2/home	6115	39	584	2749	450	1399/293	108	14
EU https://www.clinicaltrialsregister.eu/ctr-search/search	727	0	30	379	50	144/58	0	0
India http://ctri.nic.in/Clinicaltrials/advancesearchmain.php	154	0	0	4	1	24/1	1	0

It is important to note that there is a problem of uncontrolled use of SC by private medical institutions that aggressively advertise their services, often ignoring the lack of evidence and possible side effects that could lead to patient death [2].

The purpose of this article is to characterize and to provide comparative analysis of different types of human SCs and to define prospects of their practical application in medicine.

Definition and classification

The concept of "stem cell" includes a heterogeneous group of cells of different origins united by

two key properties: 1) the ability to self renew by division, and 2) the ability to differentiate with the formation of mature, specialized cell types [3]. There is no single generally accepted classification of SC. In general, there are two main groups: SCs obtained artificially (induced pluripotent SC) and SCs isolated from living organisms at different stages of ontogenesis. The latter is divided depending on the term of development of the organism into: embryonic (isolated from blastocysts); fetal (isolated at later stages of prenatal ontogenesis from relatively differentiated tissues of the embryo or fetus), they include perinatal extraembryonic (obtained from extraembryonic organs and tissues immediately after birth); adult SCs (which present in almost all tissues of the mature organism and are responsible for regeneration) (Fig. 2). The properties of each type of SCs differ significantly; their advantages and disadvantages are summarized in table. 2. Each of these groups is not homogeneous and can be further divided by different criteria, particularly by the genetic identity with the recipient: into autologous (identical to the recipient) and allogeneic (obtained from another person of the same species).

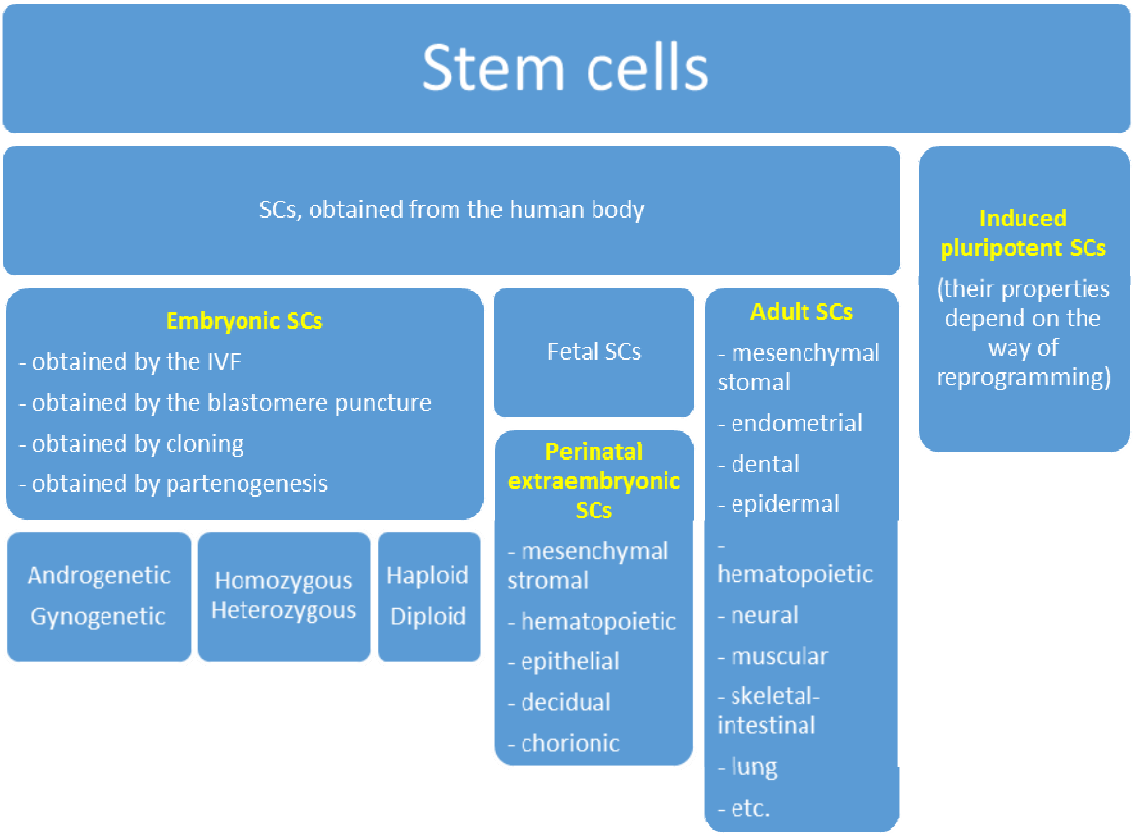

Fig. 2. Classification of human stem cells.

Embryonic stem cells

In essence, embryonic stem cells (ESCs) are the inner cell mass of the preimplantation blastocyst and have the properties of pluripotency, or rather can be differentiated into all cell types of the mature organism. In 1998, after numerous experiments with animals, James A. Thomson et al. isolated human ESC from an embryo created during in vitro fertilization for "clinical purposes", and confirmed their main properties: 1) origin from the preimplantation embryo, 2) long-term proliferation, not accompanied by differentiation, 3) stable potential to generate derivatives of all three germ layers even after long-term cultivation [4]. The authors also noted the high activity of telomerase and the expression of surface markers typical for the ESC of primates - stage-specific embryonic antigen (SSEA)-3, SSEA-4, TRA-l-60, TRA-1-81 and alkaline phosphatase. For ethical reasons, the obtained cells were not used to create chimeric embryos (this way is used to confirm pluripotency of ESC in animal experiments). Instead, a method based on their inherent ability to form teratomas has been developed to assess the potential of human ESCs differentiation [5, 6]. When ESCs are transplanted to immunodeficient mice (mainly intramuscularly) in the developing teratomas the presence of derivatives of all three germ layers is evaluated.

The ability of ESCs to form teratomas is one of the main obstacles to their practical use, despite their significant advantages over other types of SCs (high proliferative potential and a wide range of differenti-

ation). Additionally, there are a number of ethical issues associated with the obtaining of ESCs, as it is almost always accompanied by the destruction of the human embryo. To solve these problems, alternative methods of human blastocyst creation are being developed, although in most cases they raise even greater concerns in terms of bioethics. The method of blastocyst formation to some extent affects the properties of the ESCs, and should be taken into account in their classification.

Table 2

Comparative characteristics of human stem cells

Type of stem cells	Advantages	Disadvantages
Embryonic stem cells (ESC)	- a wide range of differentiation (pluripotency) - high proliferative potential	- ethical aspect associated with the destruction of the human embryo at the blastocyst stage - the inability to create autologous cells (involves human cloning) - high risk of developing teratoma, and in the case of long-term cultivation of ESC - teratocarcinoma - the complexity of obtaining (the need for micromanipulations) - relatively high financial cost
Fetal perinatal extraembryonic (hematopoietic cells of umbilical cord blood)	- lack of ethical issues in obtaining - non-invasive procedure of obtaining - in relation to adult SCs, a wider range of differentiation and proliferative potential - low probability of somatic mutations - no risk of developing teratomas - lower immunogenicity and probability of rejection compared to adult SC	- the possibility of using autologous cells only if the patient has a cryopreserved sample in a bank - a small amount of SCs in 1 sample compared to SC of peripheral blood and bone marrow - higher cost compared to peripheral blood and bone marrow SC (when using allogeneic samples) - the need for purchasing the sample preservation in the cryobank throughout the life
Adult (somatic) stem cells	- the ability to obtain autologous cells - easy to extract (without invasive procedures) - lower risk of developing tumors comparing with ESCs and IPSCs	- contain somatic mutations, the number of which increases with age - relatively narrow, tissue-specific, differentiation spectrum (multipotency) - relatively low proliferative potential
Induced pluripotent stem cells (IPSCs)	- wide range of differentiation (pluripotency) - easier way to get (comparing with ESC) - the ability to obtain autologous cells	- high risk of tumor development (including malignant) - genomic aberrations associated with the technology of "pluripotency induction", as well as long-term in vitro cultivation - low reprogramming efficiency (less than 1.5%) - "epigenetic memory"

ESCs obtained by in vitro fertilization

The most common source of human ESCs are embryos created by in vitro fertilization but not required by their biological parents. The use of genetically foreign ESCs is possible due to the low expression of main antigens, including the major complex of histocompatibility type I, reducing the likelihood of their rejection by the immune system of the recipient [7]. Since the extraction of internal cell mass is accompanied by the destruction of the embryo, compromising the principles of bioethics and a number of religions, it was proposed to use rejected and non-viable embryos for such purposes [8]. In order to minimize the number of human blastocysts used to obtain ESCs, experiments are mainly conducted with already established and artificially maintained cell lines (the ability of ESCs to maintain pluripotency and proliferative potential during long-term cultivation was previously demonstrated) [9]. At the same time, long-term cultivation of human ESCs leads to the accumulation of chromosomal aberrations [10] negatively affecting the quality of cell lines and increases the likelihood of malignant tumors formation (teratocarcinoma) after transplantation into the recipient [11, 12]. Analysis of mutations occurring in ESCs during long-term cultivation has demonstrated their general focus on reducing sensitivity to growth factors and increasing proliferative activity [13] promoting oncogenesis.

ESCs obtained by blastomere puncture

Along with blastocysts, single blastomeres extracted from 4 cell embryos may be an alternative source of ESC [14], partially solving the bioethical problems associated with the destruction of the pre-

implantation embryo [15]. However, a number of stem cell lines obtained in this way revealed potentially oncogenic changes in the genome, which are associated with their origin from the early blastomere [16]. The fact is that at the stage of the four-cell embryo bastomers are totipotent and can give rise not only to all types of cells of the adult organism, but also to extraembryonic tissues; embryoblast cells of the blastocyst have a more restricted potential for differentiation, which is limited to the cell lines of the embryo itself.

ESCs obtained by cloning

Despite the possibility to transplant ESC from an unrelated donor, the relevant task of modern medicine is to obtain cell lines with full compliance with the antigenic characteristics of the recipient. The creation of autologous ESCs is possible in the case of cloning, which is associated with moral, legal restrictions and significant technical and financial expenditures. However, in 2013, by modifying protocols of the Somatic cell nuclear transfer (SCNT) into a donor egg, a team of scientists led by Masahito Tachibana [17] achieved human ESC cell lines. During this experiment, the fetal fibroblast and the donor egg were fused (after previously removing the genetic material of an egg) using the hemagglutinating virus of Japan. 52 of the 60 obtained zygotes showed signs of fragmentation, 32 of them reached the stage of an eight-cell embryo, only 7 developed further into morula, and only 6 formed blastocysts, from which it was not possible to obtain ESC. The results were improved by pre-incubating the egg with caffeine, such a modification increased the probability of blastocyst formation to 23.5%, moreover, 4 of the 8 blastocysts formed ESC during cultivation. The authors emphasize that the cells obtained in this way contain mitochondrial genes of the donor egg, thus it can be used to treat patients with mitochondrial pathology. In 2014, similar results were obtained using somatic cells of a mature male body (35 and 75 years old), confirming the possibility to create ESC genetically identical to the patient [18].

Parthenogenetic ESCs

As an alternative to cloning, methods are being developed to create autologous human ESCs by parthenogenesis (PESC). This method is considered as more ethical because it does not require fertilization [19] and created blastocysts cannot develop further the somatic period [20]. It is known that a number of mammalian genes are expressed only on maternal or paternal chromosomes (a phenomenon known as "imprinting"), allowing the development of viable offsprings only if two heterosexual parental genomes participate in its creation. At the same time, several cases of parthenogenetic chimerisms have been officially documented in humans [21, 22, 23], indicating the possibility of parthenogenetic cell lines to participate in the formation of tissues of the adult organism. There are several methods of creating parthenogenetic embryos, some of which include the activation of an egg during the first or second meiotic division [24]; the resulting human cell lines are compatible with the MHC of the donor egg, but show a significant reduction in the expression of imprinted genes [25]. It should be noted that in the case of blocking the first meiosis the divergence of paternal and maternal chromosomes to daughter cells is blocked, resulting in the development of heterozygous PESC containing different gene variants (including MHC) in sister chromosomes. If second meiosis is blocked, the divergence of chromatids of either the maternal or paternal chromosomes is blocked, resulting in the formation of homozygous PESCs, containing almost identical allele variants on sister chromosomes (except for crossover sites) [26]. A small number of MHC gene variants increases the possibility of compatibility with the donor (in case of allotransplantation), but at the same time it makes homozygous PESCs targets of natural killers in the recipient organism (the phenomenon of "hybrid resistance") [27]. Despite the advantages of PESCs obtained during the blockade of the first meiosis, the efficiency of their production in animal studies is significantly lower compared to the blockade of the second meiotic division [28].

Since parthenogenesis involves the development of an organism from an unfertilized egg, it can be assumed that obtaining an autologous cell in a similar way is possible only for female patients of reproductive age. But experiments on mice have successfully demonstrated the possibility of using the "male version" of parthenogenesis to obtain stem cells. For this purpose, the nucleus of one secondary spermatocyte / two spermatids / two spermatozoa was/were transferred to the enucleated secondare oocyte [29]. Depending on the type of gamete (male or female) used to create the embryo, PESCs are divided into gynogenetic and androgenetic PESCs.

Parthenogenesis is also used to create embryonic haploid stem cells by activating a secondary oocyte or by injecting a single sperm into an enucleated oocyte [30]. In 2016, a human line of gynogenetic haploid SCs was obtained, demonstrating the main signs of pluripotency, including teratoma formation and differentiation into derivatives of all three germ layers [31]. Both gynogenetic and androgenetic haploid SCs are spontaneously "diploidized" during cultivation, allowing to obtain homozygous diploid SCs [32]. Due to the presence of only a half of the somatic cell genetic material, haploid SCs are a convenient model for loss of gene function experiments [33]. Additionally, haploid SCs are also used (so far in experimental work) for artificial insemination; the procedure of transferring haploid androgenetic SC to the secondary oocyte II is called reproductive semicloning [34]. In animals it was successfully demonstrated the possibility of obtaining viable offspring using this technology [35]. Moreover, genetical modification of imprinted genes in haploid gynoge-

netic SC before its injection into the egg allows to obtain viable offspring from two females, as it was shown by Chinese scientists in experiments on mice [36, 37]. Such experiments provide a good model to investigate the phenomenon of imprinting, in particular, the relative contribution of each of the imprinted genes in the development of the whole organism. While the prospects of practical application of gynogenetic haploid SC are doubtful, the genetic modification of androgenetic haploid cells to obtain transgenic animals for experimental purposes by semicloning is a very promising direction [38, 39].

Fetal stem cells

By the time of birth, SCs can be isolated from the body by a number of invasive procedures (collection of material blood for genetic analysis, abortion, including ectopic pregnancy, miscarriage), most of which might result in abortion, limiting the use of fetal SCs in practical medicine [40]. Immediately after birth it is possible to isolate a large number of SCs from extraembryonic organs and tissues, which until recently were considered as biological waste. The availability of these SCs is the reason for classifying them into a separate subgroup of extraembryonic perinatal SCs, which is one of the most promising in terms of practical application. The main advantages of this subgroup of SCs are: no ethical issues, non-invasive procedure of obtaining, low level of somatic mutations, no risk of teratomas, low immunogenicity due to low expression of HLA class I, and immunomodulatory effects due to the tolerogenic effect of HLA-G, -E [41]. The main disadvantages of extraembryonic perinatal SCs are mainly related to financial issues (the need to pay for or keep the sample in a cryobank, or purchase a sample in the absence of autologous one), as well as the relatively low absolute number of SCs in one sample. Among the extraembryonic perinatal SCs there are several subgroups: hematopoietic, mesenchymal stromal, epithelial SCs, decidual and chorionic MSCs.

Hematopoietic SCs

The main source of hematopoietic SCs is umbilical cord blood, although they can also be isolated from the placenta. As it was mentioned above, umbilical cord blood SCs are among the few cellular products approved by the official authorities of various states for application in medicine. Their main advantage is in low immunogenicity (a match of only 2-5 HLA loci is required, compared to 10 loci for adult SCs), and, therefore, a lower probability of rejection [42]. At the same time, a significant disadvantage of umbilical cord blood is the low volume of one sample (on average about 100 ml), which is not compensated by the relatively higher concentration of SCs and their proliferative potential, and in case of adult patients requires double transfusion [43]. The use of several samples of umbilical cord blood significantly increases the cost of the procedure for the patient, while the improved methods of adult SCs extraction from peripheral blood makes the latter the most profitable from a financial point of view [43].

Mesenchymal stromal cells

At the beginning of this section the difference between "mesenchymal stromal" and "mesenchymal stem" cells should be clarified. Both terms are used in the literature and are not contradict each other, because one highlights the function (stromal), and the second highlights properties (stem) of the cell. Some authors consider the term "mesenchymal stromal cell" more correct, as its participation in the formation of the stroma is obvious, while the stem properties must be confirmed by additional methods (cultivation, analysis of marker expression, etc.) [44].

Mesenchymal stromal cells (MSCs) can be obtained from Wharton's gel, umbilical cord lining, umbilical cord blood, amnion and placenta. Despite the morphological similarity, the characteristics of these cells vary greatly depending on the location. In 2004, Hwai Shi Wan and co-authors demonstrated the multipotency of Warton's gel MSCs by differentiating them into cardiomyocytes, adipocytes, and osteocytes [45]. From one cm of the umbilical cord relatively many ($1\text{-}5 \times 10^4$) MSCs can be obtained, but their population is characterized by morphological heterogeneity [46]. The distribution of cells within the Wharton's gel is uneven: in the perivascular region, the cells are compactly located, while under the amniotic epithelium they are more sparse. Moreover, cells in the periphery are characterized by longer and more numerous cytoplasmic processes compared to the perivascular area. These differences can be explained by different sources of origin of these groups of cells (somatopleura of the amniotic mesenchyme, splanchnopleura of the yolk sac and mesenchyme of the allantois) [47]. That's why it is especially important to indicate specific zone of Wharton's gel from which MSCs were obtained when investigating their properties. A comparative analysis of the three anatomical regions (umbilical cord, the border between umbilical cord and placenta, placenta) showed that the area between the umbilical cord and placenta contains the largest number of MSCs, and also have the greatest potential for proliferation, self-renewal and differentiation [48].

Compared with the MSCs of other perinatal sources (placenta, umbilical cord blood, Wharton's gel), umbilical cord lining cells have such advantages as: higher proliferative and migration activity, as well as longer survival when transplanted to immunodeficient mice [49]. Analysis of the MSCs revealed that the umbilical cord lining cells are characterized by significantly lower expression of HLA class I, higher production of tolerogenic factors TGF-β and IL-10, as well as more active proliferation comparing to the bone marrow SCs of donors older than 65 years [50].

Epithelial SCs

Epithelial SCs are mainly isolated from the amnion and epithelium of the umbilical cord lining, which are derivatives of epiblast. It is important to note that the epiblast is the source of all three germ layers in the process of gastrulation, so it's derivatives have a wide range of differentiation possibilities.

Zhou Y. and co-authors demonstrated the ability of epithelial SCs of the umbilical cord lining to suppress the T-cell immune response in the mixed lymphocyte culture, and also emphasized the importance of the soluble form of the HLA-G molecule in this process [51]. What is especially important from a practical point of view - it was found that the rejection of human keratinocytes during transplantation to immunocompetent mice was delayed in the case of their complex transplantation with epithelial SCs of umbilical cord lining [51]. The immunosuppressive properties of the latter are due to the absence of HLA-DR and costimulatory molecules CD40, CD80 and CD86 on their surface [49].

The amniotic epithelium, like the umbilical cord lining epithelium, has immunological privilege due to the expression of Fas, FasL, and HLA-G [52]. In 2005, Miki T. and co-authors demonstrated the expression of stem cell markers in human amniotic epithelium isolated from the placenta after natural childbirth [53]. The authors also noted the lack of telomerase expression in these cells and, most importantly, the lack of tumorigenic properties during transplantation to a laboratory animal.

The most effective methods of amniotic epithelial cells isolation allow to obtain up to 1.9×10^8 cells per sample of placenta, which is quite a lot compared to other extraembryonic fetal tissues [54]. But the isolated cells are quite heterogeneous in their properties and have different levels of "stemness", requiring further improvement of purification methods [52, 55].

For 1 cm^2 of the umbilical cord epithelium, it is possible to take 2×10^7 epithelial and mesenchymal SCs, while the average area of one sample is around 330 cm^2 [56]; such a high "yield" together with above mentioned advantages makes the umbilical cord lining the most promising source of SCs among other extraembryonic tissues.

Chorionic MCSs

Chorionic MSCs show a number of features compared to MSCs of other localization; first of all, they are characterized by long life period and delayed signs of aging, which is provided by maintaining the length of the telomere [57]. In addition, MSCs of the placenta have angiogenic potential, which is actively studied in experimental models of limb ischemia [58], myocardium [59] and bone fractures [60]. Exosomes produced by MSCs in vitro also demonstrate angiogenic potential, as evidenced by the formation of endothelial tubes and increased expression of angiogenesis-related genes in vitro [61].

Decidual SCs

Investigating the properties of decidual MSCs of placenta their ability to migrate towards the tumor and slow its growth was revealed [62]; this phenomenon became the basis for the development of new means of anticancer drugs targeted delivery [63].

Adult (tissue, somatic) SCs

Organs and tissues in the postnatal period of ontogenesis retain a certain proportion of poorly differentiated cells that are responsible for growth and regeneration throughout life. Their number and properties depend on age and tissue affiliation, and common characteristics include the ability to self-reproduce, maintain their number at a constant level and differentiate into different cell types [64].

In contrast to induced pluripotent or embryonic SCs adult SCs are tissue-specific and, therefore, have a narrower spectrum of differentiation, limited by their tissue affiliation (multipotency). Additionally, populations of SCs of a certain specificity are not homogeneous and consist of cells with overlapping capabilities, but with varying degrees of propensity to differentiate into certain types of mature cells [65]. For example, well-studied hematopoietic stem cells differ in their propensity to differentiate in the direction of myeloid or lymphoid branch, as well as in other parameters, including the intensity of proliferation [66]. A group of scientists, led by Mariusz Ratajczak, believe that SCs of mature tissues also differ in the degree of differentiation, and at the top of their hierarchy there are cells similar in properties to ESCs, which are called very small embryonic like stem cells, VSELSC [67]. The common properties with embryonic cells makes VSELSC very promising for cell therapy, although their existence is controversial in scientific circles, as not all scientific teams were able to obtain VSELSC and confirm their key properties [68]. The authors of the VSELSC concept explain this by improper purification and isolation protocol, as well as by low content of VSELSC in mature tissues (~ 0.01% of red bone marrow mononuclear cells) [69].

The properties of adult SCs depend on the microenvironment: stromal cells, components of the intercellular matrix, blood vessels and nerve fibers. Factors released by this microenvironment, as well as the degree of adhesion to the matrix and surrounding cells, taken together are called "stem cell niche" [70]. It is important to clarify that "niche" is not considered as a physical place of SCs localization, but as a set of factors that maintain dormant state, induce proliferation or further differentiation. It is interesting that even aging of the SCs occurs under the influence of niche, because "aging" SCs under the influence of "young" microenvironment become activated, while "young" SCs put in the "old" niches, reduce their proliferative potential [71]. Most SCs in mature tissues are at rest (G0), which is characterized by reversible cell cycle arrest and maintenance of a poorly differentiated state

[72]. Under the influence of damaging signals, SCs reversibly go into "alert" state (GAlert), which implies their higher readiness to enter the cell cycle, and therefore higher regenerative potential compared to G0 [73].

There are two strategies for maintaining the number of SCs: symmetric and asymmetric divisions. In the asymmetric division of SC, one of the daughter cells retains the properties of the maternal cell, and the other (transit amplifying cell) actively divides and then differentiates into mature tissue elements. In case of symmetrical division SC gives rise to either two SCs or two differentiated cells. Symmetrical division prevails during embryonic development, as well as in the processes of regeneration after disease and injury, as it allows to increase the number of SC [74]. Also, the transition to symmetrical division is observed in tumors with a low degree of differentiation in the late stages of development [75], which suggests the existence of a relationship between the type of cell division and the process of malignization.

In the scientific literature there is also the term "label retaining cells (LRC)", which is associated with experiments of pulsed introduction of labeled nucleotides to detect mitotic divisions. Some cells retain the label for a long period of time, either by ceasing to divide or by selectively preserving the maternal copy of DNA after each replication (immortal strands hypothesis). Studies of the intestinal epithelium have shown that label retaining cells are committed to Paneth cells and secretory cells (goblet, enteroendocrine, brush), but retain the ability to regain SC properties and participate in regeneration under special circumstances [76].

The main requirement for methods of SCs isolation is the maximum productivity with minimum invasiveness. Since SCs can be obtained from almost all tissues and organs of adult organism (with rare exceptions), it makes no sense to provide a complete list of sources - it is reasonable to consider the most popular and promising.

Endometrial SCs

Adult SCs can be isolated non-invasively. A good example is endometrial SCs, derived from menstrual discharge - they have sufficient proliferative potential, as well as immunomodulatory effects and are actively studied in the process of wound healing [77]. Some companies are already promoting the services of cryopreservation of menstrual SCs parallel with the umbilical cord SCs, while this type of adult SCs is inferior in its characteristics to many other types, making the possibility of their banking doubtful.

Dental SCs

SCs can be obtained from teeth extracted for various reasons. There are several types of dental SCs, differing in their properties: pulp SCs, periodontium SCs, SCs of deciduous teeth, the first of which are the most studied and promising. SCs of the pulp are of particular interest due to their origin from the neural crest, which allows them to be used not only to obtain tooth tissues (dentin, pulp, cement), chondrocytes, adipocytes, smooth cells, but also to create neurons [78].

Epidermal SCs

Among SCs invasive epidermal ones are the most accessible because they are located in the hair follicle between the attachment sites of the muscle that lifts the hair and the confluence of the sebaceous duct.

Among the SCs obtained by invasive means, epidermal SCs are the most accessible, as they are located in the hair follicle between the site of attachment of the m. arrector pili and the duct of the sebaceous gland. The population of these cells is quite plastic, but varies in the level of maturity, proliferative activity and tendency to differentiate in the direction of certain skin cells [79]. Epidermal stem cells of the neural crest are the most promising: they can give rise to bone/cartilage cells, neurons, Schwann cells, myofibroblasts, and melanocytes [80].

Hematopoietic SCs

The most frequently used in practical medicine are hematopoietic bone marrow SCs, which are transfused to patients with hematological diseases. As bone marrow sampling is rather traumatic, alternative sources of these SCs have recently been increasingly resorted to - cord blood (mainly for pediatric patients) and peripheral blood (the most promising source of hematopoietic SCs for patients of adult age) [81].

Mesenchymal stromal SCs

Bone marrow also contains non-hematopoietic mesenchymal SCs (MSCs) with wide potential for differentiation and proliferative activity. They attract the interest of researchers in various fields of practical medicine: currently 763 studies using these cells are registered in the US clinical trials. MSCs can also be isolated from virtually any tissue in the human body, although their properties will vary depending on the source and age of the patient. Good comparative characterization of these cells is given in the review of R. Berebichez-Fridman and P. R. Montero-Olvera [82].

MSCs of adipose tissue

Adipose tissue is an optimal source of SCs in terms of efficiency/invasiveness ratio of the extraction procedure: 1 g of this tissue yields approximately the same amount of SCs as bone marrow [83]. At the same time, the absolute amount of adipose tissue obtained by liposuction can be much larger than the maximum available amount of bone marrow collection, with incomparably less threat to the patient's health. Moreover, adipose tissue MSCs have the additional advantage of higher proliferative potential, immunomodulatory effect and the ability to secrete a number of factors (fibroblast growth factor, interferon-γ, insulin-like growth factor-1) [84].

Induced pluripotent stem cells

In 2007, Kazutoshi Takahashi and co-authors [85] published the results of their experiments on the generation of pluripotent cells from mature human skin fibroblasts using ectopic expression of 4 factors: Oct3/4, Sox2, Klf4, and c-Myc. In the same year, a team of scientists led by Junying Yu [86] obtained similar results using a modified sets of factors: OCT4, SOX2, NANOG, and LIN28; the advantage of this combination was the absence of potential oncogene c-Myc. The cells obtained in this way were similar to human ESCs in morphology, proliferation activity, gene expression, and telomerase activity. Additional evidence of pluripotency was the differentiation of the resulting cells into derivatives of the three germ layers and formation of teratomas. These methods of transformation of adult cells into SCs helped to bypass many ethical issues associated with the creation and destruction of human embryos, approaching the opportunity of using IPSCs in the clinical practice. At the same time, IPSCs cannot be considered as completely equal with ESCs, because in the process of reprogramming cells retain "epigenetic memory"; for the same reason, IPSCs differ from each other depending on the tissue affiliation of the original cell. These differences between IPSCs and ESCs are due to the fact that during the first 4 hours after fertilization there is an active total demethylation of DNA [87], while during the reprogramming of somatic cells demethylation occurs passively, selectively and rather slowly [88]. It should also be noted that, despite significant advances in the methodology for obtaining IPSCs, the effectiveness of reprogramming procedures remains quite low (less than 1.5%) [89], limiting the use of IPSCs in practical medicine. But the most significant shortcoming of IPSCs, which should be discussed in more detail, is the high level of genetic aberrations and a high risk of tumor development, including malignant ones. The similarity between IPSCs and tumor cells has even brought scientists to mind of creating an antitumor vaccine based on patient-specific IPSCs; promising results have been obtained in animal experiments, on the basis of which new directions of immunotherapy of cancer are being developed [90].

The main factors contributing to the tumorigenicity of IPSCs are: the presence of mutations accumulated during life in the original somatic cell; integration into the genome of retroviral constructs carrying reprogramming factors; long cultivation required for reprogramming. Analysis of the human IPSCs genome derived from neonatal foreskin fibroblasts found that 7% of mutations occurred during in vitro cultivation, 19% of mutations preexisted in the original fibroblasts, and 74% of mutations were due to the reprogramming process itself [91]. In this case, it should be taken into account that these SCs were taken from the newborn, because during life in somatic cells there is a gradual accumulation of mutations [92], therefore, their relative value in mutational burden of IPSCs may increase with age. For this reason, to generate IPSCs it is preferable to use as young cells as it is possible, such as umbilical cord blood [93]. Comparison of IPSCs and ESCs generated from fibroblasts of the same mouse (which implies normalization in the level of mutations before reprogramming) revealed a significantly higher mutational load in IPSCs compared with syngeneic ESCs [94], confirming the leading role of mechanism of pluripotency induction. The specific contribution of the cultivation process in the genetic aberrations of IPSCs is also ambiguous, as this factor depends on the time of cells retention in culture [95]. Based on the results of their own research, as well as literature data, Ben-David Uri and Nissim Benvenisty concluded that the genetic changes occurring during the cultivation of IPSCs and ESCs are not accidental, but aimed at stimulating proliferation and reducing sensitivity to growth factors, and also more often lead to the formation of malignant tumors when injected into laboratory animals [96]. Among other aberrations, the authors focus attention on the duplication of chromosome 12, which contains a large number of genes regulating the cell cycle, many of which contribute to the malignization of IPSCs in culture [95].

The process of reprogramming cause genetic aberrations of IPSCs primary because of the activation and overexpression of oncogenes (primarily c-Myc) and/or factors associated with certain types of malignancies (eg Oct4, Sox2, Klf4) [97], as well as repression of oncosuppressors (for example, P53) [98]. Moreover, negative effect on genome is caused by viral constructs which are used for the delivery of reprogramming factors.

Modifications of reprogramming methods

As mentioned above, each group of SCs is not homogeneous and can be divided into subgroups according to different criteria. For IPSCs these criteria are: the type of cell used for reprogramming and the method of reprogramming. The description of the latter should be discussed in more detail.

The first experiments on the generation of IPSCs, which have already become classical, were accompanied by the use of retroviral constructs with four transcription factors [85]. Further modifications of methods were aimed at reducing the number of factors [99] to one - Oct4 [100], as well as diversifying the method of their delivery [101]. The most promising are methods that are not accompanied by damage of the DNA, such as extrachromosomal episomal plasmids. The absence of a viral envelope reduces the likelihood of emergence of wild-type viruses and exogenous DNA, and the vectors themselves may be unable to replicate within an eukaryotic cell and therefore disappear during cell division [102]. The disadvantage of such methods is their relatively low efficiency compared to viral constructs.

In addition to DNA molecules, microRNAs have been successfully used for reprogramming, for example, miR-302, which regulates not only the expression of pluripotency factors, but also the epigenetic profile of IPSCs [103]. Additionally, advantage of this method is the reduction of tumorigenicity of the resulting cells by blocking the G1-S transition (due to the suppression of miR-302 of two regulators of the cell cycle E-CDK2, D-CDK4 /6) without stimulating apoptosis.

One of the most promising areas in the generation of IPSCs is the treatment of somatic cells with molecules of pluripotency factor proteins, equipped with additional domains for plasmalemma penetration [104]. At the same time, there is an evidence of low efficacy of these methods in transforming mature somatic cells comparing with embryonic ones [105]; successive introduction of Oct4-Klf4 factors first, then c-Myc and finally Sox2 solved this problem [106].

Thus, the main strategies aimed at reducing the tumorigenic potential of IPSCs are to optimize the method of reprogramming (using as few factors and structures that do not integrate in the genome), to use for reprogramming as young somatic cells as possible, and to reduce the duration of cultivation. As it is still not possible to completely avoid uncontrolled genetic aberrations of IPSCs, by the time of transplantation they are completely differentiated into the desired cell type and with subsequent complete elimination of poorly differentiated elements [107].

Prospective directions for the use of stem cells

The therapeutic effect of SCs is realized not by their direct incorporation into appropriate niches, division and differentiation, but rather by their activating effect on the cells of the recipient. This action may be associated with the secretion of biologically active molecules, as well as with alternative methods of intercellular communication, such as: tunneling nanotubules, extracellular vesicles and cytoplasmic fusion [108]. The understanding of the mechanisms of SCs action has led to the emergence of new methods of "acellular therapy", which are designed to achieve the main effects of SCs using only isolated factors or extracellular vesicles.

Extracellular vesicles are represented by exosomes, microvesicles and apoptotic bodies. Exosomes are formed as a result of exocytosis of microvesicular bodies, which, in turn, are formed by invagination the inner membrane of endosomes. The diameter of exosomes is relatively small (40-150 nm), which prevents them from exchanging organelles; mainly they serve as a transport form for miRNAs and protein factors. Microvesicles are larger in size (150 - 1000 nm in diameter), are formed by protrusion of plasmalemma with subsequent budding off; often used to carry large organelles. In experiments on the introduction of human MSCs into mice, MSCs were found to be eliminated from the body of recipient on day 14-28 after injection, while mitochondrial DNA was still detected on day 28 [109]. Apoptotic bodies are products of apoptosis and contain fragments of the cytoplasm of the destroyed cell; their diameter varies significantly from 50 to 2000 nm. The interaction of extracellular vesicles with the cells of the host organism occurs through receptor-mediated endocytosis, phagocytosis, or due to membrane fusion. Detailed comparative characteristics of different types of extracellular vesicles of the SCs are given in the review of Lisa M.A. Murray and Anna D. Krasnodembskaya [108]. Given the fact that every type of SCs has its drawbacks, artificial generation of extracellular vesicles with a given content and set of receptors on the surface is one of the most promising areas of regenerative medicine.

Conclusion

Stem cells isolated at different stages of ontogenesis from different human tissues and organs, as well as obtained artificially, differ significantly from each other in key characteristics. Among the SCs it is difficult to choose the ideal type without any drawbacks which is able to displace the rest of all types in practical application, therefore, all types of SCs have prospects for use in medicine.

Taking into account the data of the comparative analysis, it can be concluded that the greatest risks in terms of practical application are inherent in ESCs and iPSCs. In the case of the ESCs, the inevitable problem is the need to destroy the human blastocyst, which is unacceptable for many confessions and limited by the legislation of a number of countries. Alternative methods of blastocysts creation (cloning, parthenogenesis) only complicate the main ethical problem and require additional material and technical expenses. Attempts to use discarded embryo which are to be disposed may slow down the progress of IVF efficiency, as rejected material can be no less profitable (as a source of ESCs) for clinics. An additional problem of ESCs is their ability to form teratomas, which makes it impossible to transplant them directly into the recipient.

The high risk of malignization and genetic aberrations are also major obstacles to the practical application of IPSCs. Minimizing risks through the use of poorly differentiated cells for reprogramming, as well as methods that are not accompanied by the incorporation of genetic constructs into the genome, cannot guarantee complete safety. Therefore, the potential use of IPSCs is possible only if they are completely differentiated in vitro into the desired cell type with subsequent elimination of all poorly differentiated elements before transplantation into the recipient.

The most promising for use in regenerative medicine are extraembryonic perinatal and mature SCs. At the same time, mature cells have a lower potential for division and differentiation compared

to perinatal cells, and also carry a number of somatic mutations that accumulate with age. In turn, autologous extraembryonic perinatal SCs are in most cases not available to every patient, and even if available, do not always contain a sufficient number of cells suitable for use.

Given the presence of shortcomings in almost every type of SCs, acellular methods using extracellular vesicles are becoming increasingly promising. However, in order to implement such methods in practice, it is necessary to study in more detail the mechanisms and factors of SCs action.

Information about conflicts of interest

Potential or obvious conflicts of interest, related to this manuscript, at the time of publication does not exist and is not expected.

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Потоцька О.Ю., Шевченко О.М. Порівняльна характеристика стовбурових клітин людини.

РЕФЕРАТ. Терапія стовбуровими клітинами (СК) є одним із найперспективніших методів у практичній медицині; продукти на основі СК активно вивчаються в клінічних випробуваннях, а деякі вже офіційно дозволені до застосування в багатьох країнах світу. Мета цієї статті полягає у порівняльному аналізі різновидів СК людини, способів їх отримання та перспектив використання. СК можна розділити на основні групи залежно від терміну розвитку організму-донора. Ембріональні стовбурові клітини виділяють з бластоцисти, отриманої в результаті екстракорпорального запліднення, клонування, напівклонування або партеногенезу (гіногенетичні та андрогенетичні СК). Фетальні СК можуть бути виділені з тканин зародка та плоду до моменту народження, або в результаті процедури переривання вагітності (у тому числі ектопічної). У складі фетальних СК виділяють перинатальні екстраембріональні, які отримують із позазародкових органів (пуповини, амніону, плаценти) після пологів; серед них розрізняють гемопоетичні, мезенхімальні, епітеліальні та децидуальні СК. Зрілі (соматичні, тканиноспецифічні) СК можуть бути виділені з різних тканин та органів зрілого організму протягом усього життя; їх властивості залежать від місця локалізації, і навіть віку пацієнта. Додатково СК можуть бути створені штучним шляхом з диференційованих клітин за рахунок модифікації генної експресії; вони виділені до групи індукованих плюрипотентних СК. Кожна з груп СК не є однорідною, а також має низку переваг та недоліків, які проаналізовані в даному огляді. Також приділено увагу перспективному напрямку використання екстрацелюлярних везикул СК в якості альтернативи клітинної терапії.

Ключові слова: ембріональні стовбурові клітини, перинатальні екстраембріональні стовбурові клітини, зрілі (соматичні) стовбурові клітини, індуковані плюрипотентні стовбурові клітини, екстрацелюлярні везикули.