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PROSPECTS FOR THE USE OF UMBILICAL CORD BLOOD IN THE TREATMENT OF DISEASES OF THE CARDIOVASCULAR SYSTEM

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Cardiovascular diseases are currently the most common cause of death worldwide. In this regard, experimental and clinical studies of the effectiveness of therapy of ischemic and non-ischemic heart diseases using stem cells are relevant. The purpose of this review was to evaluate the prospects of using cord blood stem cells in the treatment of cardiovascular diseases.

Methods. The following databases were searched: "BIGG International database of GRADE guidelines", "Database of GRADE EtD's and Guidelines", "Dynamed", "ebmafrica.net", "ECRI", "MAGIC authoring and publication platform (MAGICapp)", "National Health and Medical Research Council (NHMRC) portal", "NICE Evidence", "Pubmed", "TRIP database", "U.S. Preventive Services Task Force".

Results. An analysis of research related to this problem, which was conducted in recent years, was made, and considerations regarding the prospects of using umbilical cord blood in the treatment of diseases of the cardiovascular system were outlined.

Conclusions. Despite some successes, realizing the full potential of cord blood stem cells in the treatment of cardiovascular diseases still requires further serious, targeted and well-funded research and expanded clinical trials.

Key words: cardiovascular diseases; umbilical cord blood; stem cells.

In a relatively short period, a lot of data on the properties of hematopoietic progenitor cells of umbilical cord blood (UCB) and the possibility of their clinical application have been obtained. At the same time, many scientists are looking for the possibilities of clinical application of other types of stem cells (SC) found in UCB. Since UCB contains a population of SCs with unique qualitative characteristics that can differentiate into specialized tissues, it is recognized as a promising cellular raw material for the restoration of damaged tissues and even for growing organs. The data obtained in recent decades convincingly testify to the high differentiation potential of SC UCB. Numerous arguments have also been published in favor of the use of SC UCB for the purpose of improving tissue healing and protecting them from damage. This has given rise to considerable interest in the therapeutic use of cord blood in various disorders, when regeneration or replacement of critically damaged or defective cell lines is required, including pathologies that cause damage to epithelial and neuronal tissues.

In recent years, there have been many reports of clinical trials of the use of SC in a wide range of medicine areas. Experiments on cell cultures and animal models gave reason to assume that these cells could be used therapeutically in regenerative medicine.

The most common cause of death worldwide today is cardiovascular disease (CVD), such as congestive heart failure due to ischemic heart disease, as a result of angina pectoris and myocardial infarction and their complications. This is due to the fact that the myocardium damaged as a result of these diseases cannot fully regenerate. Instead, remodeling of its tissue takes place, which cannot ensure

further full functioning of the organ. Very often, the only way out for a patient is a donor heart transplant. However, the possibilities of finding and timely obtaining a donor organ that would be ideal for transplantation to a specific recipient are very limited. Therefore, the emphasis is on finding an alternative and effective therapy for the treatment of this condition [1, 2]. Currently, experimental and clinical studies of the effectiveness of therapy for ischemic and non-ischemic heart diseases using SC aimed at restoring the myocardium are being actively conducted. The first data from preclinical and clinical trials have shown that cell therapy can promote the replacement of damaged myocytes and revascularization of the myocardium after a heart attack. SCs, which have the potential to differentiate into cardiomyocytes and endotheliocytes, can be collected from different sources. These can be mononuclear and mesenchymal stromal/stem cells (MSC) of the bone marrow (BM), UCB SC, myoblasts, stromal cells isolated from adipose tissue, endometrial mesenchymal cells [3–11].

The results of numerous experimental studies show that highly selective HSCs, which are rich in BM and UCB, can participate in the recovery of the myocardium by reducing apoptosis, neovascularization and stimulation of cardiomyogenesis. This served as the basis for the emergence of a new direction in the treatment of coronary heart disease — cellular cardiomyoplasty [12–14].

Autologous BM MSCs are already used in clinical practice to minimize complications after myocardial infarction [15–17]. However, the obtained results were not always unambiguous, and sometimes showed slight or temporary improvements, which may have been due to extracellular factors [18–22]. In recent years, the mechanisms of SC action are still debated, and are mainly explained by their paracrine action, which is asso ciated with the release of cytokines [1, 19, 23–28]. The idea that exogenous MSCs, after entering the recipient's body, secrete biologically active substances that determine their regenerative and protective effects arose due to the fact that MSCs have a very low engraftment rate [29]. Factors that can contribute to the regeneration process include stromal cell factor (SDF) [30, 31], granulocyte colony-stimulating factor (G-CSF), macrophage colony-stimulating factor (M-CSF), hepatocyte growth factor (HGF), platelet-derived growth factor (PDGF), placental growth factor (PlGF), prostaglandin E2 (PGE2), inducible nitric oxide synthase (iNOS), interleukin-6 (IL-6) [31], interleukin-15 (IL-15) [32], insulin-like growth factor-1 (IGF-1) [21], transforming growth factor (TGF-β) [31, 33], tumor necrosis factor (TNF-α) [34, 30], fibroblast growth factors-2 and -7 (FGF-2, FGF-7) [31], vascular endothelial growth factor (VEGF) [30, 31, 35], metalloproteinases 1, 2, 3 and 9 (MMP1, MMP2, MMP3, MMP9) [31, 34, 36], indoleamine 2,3-dioxygenase (IDO), heme oxygenase-1 (HO1), plasminogen activator (PA), thymosin-β4 (Tβ4), chemoattractant monocyte protein-1 (MCP-1) [31].

Indeed, it is well known that some of the mentioned substances contribute to the proliferation, recruitment (accumulation) and survival of SC in the tissues of the recipient. Thus, SDF helps the homing of progenitor cells [30, 37, 38], Tβ4 promotes cell migration, bFGF enhances the proliferation of endothelial and smooth muscle cells, G-CSF accelerates the proliferation and differentiation of neutrophils, M-CSF enhances the proliferation and differentiation of monocytes, SFRP1 — accelerates cell development, SFRP2 — accelerates cell development and inhibits apoptosis IGF-1 — regulates cell growth and proliferation, inhibits apoptosis [31]. Factors of angiogenic action are important components of SC secretomes in the aspect of protection and restoration of heart tissues: VEGF — stimulates proliferation and migration of endothelial cells, formation of blood vessels [30], FGF-7 — induces proliferation of endothelial cells, FGF-2 — induces proliferation of endothelium and smooth muscle muscles, PDGF — stimulates the proliferation of smooth muscles, MCP-1 —enhances angiogenesis, promotes the recruitment of monocytes, PlGF — promotes angiogenesis, TGF-β — accelerates cell maturation. Realization of the listed effects requires appropriate remodeling of the extracellular matrix [31]. The main role in this process is played by matrix metalloproteinases, plasminogen activator and tumor necrosis factor-β, which are secreted by SC [31]: MMP9 — loosens the intercellular substance, and MMP1 and MMP2 — loosen the intercellular substance and contribute to the formation of tubules, PA — degrades the intercellular substance, TNF-α — degrades intercellular substance, modulates cell proliferation. The immunomodulating effect of some substances secreted by SCs should also not be underestimated: IDO — inhibits innate and adaptive proliferation of immune cells, HO1 — inhibits the proliferation of T cells, HGF — inhibits the proliferation of CD4+ T cells, IL-6 — regulates inflammation, induces VEGF, PGE2 and iNOS suppress inflammation [31].

In general, both in experiments in vitro and in preclinical and clinical studies. It has been accumulated a lot of data which indicate the multifactorial mechanism of cardioreparative action of MSCs. Today, scientists consider three main mechanisms underlying the therapeutic effect of MSCs in cardiovascular diseases. This is a contribution to the reduction of fibrosis, stimulation of angiogenesis and restoration of contractile function [30, 39–42] due to both their own engraftment and differentiation [43] and their stimulation of endogenous heart stem cells for proliferation and differentiation [44]. These effects occur in concert and together lead to the replacement of scarred or dysfunctional tissue of the myocardium with a full-fledged tissue with contractile and perfusion capabilities [41]. However, it was established that the functional capabilities of SC populations obtained at different ages can differ significantly. The development of CVD is associated, in particular, with an age-related decrease in the level of circulating CD133+ and CD34+ HSCs, which come from the BM. As shown by the results of research by a group of scientists from eight research centers in the USA, Germany and Singapore [45], with age, the number of blood cells decreases and their regenerative capacity decreases, which complicates the use of autologous cell therapy for heart regeneration. That is, it was shown that SCs of patients of the older age group are not suitable for therapeutic use. The activity and therapeutic potential of SC from UCB collected and preserved at birth, on the contrary, were the highest. Comparison of the immunological properties of MSCs from the UCB of a newborn child and from the BM of a 65-year-old donor showed that the MSCs of the UCB have a higher proliferative potential and are more capable of activating the body's immune defense factors. After their transplantation, immunological resistance from the recipient's body was minimal [45].

As discussed above, the use of a patient's own HSCs to augment angiogenesis has several drawbacks, including reduced function of these cells and logistical issues associated with harvesting cells from individual patients. Chinese scientists have obtained data that indicate the possibility of rejuvenating old human BM, namely, multipotent mesenchymal stromal cells (MMSCs), with the help of neurotrophic factor of neuronal origin (NDNF). This neurotrophic factor really slowed down the aging processes and apoptosis of MSCs of adult BM, promoted engraftment and survival of implanted SCs in the ischemic area of the heart of mice, which led to improvement of cardiac function after myocardial infarction [46]. Comparison of the transcriptional signatures of BM MSCs and PC MSCs indicates different gene expression profiles. For example, UCB MSCs show higher expression of genes related to cell adhesion, proliferation, and neurotrophic support of the immune system, suggesting that these cells would be better for cell therapy than BM MSCs [47]. Thus, UCB may become an affordable source of allogeneic HSCs, optimal for cell therapy.

There are immunological arguments and historical examples that show that the use of UCB for non-hematopoietic indications, such as for growth factor production, angiogenesis stimulation, and immunomodulation in cases where PC is used for regenerative purposes in immunocompetent recipients, may not require complete human leukocyte antigen matching (HLA) and immunosuppression. This can be confirmed by the results of research by Chinese scientists [48]. 114 patients suffering from non-hematopoietic degenerative disorders were treated with allogeneic UCB not matched by HLA. Doses were used that contained $1–3\times10^7$ UCB mononuclear cells per course of treatment, with 4–5 courses of intrathecal and intravenous administration. The safety assessment included the analysis of adverse events (in particular, graft-versus-host reaction — GvHD), hematological, immunological and biochemical parameters. As a result of the therapy, there were no serious unwanted effects. 30 days after the last injection, no deviations from normal ranges were detected in hematological, immunological and biochemical parameters. Therefore, the modern paradigm of cord blood transplantation is primarily that strict coincidence of HLA and immunosuppression is not required to prevent GvHD.

As is known, UCB is rich in primitive SCs and progenitor cells, which are less mature and less functionally active than similar cells of BM and peripheral blood of adults, which allows to achieve long-term repopulation of SCs in vivo. They have a higher proliferative potential compared to HSCs with BM [49–51]. This is apparently due to longer telomere length [52, 53].

Studies show that autologous HSCs mobilized from the BM can be recruited into ischemic tissue and stimulate angiogenesis. Critical observations in preclinical studies revealed an increase in endogenous microvascular collateralization that was not directly related to the anatomical

incorporation and differentiation into the vascular endothelium of donor blood cells [54].

There are some preliminary clinical data that confirm the possibility of using UCB to improve cardiac function in myocardial infarction (MI) [55–57], but they do not contain clear evidence of sustained improvement in patients' condition. It was shown that these hematopoietic and stromal cells can *in vitro* form sarcomometric structures typical for cardiomyocytes with the expression of some genes characteristic of these cell types: atrial natriuretic peptide, brain natriuretic peptide and contractile proteins, including myosin heavy chain, myosin light chain and alpha-actin [58]. Transplantation of SCs separated by marker antigens in human CVD, such as MI, needs to be substantiated by experimental studies that will allow the procedure to be tested. The possibility of optimization of the expansion protocol and subsequent differentiation of CD133+ SCs from human UCB into a cardiomyocyte-like cell line was studied [59]. CD133+ cells from human PC were first selected by immunomagnetic separation, and their purity was confirmed by flow cytometry. For expansion and differentiation, a formulation of a culture medium containing sequential signaling factors was developed. CD133+ cells were proliferated for 6 days under optimal conditions in the absence of serum in combination with fibronectin and evaluated under a microscope as well as by the proliferation assay with AlamarBlue. Multiplied CD133+ cells were then seeded in plates with a medium promoting differentiation into cardiomyocytes and cultured for 4 weeks. With this protocol, CD133+ cells from human cord blood can be routinely propagated in a serum-free medium for recovery and growth in vitro up to 6-fold. The addition of recombinant human thrombopoietin to the rest of the factors in the expansion medium was associated with greater cell expansion. Proliferated CD133+ cells from human PC after *in vitro* differentiation had a cardiomyocyte-like phenotype as judged by the expression of specific cardiac intracellular markers, including cardiac-specific α-actin, myosin heavy chain, and troponin I. This phenotypic change was associated with the expression of cardiac-specific transcription factors Gata-4 and MEF2C. In addition, the change in phenotype was associated with the activation of nuclear receptors-transcription factors, including PPARα, PPARγ, RXRα, and RXRβ. The authors believe that such a protocol is a significant achievement and overcomes the technical hurdle of producing cardiomyocyte-like cells from human CD133+ PC SCs. In addition, it is favorably distinguished by the simplicity and stability of reproduction. This will enable more active manipulation of these cells in the direction of better engraftment and repair in patients with MI [59].

As part of the "Safety Study of Adult Mesenchymal Stem Cells for Treatment of Acute Myocardial Infarction (NCT00114452)" [60], a double-blind, placebo-controlled study was conducted, which proves the basic safety and provides preliminary efficacy data for allogeneic SCs from BM in post-infarction patients. Based on the obtained results, Chilean and American researchers planned a joint randomized, double-blind, controlled prospective study of patients with compensated heart failure in the dilatation phase [61]. The aim of this study was to determine the safety and clinical efficacy of UCB MSCs transplanted by intravenous infusion in patients with heart failure and reduced ejection fraction. 30 patients were selected, in whom left ventricular ejection fraction of the myocardium was monitored for 3 months before the next randomization. The patients were divided into 2 groups: the 1st group of 15 patients received a single injection of UCB MSCs (1×10^6 cells/kg), and the other 15 patients were the control group. Each patient received standard therapy for heart failure, with the maximum tolerated dose without side effects. The day of infusion was taken as day "0". From this point, the follow-up period was divided into 0–3, 3–6, and 6–12 months. UCB MSCs *in vitro* showed a 55-fold increase of gene expression of hepatocyte growth factor, which is known to be involved in myogenesis, cell migration, and immunoregulation, compared to MSCs obtained from BM. Patients treated with UCB MSCs had no adverse effects related to cell infusion, and none of the patients tested at days 0, 15, and 90 showed alloantibodies to UCB MSCs ($n = 7$). Only the UCB MSC group showed a significant improvement in left ventricular ejection fraction at 3, 6, and 12 months of follow-up, as assessed by both transthoracic echocardiography ($P = 0.0167$ vs. baseline) and cardiac MRI ($P = 0.025$ against the baseline). The change in echocardiographic left ventricular ejection fraction from baseline to month 12 was significantly different between groups (+7.07 ± 6.22% vs. +1.85 ± 5.60%; $P = 0.028$). In addition, at all follow-up time points, patients treated with UCB MSCs showed improvements in New York Heart Association functional class ($P = 0.0167$ vs. baseline) and Minnesota Living with Heart Failure Questionnaire

($P < 0.05$ vs. baseline lines). At the end of the study, the groups did not differ in terms of mortality, heart failure rates, arrhythmias, or incident malignancy. Thus, intravenous infusion of UCB MSCs in patients with stable heart failure and reduced ejection fraction under optimal medical treatment was safe. Improvements in left ventricular function, functional status, and quality of life were observed in patients receiving UCB MSCs [61].

As it was shown [62], the application of autologous PC is justified in open heart surgery in newborns. On average, 92±16 ml of PC were collected. Autologous PC was used during surgery in 14 cases. The average age of newborns at the time of surgery was 4.7±2 (3–8) hours. Patients did not require intensive care unit transfer, surgical intervention, mechanical ventilation, or preoperative medication. Twelve of the patients underwent bloodless open heart surgery; 8 of them did not require transfusion of homologous blood at all in the postoperative period. During the study, 1 fatal result (Ebstein's anomaly) was registered. Thus, due to the use of autologous PC in the first hours of life, complete surgical repair of a complex critical congenital heart defect in newborns can be successfully achieved.

In another study conducted by the same Ukrainian physicians [63], patient groups were similar in terms of diagnoses, birth weight, cardiopulmonary bypass surgery protocol, and surgical technique, except for operative time and blood control strategy. The mean preoperative hematocrit was not significantly different between groups (45% vs. 45%), but was significantly lower in the experimental group compared with the control group during cardiopulmonary bypass surgery (24% vs. 31%). On the 1st day after surgery, the hematocrit in the experimental group progressively increased to 38%. The level of lactate in the serum was higher in the experimental group until the 2nd day after surgery. There were no significant differences in postoperative clinical profiles. During the stay in the hospital, there were no deaths or side effects related to autologous PC transplantation. Therefore, the authors once again prove that autologous PC transplantation is a safe and effective alternative to homologous blood during open heart surgery in newborns. They also note the positive economic effect of this approach.

A largely unmet clinical need is the regenerative treatment of dilated non-ischemic cardiomyopathy. Intracoronary administration of autologous BM stem cells has shown positive results in the treatment of post-infarction and chronic ischemia. Limitations of this procedure include: invasiveness of CM extraction and cardiac catheterization, and reliance on SC populations that are senescent and may be infirm.

In rare cases, children with congenital heart valve defects require a complete heart valve replacement. Many scientific groups are actively working on growing heart valves and vascular implants from SC. The general principles of heart valve bioengineering are reduced to the following stages: 1) isolation of SC (for example, from UCB), 2) seeding of SC into a three-dimensional matrix, 3) conditioning of SC in vitro, which makes possible the development of new tissue under the influence of appropriate growth factors. Decellularized membranes obtained from animal tissues or cadaveric materials of people or polymeric material are used as a matrix [64–67]. Thus, in one of the studies, cadaveric materials of people after their 3-week cultivation. The cell cultures were then further cultured for one week. By the end of cultivation, the cell population acquired an endothelial nature, which was confirmed by the data of immunofluorescence scanning. As the research results showed, the cells formed endothelial monolayers in the process of cultivation, which merged with each other over the decellularized matrix [68]. In the case of implantation of a donor valve in children, it is first completely deprived of cellular elements. Observations for more than 5 years have shown that such heart valves devoid of cells grow in parallel with the growth of the child's body [69, 70]. Some working groups plan to colonize these heart-valvular structures with autologous UCB SCs, endothelial cells (including UCB endothelial cells), umbilical cord vascular cells, or MSCs (from BM or from UCB) and hope that this procedure will lead to further improvement of the clinical situation [71, 72]. However, according to the German researchers (the authors of these reports), due to the extremely high organizational and financial costs, it can be expected that there will be only a few centers specializing in creating such valves from fresh UCB and processing them in a way that corresponds German laws on medicinal products.

Significant differences in the efficiency of cardiac differentiation may be associated with the variability of pluripotent SCs. Korean scientists compared global gene expression profiles of two types of pluripotent

SCs, which show significant differences in cardiac differentiation potential [73]. 12 activated genes associated with heart development were identified. The only gene among these genes that is induced at the early stage of pluripotent SC differentiation in the cardiomyocyte direction is the Gata6 gene. Knockdown of Gata6 expression of pluripotent stem cells reduced their ability to differentiate into cardiomyocytes. The existence of a positive correlation between Gata6 levels and the efficiency of differentiation in the cardiomyocyte direction was confirmed in several SC lines of different origins. Therefore, Gata6 can be used as a biomarker for the selection of pluripotent SC lines, which are best suited for obtaining cardiomyocytes and can be used for therapeutic purposes.

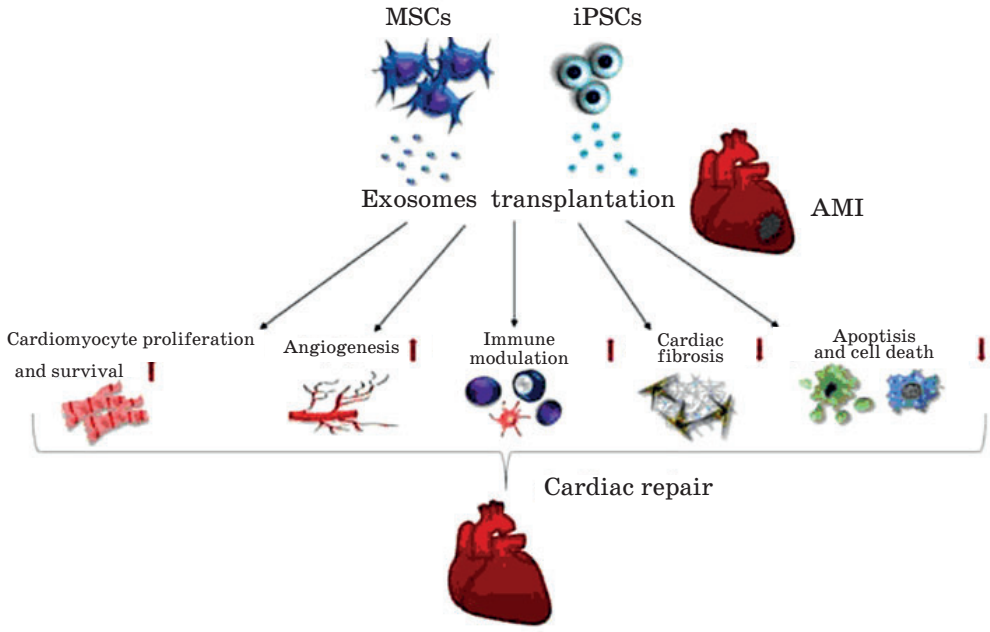
UCB angioblasts, which are successfully used in the bioengineering of structures of the cardiovascular system, are also considered valuable [72]. It is known that the main reason for the development of ischemic diseases is the dysfunction or loss of blood vessels. Over the past two decades, endothelial progenitor cells (EPCs) have been demonstrated to play a significant role in neoangiogenic and neovasculogenic processes. Due to their ability to self-regenerate, circulate, targeting to ischemic areas, and differentiate into mature endothelial cells, EPCs obtained from various sources (including UCB) have great potential for use as therapeutic agents in proangiogenic strategies for the treatment of ischemic conditions. However, the development of EPC-based therapies requires an accompanying non-invasive imaging protocol for in vivo tracking of transplanted cells [74]. Although EPCs are a promising source for cell therapy, the pathophysiological conditions induced by ischemia slow down the rate of vascular repair, causing cell death. In order to overcome this problem, Korean researchers tried to develop a cell-targeted peptide delivery and priming system to improve neovascularization due to EPC [75]. To do this, they used a specially designed bacteriophage M13, which contains nanofibrous tubes that include ~2700 multifunctional motifs. The M13 nanofiber was modified by making structural changes in two functional motifs. This led to the activation of intracellular and extracellular processes such as EPC proliferation and migration and vessel formation, which significantly increased neovascularization during ischemia.

In recent years, combined cell implantation has been widely used in tissue engineering. Chinese researchers conducted a meta-analysis, the purpose of which was to establish the advantages of combined transplantation of MSCs and EPCs compared to transplantation of a single cell type. Although no obvious difference in angiogenesis was found after combined cell transplantation (EPCs and MSCs) and transplantation of EPAs alone, an improvement in the function of damaged organs was observed after cotransplantation. The combined transplantation of EPCs and MSCs significantly more effectively compared to the transplantation of MSCs alone, contributed to the regeneration and angiogenesis of bones, as well as the revascularization of vessels and tissue repair in cerebrovascular diseases; however, no obvious difference in such effects was observed in CVD [76].

Cardiovascular three-dimensional bioprinting has great potential for use in clinical settings. Alginate, collagen, gelatin, hyaluronic acid, and decellularized frameworks of the extracellular matrix were used as biomaterials for 3D bioprinting of myocardial tissue [77–79]. However, 3D bioprinted scaffolds have a high probability of rapid degeneration, which ultimately leads to a decrease in physical or mechanical stability [80].

During the last decades, SC-based therapy has become one of the most promising areas of regenerative medicine. The use of novel cellular therapeutics for the treatment of CVD can potentially achieve the ambitious goal of effective cardiac regeneration. However, despite highly positive results from preclinical studies, data from phase I/II clinical trials are inconsistent, and evidence of improvement in cardiac remodeling and performance is quite limited. The main problems faced by cardiac SC after its introduction into the recipient's body are related to inefficient delivery of cells to the site of damage, low retention of cells in the target organ, and a weak effect on the stimulation of endogenous SC to tissue regeneration. According to preclinical and clinical studies, various SCs (adult SCs, embryonic SCs, and induced pluripotent SCs) represent the most promising cell types for use in regenerative medicine. Therefore, in addition to selecting the appropriate cell type, researchers have developed several strategies to produce second-generation SC products with improved regenerative capacity. Thus, it was found that genetic and non-genetic modifications, chemical and physical preliminary preparation and application of biomaterials significantly increase the regenerative capacity of transplanted SCs [23].

Although it has been shown in some disease models that administration of PC cells leads to significant morphological and functional improvement of damaged tissues, little is known about the mechanisms that mediate the mobilization and protective functions of PC cells or their regulation and maintenance of tissue healing. The vast majority of available studies indicate that UCB cells, similar to SCs derived from other sources (BM, adult peripheral blood, peripheral tissues and organs), act primarily as trophic agents for tissue repair, secreting factors or stimulating mechanisms that modulate the level of local inflammation and angiogenesis, protect resident cells from apoptosis triggered by damage, and stimulate tissue repair mechanisms. In this regard, more and more attention is being paid to the secretome of MSCs [81, 82]. This relatively new object of research is defined as a set of bioactive factors produced by MSCs: soluble proteins and peptides, nucleic acids, lipids and products of their metabolism. The therapeutic effect of MSC-derived secretomes is based on their ability to deliver genetic material, growth factors, and immunomodulatory factors to target cells, which promotes tissue repair and regeneration. The results of many studies indicate that injections of secretomes obtained from MSCs are a new cell-free therapeutic approach in the treatment of degenerative and inflammatory diseases of the gastrointestinal tract, hepatobiliary, respiratory, musculoskeletal, cardiovascular and nervous systems. The lack of side effects inherent in MSC-based therapy, such as a low level of engraftment, unwanted differentiation of grafted cells, and the risk of development, makes secretomes a particularly attractive means of regenerative medicine. They are also characterized by excellent immune tolerance and stability. A significant advantage of the secret over MSCs that produce them is the possibility of their mass production from conditioning media of commercially available cell lines, which will avoid the invasive procedure of collecting cells. Due to their high stability, MSC secretomes can accumulate and be stored for a long time, i.e., be a continuously available agent for the treatment of acute conditions, including fulminant hepatitis, cerebral ischemia, and myocardial infarction [82]. In the process of MSC cultivation, various biologically active factors accumulate in the conditioning medium, which are contained in it both in a free state and inside extracellular vesicles — exosomes. Numerous studies have shown that MCK-derived exosomes, due to their anti-inflammatory, anti-apoptotic, pro-angiogenic and anti-fibrotic properties, can be a substitute for cell therapy. The therapeutic effects of MCC-derived exosomes have made them a promising target for cardiac regeneration and repair [83]. The figure (Figure) taken from a review article [1] shows the expected effects of transplantation of exosomes obtained from MSCs and induced



Stem cell-derived exosomes and their influence on various aspects of post-infarction myocardial repair [1]

MSCs pluripotent stem cells (iPSCs) on various aspects of regeneration after MI.

Numerous experimental data indicate that exosomes, which contain many lipids, proteins, metabolites, and RNA, play a key role in the mechanism of paracrine action of MSCs. In particular, encapsulated miRNAs were identified in their composition, which are important positive regulators of angiogenesis in pathological conditions of insufficient blood supply to the heart [82]. Currently, methods of enhancing the biological activity of exosomes are being actively developed to improve the recovery of heart tissue. Thus, in a model of myocardial infarction in rats, it was shown that exosomes isolated from UCB MSCs, which were transfected with Akt using an adenovirus, contributed to a significant improvement in cardiac function. In addition, they significantly accelerated the proliferation and migration of endothelial cells, the formation of a tubular structure in vitro, and the formation of blood vessels *in vivo*. The authors of this study [8] note that the expression of platelet-derived growth factor D was significantly increased in UCB MSCs with overexpression of Akt. Based on the results of this study, the authors conclude that exosomes obtained from Akt-modified UCB MSCs are effective in the therapy of myocardial infarction through the promotion of angiogenesis. At the same time, an important role in Akt-mediated angiogenesis is played by platelet-derived growth factor D, the expression of which in MSCs is significantly increased as a result of Akt transfection.

Thus, it can be asserted that modern medicine has already begun to use UCB SCs for the treatment of various pathologies, in particular — CVD, which, in fact, are the result of the death or loss of function of certain cell populations of the myocardium and blood vessels (cardiomyocytes, endotheliocytes, nerve cells) and which can be corrected by cellular factors of young healthy cells. The obtained results indicate the safety and beneficial therapeutic effects, sometimes long-term, sometimes temporary, of cell therapy of CVD using UCB. In addition, unlike SCs obtained from most other sources, UCB SCs are readily available, multipotent, immunologically naшive, and their acquisition and use do not face serious ethical problems. However, as before, important questions remain regarding the ability of cord blood cells to function as cellular replacements for damaged cells. Expanding the scope of UCB SCs application for the treatment of various pathologies, including cardiovascular and neurodegenerative diseases, will save and improve the lives of millions of patients every year. However, realizing this potential will require further robust, targeted and well-funded research and expanded clinical trials.

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ПЕРСПЕКТИВИ ВИКОРИСТАННЯ ПУПОВИННОЇ КРОВІ В ЛІКУВАННІ ЗАХВОРЮВАНЬ СЕРЦЕВО-СУДИННОЇ СИСТЕМИ

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Серцево-судинні захворювання на сьогодні є найбільш поширеною причиною смертності у всьому світі. У звязку з цим актуалтними є експериментальні та клінічні дослідження ефективності терапії ішемічних і неішемічних захворювань серця з використанням стовбурових клітин.

Метою огляду було оцінити перспективи використання в лікуванні серцево-судинних захворювань стовбурових клітимн кордової крові.

Методи. Проведено пошук в базах даних: «BIGG International database of GRADE guidelines», «Database of GRADE EtD's and Guidelines», «Dynamed», «ebmafrica.net», «ECRI», «MAGIC authoring and publication platform (MAGICapp)», «National Health and Medical Research Council (NHMRC) portal», «NICE Evidence», «Pubmed», «TRIP database», «U.S. Preventive Services Task Force».

Результати. Зроблено аналіз досліджень, повязаних з цією проблемою, які проводились упродовж останніх років, та викладено міркування щодо перспектив використання пуповинної крові в лікуванні захворювань серцево-судинної системи.

Висновки. Незважаючи на певні успіхи, реалізація повною мірою потенціалу стовбурових клітин кордової крові в лікуванні серцево-судинних захворювань все ще потребує подальших серйозних, цілеспрямованих та добре фінансованих досліджень і розширених клінічних випробувань.

Ключові слова: серцево-судинні захворювання; пуповинна кров; стовбурові клітини.