DE GRUYTER OPEN

POLISH HYPERBARIC RESEARCH 1(54)2016
Journal of Polish Hyperbaric Medicine and Technology Society

THE POSSIBILITIES OF STEM CELL APPLICATION IN REGENERATIVE MEDICINE

Sabina Galiniak [1)], Izabela Krawczyk-Merć [1)], Agnieszka Pedrycz [2)]

[1)] Institute of Histology and Embryology Medical Department of the University of Rzeszów, Poland
[2)] Histology and Embryology Department with the Experimental Cytology Laboratory of the Medical University of Lublin, Poland

ABSTRACT

Stem cells are characterized by their ability to self-renew and differentiate into various cell types. They offer great potential for a wide range of applications, however, medical studies on the use of embryonal stem cells are largely limited to bioethical issues searching for alternative sources of stem cells, which include isolating cells from adult organisms or inducing pluripotentiality of somatic cells by administration of transcription factors. Nowadays, stem cells are used to study the mechanisms of cell differentiation and treat diseases that are commonly considered to be incurable, such as diabetes and neurodegenerative diseases, as well as enable regeneration of skin damage and myocardium. This review introduces the subject of stem cells, their sources and application in regenerative medicine.
Key words: stem cells, induced pluripotent cells, cell therapies, diabetes, neurodegenerative diseases.

ARTICLE INFO

PolHypRes 2016 Vol. 54 Issue 1 pp. 49-64
ISSN: 1734-7009 **eISSN:** 2084-0535
DOI: 10.1515/phr-2016-0007
Pages: 16, figures: 2, tables: 0
page www of the periodical: www.phr.net.pl

Publisher
Polish Hyperbaric Medicine and Technology Society

Informing article

Delivery date: 19.11.2015r.
Date of approval for print: 12.01.2016r.

INTRODUCTION

The non-specialised cells that have the capability to self-renew and differentiate into various types of cells are known as stem cells. For over a hundred years this has been evoking enormous interest among scientists. Methods of their utilisation in regenerative processes and in genetic and degenerative diseases are constantly being designed [1]. The said cells constitute a universal model in the investigation of the basis of the cell differentiation process [2].

Amongst them, 4 classes can be distinguished:

- totipotent cells – occur in the zygote until reaching the stage of eight cells. Their differentiation proceeds towards the cells of all germ layers – including placental cells. They are non-specialised cells, subject to asymmetrical and symmetrical divisions. They are characterised by a high proliferation ability.
- pluripotent cells – constitute the internal mass of blastocyst, from where they can be isolated for testing. Their differentiation proceeds towards all germ layers with the exclusion of extraembryonal tissues, including placenta;
- multipotent cells – occur in both adult and foetal organisms. They differentiate to a limited number of cells of a single germ layer;
- unipotent cells – occur in an organism of an adult human and differentiate only into a single type of cells [3].

With regard to the source of origin stem cells, these can be divided into: embryonal stem cells and stem cells isolated from mature organisms.

FACTORS REGULATING THE PLURIPOTENTIAL CAPACITY OF DIFFERENTIATING EMBRYONAL STEM CELLS

Embryonal stem cells (ESC) originate from the inner cell mass of blastocyst (ICM), which next to trophectoderm are isolated during embryogenesis.

They were first isolated and described in mice in 1981 [4,5], and next in a rhesus monkey [6], human [7] and rat [8]. They are characterised by specific properties differentiating them from other stem cells. They are clonogenic, which enables their long-term maintenance in the form of cultures of genetically identical cells. ESCs are pluripotent [7].

In the course of spontaneous differentiation, they generate embroyoid bodies (EB). They have been indicated to have the expression of markers characteristic of all three germ layers [9].

Stem cells, with pluripotent differentiation capacity, contain a conservative network of transcription factors that control their activity. Transcription factors take the regions of the promoter of genes responsible for maintaining pluripotence and early differentiation, thanks to which the expression of genes specific of a particular line is not realised [10].

Amongst them we may distinguish: OCT4 – *Octamer-binding transcription factor* 4, NANOG – *Nanog homeobox* and SOX2 – *Sex determining region Y box containing gene 2*. It has been revealed that *NANOG* overexpression in human stem cells intensified the proliferation of pluripotent cells [11] whereas suppression promotes their differentiation [12]. Differentiation is a gradual process inducing further changes in a cell. Maintenance of cellular pluripotence depends on external factors, inter- and extracellular signalling [Fig. 1, Fig. 2].

One of such factors are cytokins. Among them there is aktivin from the family of the transforming growth factor type beta TGF-β and protein synthesised in nodal cells. They regulate the *NANOG* expression activation maintaining cells in a non-differentiated state with preservation of their self-renewal capacity.

The combination of one of such factors with a transmembrane receptor with the activity of serine/threonine kinase leads to the process of signal transduction in a cell and type I receptor activation. It phosphorylates proteins responsible for generation of heterodimeric SMAD complex (*Sma and Mad related proteins*).

The complex is composed of SMAD2 and SMAD3 subunits. It has the capability of cumulating in the cell nucleus, thus regulating gene transcription [10,13]. The family of TGF-β proteins also includes the BMP proteins (*Bone Morphogenetic Proteins*). It induces differentiation of human ESC thus inhibiting the *NANOG* expression through the activation of a complex made up from SMAD1, SMAD5 and SMAD8 subunits [14].

Signalling leading to the maintenance of pluripotentiality also occurs due to the activity of growth factors, which transmit the signal through mitogen-activated protein kinases (MAPK). Such a growth factor is a fibroblast growth factor (FGF2), which by stimulating MAPK and kinases (Akt kinase and extracelullar signal-regulated kinases, ERK) maintains the pluripotentiality of human ESC. They are undifferentiated and have the capacity to replicate [15].

The preservation of the renewal capacity of stem cells is also based on secreted Wnt glycoproteins, which at the same time inhibit the process of cell differentiation [16]. Proteins secreted outside a cell join the transmembrane LPR5/6 and Frizzled receptors with a domain rich in cysteine, indicating affinity to Wnt [17].

As a result of Wnt interaction with the receptor there is a change in the destination of β-catenin, which instead of being subject to degradation due to phosphorylation through glycogen synthase kinase (GSK3-β), is accumulated in the nucleus and formulates a complex with TCF, which induces transcription of target genes for the Wnt route leading to self-replication of stems cells and inhibiting their division, thus refraining them from differentiating into adult cells [16].

Other factors that control the proliferation of the process of cellular differentiation are Notch proteins. Ligand binding with Notch induces proteolysis of the cytoplasmic part of the Notch domain. It is transported to the cell nucleus, where it induces expression of the transcription factors Hes1 and Hes5 acting as gene differentiation suppressors. The result is ESC maintenance in a non-differentiated state [18,19].

The enrichment of the medium in a laboratory-kept culture of stem cells with growth factors is conducive to their differentiation towards specified cell lines or germ layers. Tests showed that if the applied growth factor is the hepatocyte growth factor (HGF) and β nerve growth factor (βNGF) the stem cells differentiate to three germ layers. An ESC culture in the presence of aktivin-A and TGF-β differentiates stems cells towards the mesoderm. Retinoic acid and epidermal growth factor

(EGF) promote differentiation of embryonal stem cells towards ectoderm and mesoderm [20]. Schuldiner et al. [21] proved that retinoic acid and βNGF are strong stimulants for the differentiation of human ESC towards neurons.

Chadwick et al. [22], on the other hand, showed that under the influence of cytokins and BMP-4 human ESC differentiate into haematopoetic cells. It appears that also the conditions of embryonal stem cells cultures have an impact on their differentiation capacity.

The conducted tests revealed that hypoxia (1 and 5% O_2) reduces the expression of pluripotentiality markers of human ESC, at the same time boosting the expression of genes connected with angiogenesis and vasculogenesis. Among these genes there were genes encoding the growth factor of the vascular endothelium [23].

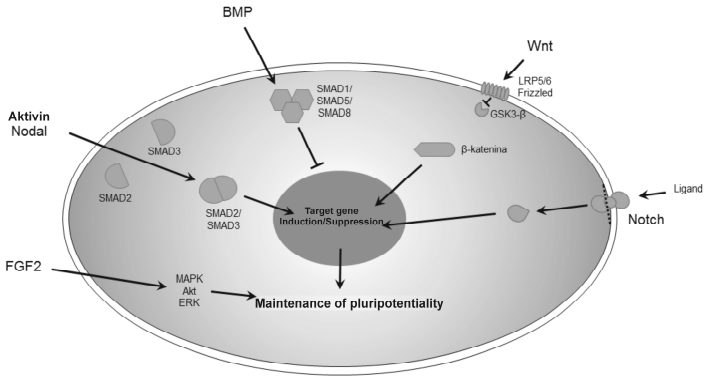

Fig.1. Cellular signalling maintaining ESC pluripotentiality [description in the text].

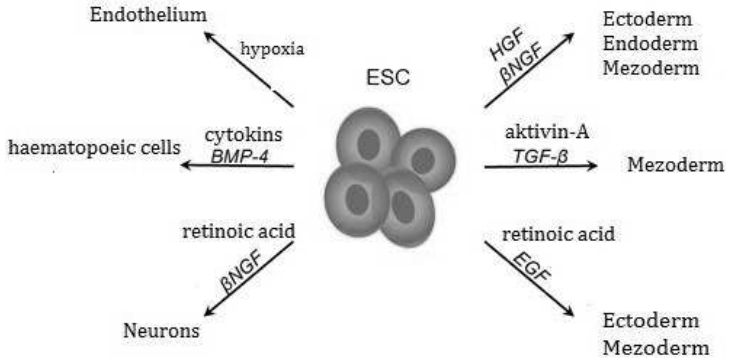

Fig.2. The effect of external factors on ESC differentiation [description in the text].

STEAM CELLS ISOLATED FROM MATURE ORGANISM

Bone marrow-derived stem cells

Bone marrow-derived stem cells (BMDC) constitute a mixture composed of 2% of multipotent stem cells and 98% progenitor cells with different scopes of plasticity, and with an allowance for an occurrence of a small quantity of pluripotent cells [24]. Bone marrow produces approximately 5 million cells per second, and its stem cells have been utilised in medicine for over 50 years in the therapy of autoimmune or haematological diseases [25,26]. Bone marrow is a source of haematopoetic (HSC) and mesenchymal (MSC) stem cells [27].

Mesenchymal stem cells (MSC) isolated from bone marrow belong to somatic stem cells, which raise the most interest in regenerative medicine due to their potential to differentiate into osteocytes, adipocytes, chondrocytes or endothelial cells [28]. They constitute approximately 0.01% of all mononuclear cells present in the bone marrow [29].

The majority of mesenchymal stem cells occur in neonates, whereas in individuals above 80 years of age their count is decreased by 50%. Due to their capacity of multidirectional differentiation, they are an ideal tool for tissue engineering and regenerative medicine [28]. Mesenchymal stem cells are characterised by the presence of CD73, CD105, CD166, CD90 and CD29 antigens, and contrary to the cells of the haematopoietic system, they do not contain CD34, CD45, CD14 antigens [30, 31].

Mesenchymal stem cells have also been detected outside the bone marrow and in many other tissues including muscles, adipose tissue, hair follicles, tooth roots, placenta, skin, cord blood, lungs, liver and spleen [32]. It was proven that mesenchymal stem cells reveal immunosuppressive properties [33], as well as have the capability to synthesise and release numerous cytokins,

such as interleukins and growth factors, which participate in haematopoesis regulation [34].

Besides this, these cells release HGF and the endothelial growth factor, which play a role in the process of regeneration of damaged tissues. Due to their large proliferation potential and capability to differentiate into various MSC tissues they are a promising material to be used in a cell therapy of multiple diseases [32].

Haematopoietic stem cells (HSC) can differentiate into specialised blood cells. They are multipotent cells with a high proliferation capacity. They migrate from bone marrow to peripheral blood, where they are not morphologically different from leukocytes. Haematopoietic stem cells do not contain the CD38 marker characteristic of leukocytes, however they reveal the presence of: CD34, CD59, Thy1 and C-kit markers. The CD34 marker has become a characteristic feature of these cells and is used in their isolation, as it does not occur on the surface of fully differentiated blood cells [26, 35, 36].

Moreover, haematopoietic stem cells participate in the process of wound healing, particularly vast ones with a significant inflammatory domain. Their mobilisation occurs as a result of the release of numerous cytokins and growth factors from damaged tissues and the activation of metaloproteinases, which generate, for instance, neutrophil and monocyte precursors, these in turn migrating to the place of injury, initiating the cleansing process [37].

Cord blood stem cells

Cord blood is a body fluid constituting an alternative source of stem cells to bone marrow and peripheral blood [26,38]. The first successful allogenic cord blood transplantation was carried out in 1988 when cord blood was transplanted into a six year old boy as a form of treatment of Fanconi anaemia [39].

Cord blood is a source of at least three types of stem cells: haematopoietic, mesenchymal and is similar to embryonal cells. Haematopoietic stem cells of the cord blood are precursors to the cells of all haematopoesis lines. They constitute 0.02-1.42% of the total quantity of cells and are capable of differentiating into mature blood cells [40].

Recent studies prove that they can also differentiate *in vivo* towards haepatocytes [41]. Cord blood is one of the most important and most easily available sources of mesenchymal stem cells that undergo differentiation into osteocytes [42] and chondrocytes [43], muscle cells [44] and haepatocytes [45].

Moreover, the capacity to perform *in vitro* differentiation by mesenchymal cord blood cells into cardiomyocytes is indicated [46]. Embryonic-like stem cells constitute 0.16% of all mononuclear cells present in cord blood. They are characterised by a high plasticity and capability to differentiate into the cells of all three germ layers [40,47].

Cord blood is a vastly accepted source of stem cells, hence its collection during child birth (both natural and Caesarian section), as well as storage in cord blood banks is becoming increasingly popular [48]. The procedure of its acquisition is safe for the mother and the infant. Cord blood contains "young" stem cells of a high proliferation potential [38].

Their transplantation is characterised by only a small risk of transplant rejection, as these cells are not sufficiently mature and do not generate a strong immunological conflict in an unrelated recipient [49]. Unfortunately the number of stem cells obtained from a single portion of cord blood is smaller as compared with bone marrow or peripheral blood, which causes this type of therapy to be available mainly to paediatric patients [50].

Peripheral blood stems cells

The continuous advancement of medicine has resulted in the discovery of an alternative source of stem cells to bone marrow or cord blood [51]. The application of a granulocyte colony-stimulating factor (G-CSF) has enabled mobilisation of haematopoeic stem cells HSC to peripheral blood and their effective collection [51,52]. Peripheral blood has become an important source of haematopoeic stem cells used for transplantology purposes [26].

It is mainly transplanted to unrelated recipients [53]. In comparison with HSC cells from bone marrow, the cells originating from peripheral blood indicate faster migration to bone marrow and a quicker regeneration of the circulatory system.

This is due to the presence of membranous PMP microparticles (*Platelet Microparticles*) [26]. As opposed to the collection of bone marrow cells, cell collection from peripheral blood does not require hospitalisation and is performed without anaesthesia with the donor being administered solely G-CSF injections. Donors can present side effects, such as pain in the bones, headache and flu-like symptoms – feeling unwell, nausea or subfebrile temperature [54].

Adipose tissue stem cells

Adipose tissue is a source of stem cells that raises great hopes due to the availability of material, little invasiveness of the collection method and the simplicity of both the isolation and growth of collected cells [55,56]. Moreover, it is a source of precursor cells, which does not raise any ethical considerations [57].

Similarly to bone marrow, adipose tissue is of mesodermal origin and the cells isolated from it can replicate and differentiate into numerous tissue types [56,58]. Stem cells originating from adipose tissue intensively release growth factors (FGF2, HGF, TGF-β) and cytokins (G-CSF, interleukin 6, 7, 8, 11 and 12, tumour necrosis factor) [59].

Recent studies indicate that the adipose tissue stem cells have a great biological significance and therapeutic potential [60]. They have the capability to differentiate towards nerve cells [61], endothelial cells [62] or smooth muscle cells [63].

Satellite cells of striated muscle tissue

Satellite cells were described 50 years ago as mononuclear cells located between the membrane of muscle fibres and the basal membrane surrounding each fibre. These are progenitor cells of skeletal muscles responsible for their postnatal growth and regeneration. Besides the capacity to transform into myoblasts, they also exhibit the capability to self-renew their population [64,65].

In adults these are usually inactive cells that constitute the reserve of cells capable of proliferating in response to damage, which leads to muscle regeneration and an increase in the quantities of satellite cells.

Despite the supplementation of the satellite cell pool during muscle growth their number decreases with age [66]. Moreover, an occurrence of a population of mesenchymal stem cells was also noted in skeletal muscles capable of differentiating into numerous cells of mesodermal origin [67].

INDUCED PLURIPOTENT CELLS

The acquisition of embryonal stem cells has always raised a lot of ethical doubts, since in the isolation of embryonal cell lines the embryo is destroyed. Thus, the scientific research focused on seeking alternative sources of pluripotent stem cells. In the 1950s basic laws governing the processes leading to the induction of pluripotentiality were described.

Transplantation of a cell nucleus from an embryo into a nucleus-deprived oocyte has activated the mechanism of development of a regular embryo [68]. Gurdon [69] proved that a transplanted nucleus may promote formation of differentiated cells and at the same time contain genetic information necessary to generate all kinds of somatic cells.

A considerable breakthrough were the studies carried out by Takahashi and Yamanaka [70], who showed that somatic cells can be reprogrammed, thus inducing their pluripotentiality.

The researchers introduced four transcription factors – Oct3/4, Sox2, c-Myc and Klf4 defined as "Yamanaka cocktail" into the fibroblast in mice. They observed that the said fibroblast indicated morphology and properties characteristic of embryonal stem cells. Somatic cells which are subject to reprogramming are referred to as induced pluripotent stem cells (iPS). In the consecutive years of the 20th century [71,72] successful reprogramming of human somatic cells, mainly fibroblasts, was conducted with the use of a cocktail of transcription factors.

Human iPS cells have the morphology, proliferation capacity and gene expression approximated to ESC. They contain similar surface antigens and capability to differentiate into the cells of three germ layers. Thus far, the iPS cells have been obtained as a result of reprogramming (besides fibroblasts [70,71]) keratynocytes [73], lymphocytes [74], stomach and liver cells [75].

The iPS cells are relatively easily to obtain from each somatic cell, however the efficiency of reprogramming is low and amounts to approximately 0.01-0.05%. An additional flaw of iPS cells is the fact that they may form tumours, whereas viral transfection may lead to achieving an unstable cell population [76].

STEM CELLS IN REGENERATION

Stem cells – the hope of regenerative medicine – generate specialised cell populations, which could replace damaged tissues and patient organs.

Currently conducted therapies with their use are an object of interest of researchers, with the research being focused on the development of innovative treatment methods of multiple diseases, including diabetes, neurodegenerative diseases – Alzeheimer's, Parkinson's, multiple sclerosis or amyothropic lateral sclerosis, as well as dermal or myocardial damage.

Diabetes mellitus

The pancreas is an important organ, whose cells are responsible for secretion of significant digestive enzymes. Approximately 1% of its mass is constituted by the Langerhans islets (or pancreatic islets), which are responsible for carbohydrate metabolism, and 80% of their cells are β cells that secret insulin.

The most common disturbance in pancreatic functions, affecting approximately 0.5% of the world population is type I diabetes (insulin-dependent). In individuals suffering from this disease, β cells are destroyed by their own immunological system.

The consequence is chronic hyperglycaemia, which may lead to blindness, kidney damage, stroke, neuropathy, or even limb amputation [26,77]. No significant progress has been noted in relation to diabetes treatment since the discovery of insulin 90 years ago. Insulin administration does not reflect physiological secretion of this hormone.

Therefore, temporary hypoglycaemia or hyperglycaemia is quite common. Nonetheless, at present it is the most effective method of treating diabetes. In search for other methods a successful transplantation of cells isolated from pancreatic islets was carried out on a group of patients.

This procedure restored the proper glucose level in the blood. However, this therapy is limited by deficiency of organs available for transplantation [78,79]. Great hope is seen in cell therapy with the use of stem cells. In recent years, significant progress has been made in this area.

The most recent studies show that it is possible to direct the differentiation of stem cells in *in vitro* culture towards the production of insulin-producing cells, which may eventually be transplanted into damaged tissues in patients with diabetes.

It was proven that β cells can emerge as a result of differentiation of both embryonal and adult stem cells from the pancreas, liver and bone marrow. Lumelsky et al. [80] showed that embryonal stem cells in mice produce pancreatic hormones in the presence of glucose.

These arrange into three-dimensional structures resembling pancreatic islets, and following their injection into mice with diabetes they undergo quick vascularisation. Assady et al., on the other hand, [81] proved that insulin secretion by differentiating human ESC depends on the degree of culture differentiation and the appearance of markers characteristic of β cells.

In a different experiment, administration of insulin-producing cells to mice with diabetes caused reversal of hyperglycaemia within a period of approximately 3 weeks.

Unfortunately, this simultaneously led to an occurrence of teratomas [82]. Tateishi et al. [83] proved that iPS cells originating from fibroblasts also differentiate and form cell clusters resembling pancreatic islets.

Cells forming such clusters when subjected to glucose stimulation released in their experiment peptide C. A significant fact that may facilitate the use of stimulated cells in the regeneration of a damaged pancreas is that the said cells produce hormones, reduce glucose level and create three-dimensional aggregates reminding of pancreatic islets both in *in vitro* and *in vivo* conditions [84].

Despite the enormous progress, thus far the complex regulatory mechanisms which control physiological insulin secretion have not been reproduced [26,85]. An alternative solution would consist in the development of pharmaceuticals with the use of stem cells, which could evoke regeneration of native pancreatic islets [86].

Neurodegenerative diseases

The central nervous system, particularly in adults is an example of a system that is deprived of regenerative capabilities [87].

Alzheimer's disease belongs to neurodegenerative diseases, with the symptoms involving dementia, i.e. a loss or impairment of supreme cortical functions such as memory, thinking, orientation or capability of correct judgement of situation [88]. The cause of Parkinson's disease is atrophy of cells located in the brain black matter.

Its symptoms include muscle stiffness, tremor and poorer movement coordination [89]. Despite the fact that both diseases are treatable, restoration of full efficiency in patients is not feasible due to inducing an irreversible loss of neurons and glial cells.

Thanks to the progress made in the research on stem cells and the nervous system there is hope for development of innovative therapeutic methods, which would aim at regeneration of damaged tissues [90]. Transplantation of neuronal stem cells seems to be helpful in delaying or even preventing the onset of Alzheimer's disease [91].

It could increase cognitive capabilities and reduce the inflammatory state [92]. Ager et al. [93] showed that the population of human neuronal stem cells differentiates into immature neurons and glial cells. Transplantation of such cells improves endogenous synaptogenesis and does not affect amyloid β accumulation, which is the underlying cause of Alzheimer's disease. Park et al. [94] revealed that human mesenchymal stem cells administered to rats with experimentally induced Parkinson's disease prevent neuron loss.

Dopamine neurons originating from human ESC have a long durability, restore motor functions and stimulate mesencephalon regeneration in an animal disease model [95]. Moreover, it was proven that after being transplanted into the brain of a mouse foetus, the iPS cells migrate to various brain regions differentiating into glial cells and neurons, including their subtypes – GABA-ergic, glutamatergic and catecholaminergic.

What is more, the iPS cells differentiate towards dopamine neurons characteristic of the mesencephalon and improve brain functions in a rat model of the Parkinson's diseases [96].

Multiple sclerosis is a demyelinating multifocal disease damaging the central nervous system, which affects over 2 million individuals all over the world, and at the same time it is the most common non-traumatic cause of disability in young people. It was also shown that transplantation of mesenchymal stem cells in mice with an induced encephalitis and myelitis reduces functional deficits, leads to the development of oligodendrocytes and myelin regeneration.

This is undoubtedly the exit point for new therapies aimed at re-myelinisation in the process of multiple sclerosis treatment [97]. Burt et al., on the other hand, [98,99] documented that autollogic transplantation of non-myeloablative haematological stem cells in patients with the relapsing-remitting type of multiple sclerosis improves the neurological functioning and the quality of life of patients, as well as inhibits disease advancement.

A clinical study on patients with secondary progressive multiple sclerosis showed that following autollogic infusion of mesenchymal bone marrow stem cells the visual acuity is improved, visual potentials are induced and the area of the optic nerve is extended, which suggests the neuroprotective activity of stem cells [100]. Amyotrophic lateral sclerosis is a neurodegenerative impairment of upper and lower motor neurons characterised by progressive weakness and muscular atrophy.

Studies indicate that through an increase in the expression in glial-derived neutrophic factor, haematopoeic stem cells show a protective activity towards motoneurons [101]. Vercelli et al. [102] documented that human mesenchymal bone marrow stem cells are able to survive and migrate in the lumbar section of the spinal cord in mice, where they prevent astrocytosis and microglia, thus delaying the loss of motoneurons.

The clinical studies conducted by Mazzini et al. [103,104] revealed that autollogic administration of mesenchymal bone marrow stem cells into the spinal cord of patients with amyotrophic lateral sclerosis is safe for patients, which provides justification for further research.

Skin regeneration

Skin constitutes the first line of defence, which protects the organism against dehydration, injuries and infections. In order to meet these expectations, the skin evolved into a water-impermeable layer, which regenerates in the entire lifetime, whereas a hair follicle is subject to continuous growth and degeneration cycles [105].

The stem cells of the epidermis and hair follicles ensure maintenance of dermal homeostasis and hair regeneration and participate in the process of wound healing [106]. These cells are found in the basal layer of the epidermis as well as the germinal matrix and the region of bulging of a hair follicle [107].

They are characterised by a high proliferation potential, capability to self-renew, an extended cellular cycle and a state of metabolic dormancy [108]. Epidermal stem cells are precursors of mature keratinocytes and as far as we know their insufficient number is often the cause of a hindered wound healing process [109].

Stem cells which are capable of self-renewal and replication of not only the epidermis but also the skin appendages can be used in the treatment of various skin conditions, including severe burns [110], skin cancer [111], alopecia [112] or acne [113].

Shabbir et al. [114] revealed that exosomes of mesenchymal stem cells activate signal paths necessary in the process of wound healing (Akt, ERK), as well as induce expression of a number of growth factors, including HGF and NGF. Capturing of MSC exosomes by the cells of the endothelium of the umbilical vein lead to formation of a pipe structure by those cells.

Mesenchymal stem cells of the bone marrow administered directly into wounds accelerate their healing in humans and mice [115], with the procedure of skin regeneration being minimally invasive [116]. There

are also reports confirming the capabilities of human haematopoeietic stem cells to differentiate towards keratinocytes [117].

Regeneration of the myocardium

Cardiovascular diseases, which encompass, among others, hypertension, ischaemic heart disease and congestive heart failure, are classified as the most common cause of death in highly developed countries. Despite the fact that modern medicine allows for a significant delay in the courses of the above diseases, the scale of mortality does not decrease [118,119].

Myocardium is mainly composed of cardiomyocytes, fibroblasts, elements of vascular vessels: smooth muscles endothelium and cells, as well as macrophages and extracellular matrix [120,121].

The dominant cells in the myocardium are fibroblasts, whereas cardiomyocytes, despite constituting only 30% of the total cell count, take up approximately 70% of the organ's volume [122,123].

Post-infarction heart failure results, among other things, from the insufficient supply of myocardial tissue with oxygen, which results in a progressive loss of cardiomyocytes. This leads to a number of unfavourable consequences, such as extension and overgrowth of live

cells, post-infarction heart remodelling manifested in an extension of its left ventricle and an occurrence of scar tissue, which significantly weakens the heart.

The result is progressive heart failure and death [124,125]. Contrary to other tissues and organs, such as: liver, intestine, skeletal muscle, bone or skin, the heart is an organ with a limited regeneration capacity. However, recent studies give hope that the process of regeneration is possible thanks to the use of stem cells.

A number of experiments of animals and clinical studies have been conducted on embryonal and adult stem cells as sources of cells for regeneration of damaged cardiac tissues [126].

Embryonal stem cells can differentiate into any cell of the organism, including those that play a significant role in the regeneration of the myocardium. A series of *in vivo* [127] and *in vitro* [128] tests have been carried out with the use of mouse and human cells, which proved that they differentiate spontaneously, thus creating the cells of smooth muscles and the endothelium.

Moreover, human embryonal stem cells have the capacity to differentiate into myocytes with the structural and functional properties resembling those of cardiomyocytes [129]. Within the scope of adult stem cells, particular attention should be paid to skeletal myoblasts, bone marrow cells, induced pluripotent stem cells and cardiac stem cells.

The first that were used in the studies on regenerative heart therapy were skeletal myoblasts [130]. Thanks to their use, an improvement was noted in the functioning of the transplanted tissue, however it was observed that the generated myoblasts did not integrate electrically with native cardiomyocytes, due to a lack of expression of key proteins – N-cadherin and connexin 43, thus resulting in severe disturbances in the heart rhythm [130,131,132].

Major progress in regenerative therapy results from the application of bone marrow stem cells. Research has shown that an injection of such cells into the post-infarction scar leads to a faster heart regeneration, formation of blood vessels and improvement of working parameters of the left ventricle [133,134].

It constitutes a solid basis for the continuation of tests on the use of human bone marrow stem cells. One of the successes connected with the use of these cells involved the administration of mesenchymal cells during an angioplasty to patients with acute myocardiac infarction in whom an improvement of the left ventricular ejection fraction was observed [135,136].

Data from literature prove that the myocardium contains a small population of endogenous cardiac stem cells (eCSC) [134], which have the ability to proliferate, self-renew and differentiate towards cardiomyocytes, smooth muscle and endothelial cells [137].

Clinical studies have confirmed that their injection into the place of infarct causes a reduction in the scar tissue area and an improvement in heart contractibility [138]. Thus, endogenous cardiac stem cells can successfully be used in autologic regenerative therapy.

CONCLUSIONS

The potential of embryonal and adult stem cells constitutes a challenge for scientists, as well as an opportunity for patients with diseases thus far considered to be untreatable. However, what seems to be of key importance is ensuring proper culture conditions to guarantee obtaining a genetically uniform cell population, thus diminishing possible complications following their implantation.

Moreover, it is important to resolve the issue of survival and effectiveness of cells used in the replacement of damaged tissues, which certainly still requires numerous tests performed both in *in vitro* and *in vivo* conditions.

BIBLIOGRAPHY

1. Angelos MG, Kaufman DS. Pluripotent stem cell applications for regenerative medicine. Curr Opin Organ Transplant 2015; 20(6):663-70, DOI 10.1097/MOT.0000000000000244.
2. Paździorek PR. Mathematical model of stem cell differentiation and tissue regeneration with stochastic noise. Bull Math Biol 2014; 76(7):1642-69, DOI 10.1007/s11538-014-9971-5.
3. Jaenisch R, Young R. Stem cells, the molecular circuitry of pluripotency and nuclear reprogramming. Cell 2008; 13: 567-582, DOI 10.1016/j.cell.2008.01.015.
4. Evans MJ, Kaufman MH. Establishment in culture of pluripotential cells from mouse embryos. Nature 1981; 292(5819):154-6.
5. Kaufman MH, Robertson EJ, Handyside AH, Evans MJ. Establishment of pluripotential cell lines from haploid mouse embryos. J Embryol Exp Morphol 1983; 73:249-61.
6. Thomson JA, Kalishman J, Golos TG, Durning M, Harris CP, Becker RA, Hearn JP. Isolation of a primate embryonic stem cell line. Proc Natl Acad Sci USA 1995; 92(17):7844-8.
7. Thomson JA, Itskovitz-Eldor J, Shapiro SS, Waknitz MA, Swiergiel JJ, Marshall VS, Jones JM. Embryonic stem cell lines derived from human blastocysts. Science 1998; 282(5391):1145-7.
8. Tabei I, Hashimoto H, Ishiwata I, Tokieda Y, Tachibana T, Akahori M et al. New approach for the establishment of an hepatocyte cell line derived from rat early embryonic stem cells. Hum Cell 2003; 16(1):39-46.

9. Itskovitz-Eldor J, Schuldiner M, Karsenti D, Eden A, Yanuka O, Amit M et al. Differentiation of human embryonic stem cells into embryoid bodies compromising the three embryonic germ layers. Mol Med 2000; 6(2):88-95.
10. Pera MF, Tam PP. Extrinsic regulation of pluripotent stem cells. Nature 2010; 465(7299):713-20, DOI 10.1038/nature09228.
11. Darr H, Mayshar Y, Benvenisty N. Overexpression of NANOG in human ES cells enables feeder-free growth while inducing primitive ectoderm features. Development 2006; 133(6):1193-201.
12. Massagué J, Seoane J, Wotton D. Smad transcription factors. Genes Dev 2005; 19(23):2783-810.
13. Lie KH, Tuch BE, Sidhu KS. Suppression of NANOG induces efficient differentiation of human embryonic stem cells to pancreatic endoderm. Pancreas 2012; 41(1):54-64, DOI 10.1097/MPA.0b013e31822362e4.
14. Kee K, Gonsalves JM, Clark AT, Pera RA. Bone morphogenetic proteins induce germ cell differentiation from human embryonic stem cells. Stem Cells Dev 2006; 15(6):831-7.
15. Eiselleova L, Matulka K, Kriz V, Kunova M, Schmidtova Z, Neradil J et al. A complex role for FGF-2 in self-renewal, survival, and adhesion of human embryonic stem cells. Stem Cells 2009; 27(8):1847-57.
16. ten Berge D, Kurek D, Blauwkamp T, Koole W, Maas A, Eroglu E et al. Embryonic stem cells require Wnt proteins to prevent differentiation to epiblast stem cells. Nat Cell Biol 2011; 13(9):1070-5, DOI 10.1038/ncb2314.
17. Wu CH, Nusse R. Ligand receptor interactions in the Wnt signaling pathway in Drosophila. J Biol Chem 2002; 277(44):41762-9.
18. Artavanis-Tsakonas S, Rand MD, Lake RJ. Notch signaling: cell fate control and signal integration in development. Science 1999; 284(5415):770-6.
19. Kobayashi T, Kageyama R. Hes1 regulates embryonic stem cell differentiation by suppressing Notch signaling. Genes Cells 2010; 15(7):689-98, DOI 10.1111/j.1365-2443.2010.01413.x.
20. Schuldiner M, Yanuka O, Itskovitz-Eldor J, Melton DA, Benvenisty N. Effects of eight growth factors on the differentiation of cells derived from human embryonic stem cells. Proc Natl Acad Sci USA 2000; 10;97(21):11307-12.
21. Schuldiner M, Eiges R, Eden A, Yanuka O, Itskovitz-Eldor J, Goldstein RS, Benvenisty N. Induced neuronal differentiation of human embryonic stem cells. Brain Res 2001; 913(2):201-5.
22. Chadwick K, Wang L, Li L, Menendez P, Murdoch B, Rouleau A, Bhatia M. Cytokines and BMP-4 promote hematopoietic differentiation of human embryonic stem cells. Blood 2003; 102(3):906-15.
23. Prado-Lopez S, Conesa A, Armiñán A, Martínez-Losa M, Escobedo-Lucea C, Gandia C et al. Hypoxia promotes efficient differentiation of human embryonic stem cells to functional endothelium. Stem Cells 2010; 28(3):407-18, DOI 10.1002/stem.295.
24. Kurpisz M. Próby przedkliniczne i kliniczne zastosowania komórek macierzystych do regeneracji mięśnia sercowego. Postępy biol komórki 2010; 37(1):209-223 Polish [Stem cells for heart regeneration – preclinical and clinical trials].
25. Miura Y. Human bone marrow mesenchymal stromal/stem cells: current clinical applications and potential for hematology. Int J Hematol 2015; [Epub ahead of print], DOI 10.1007/s12185-015-1920-z.
26. Sikora MA, Olszewski WL. Komórki macierzyste – biologia i zastosowanie terapeutyczne. Postępy Hig Med Dosw 2004; 58:202-208 Polish [Stem cells – biology and therapeutic application].
27. Wu Y, Wang J, Scott PG, Tredget EE. Bone marrow-derived stem cells in wound healing: a review. Wound Repair Regen 2007; 15 Suppl 1:S18-26, DOI 10.1111/j.1524-475X.2007.00221.x.
28. Oswald J, Boxberger S, Jørgensen B, Feldmann S, Ehninger G, Bornhäuser M, Werner C. Mesenchymal stem cells can be differentiated into endothelial cells in vitro. Stem Cells 2004; 22(3):377-84.
29. Jones EA, Kinsey SE, English A, Jones RA, Straszynski L, Meredith DM et al. Isolation and characterization of bone marrow multipotential mesenchymal progenitor cells. Arthritis Rheum 2002; 46(12):3349-60.
30. Barry F, Boynton R, Murphy M, Haynesworth S, Zaia J. The SH-3 and SH-4 antibodies recognize distinct epitopes on CD73 from human mesenchymal stem cells. Biochem Biophys Res Commun 2001; 289(2):519-24.
31. Barry FP, Boynton RE, Haynesworth S, Murphy JM, Zaia J. The monoclonal antibody SH-2, raised against human mesenchymal stem cells, recognizes an epitope on endoglin (CD105). Biochem Biophys Res Commun 1999; 265(1):134-9.
32. Bianco P, Robey PG, Simmons PJ. Mesenchymal stem cells: revisiting history, concepts, and assays. Cell Stem Cell 2008; 2(4):313-9, DOI 10.1016/j.stem.2008.03.002.
33. Bartholomew A, Sturgeon C, Siatskas M, Ferrer K, McIntosh K, Patil S et al. Mesenchymal stem cells suppress lymphocyte proliferation in vitro and prolong skin graft survival in vivo. Exp Hematol 2002; 30(1):42-8.
34. Wagner W, Roderburg C, Wein F, Diehlmann A, Frankhauser M, Schubert R et al. Molecular and secretory profiles of human mesenchymal stromal cells and their abilities to maintain primitive hematopoietic progenitors. Stem Cells 2007; 25(10):2638-47.
35. Hao QL, Smogorzewska EM, Barsky LW, Crooks GM. In vitro identification of single CD34+CD38- cells with both lymphoid and myeloid potential. Blood 1998; 91(11):4145-51.
36. Craig W, Kay R, Cutler RL, Lansdorp PM. Expression of Thy-1 on human hematopoietic progenitor cells. J Exp Med 1993; 177(5):1331-42.
37. Kirby GT, Mills SJ, Cowin AJ, Smith LE. Stem cells for cutaneous wound healing. Biomed Res Int 2015; 2015:285869, DOI 10.1155/2015/285869.
38. Baksh D, Yao R, Tuan RS. Comparison of proliferative and multilineage differentiation potential of human mesenchymal stem cells derived from umbilical cord and bone marrow. Stem Cells 2007; 25(6):1384-92.
39. Gluckman E, Broxmeyer HA, Auerbach AD, Friedman HS, Douglas GW, Devergie A et al. Hematopoietic reconstitution in a patient with Fanconi's anemia by means of umbilical-cord blood from an HLA-identical sibling. N Engl J Med 1989; 321(17):1174-8.
40. Roszek K, Komoszyński M. Kontrola i kierunki różnicowania komórek macierzystych krwi pępowinowej oraz ich zastosowanie terapeutyczne. Postępy Hig Med Dosw 2008; 62:660-667 Polish [Regulation and direction of umbilical cord blood stem cells differentiation and their therapeutic application].
41. Fujino H, Hiramatsu H, Tsuchiya A, Niwa A, Noma H, Shiota M et al. Human cord blood CD34+ cells develop into hepatocytes in the livers of NOD/SCID/gamma(c)null mice through cell fusion. FASEB J 2007; 21(13):3499-510.
42. Esposito M, Lucariello A, Costanzo C, Fiumarella A, Giannini A, Riccardi G, Riccio I. Differentiation of human umbilical cord-derived mesenchymal stem cells, WJ-MSCs, into chondrogenic cells in the presence of pulsed electromagnetic fields. In Vivo 2013; 27(4):495-500.
43. Ciavarella S, Dammacco F, De Matteo M, Loverro G, Silvestris F. Umbilical cord mesenchymal stem cells: role of regulatory genes in their differentiation to osteoblasts. Stem Cells Dev 2009; 18(8):1211-20, DOI 10.1089/scd.2008.0340.
44. Gang EJ, Jeong JA, Hong SH, Hwang SH, Kim SW, Yang IH et al. Skeletal myogenic differentiation of mesenchymal stem cells isolated from human umbilical cord blood. Stem Cells 2004; 22(4):617-24.
45. Talaei-Khozani T, Borhani-Haghighi M, Ayatollahi M, Vojdani Z. An in vitro model for hepatocyte-like cell differentiation from Wharton's jelly derived-mesenchymal stem cells by cell-base aggregates. Gastroenterol Hepatol Bed Bench 2015; 8(3):188-99.
46. Qian Q, Qian H, Zhang X, Zhu W, Yan Y, Ye S et al. 5-Azacytidine induces cardiac differentiation of human umbilical cord-derived mesenchymal stem cells by activating extracellular regulated kinase. Stem Cells Dev 2012; 21(1):67-75, DOI 10.1089/scd.2010.0519.
47. McGuckin C, Forraz N, Baradez MO, Basford C, Dickinson AM, Navran S, Hartgerink JD. Embryonic-like stem cells from umbilical cord blood and potential for neural modeling. Acta Neurobiol Exp (Wars) 2006; 66(4):321-9.
48. Fazzina R, Mariotti A, Procoli A, Fioravanti D, Iudicone P, Scambia G et al. A new standardized clinical-grade protocol for banking human umbilical cord tissue cells. Transfusion 2015; 55(12):2864-2873, DOI 10.1111/trf.13277.
49. Gang EJ, Hong SH, Jeong JA, Hwang SH, Kim SW, Yang IH et al. In vitro mesengenic potential of human umbilical cord blood-derived mesenchymal stem cells. Biochem Biophys Res Commun 2004; 321(1):102-8.
50. Hofmeister CC, Zhang J, Knight KL, Le P, Stiff PJ. Ex vivo expansion of umbilical cord blood stem cells for transplantation: growing knowledge from the hematopoietic niche. Bone Marrow Transplant 2007; 39(1):11-23.
51. Körbling M, Freireich EJ. Twenty-five years of peripheral blood stem cell transplantation. Blood 2011; 117(24):6411-6, DOI 10.1182/blood-2010-12-322214.
52. Kasai M, Kiyama Y, Kawamura A. Application of peripheral blood stem cells (PBSC) mobilized by recombinant human granulocyte colony stimulating factor for allogeneic PBSC transplantation and the comparison of allogeneic PBSC transplantation and bone marrow transplantation. Transfus Apher Sci 2002; 26(2):121-7.
53. Blau IW, Basara N, Lentini G, Guenzelmann S, Kirsten D, Schmetzer B et al. Feasibility and safety of peripheral blood stem cell transplantation from unrelated donors: results of a single-center study. Bone Marrow Transplant 2001; 27(1):27-33.
54. Hölig K. G-CSF in Healthy Allogeneic Stem Cell Donors. Transfus Med Hemother 2013; 40(4):225-35, DOI 10.1159/000354196.

55. Francis MP, Sachs PC, Elmore LW, Holt SE. Isolating adipose-derived mesenchymal stem cells from lipoaspirate blood and saline fraction. Organogenesis 2010; 6(1):11-4.
56. Schäffler A, Büchler C. Concise review: adipose tissue-derived stromal cells--basic and clinical implications for novel cell-based therapies. Stem Cells 2007; 25(4):818-27.
57. Kim EH, Heo CY. Current applications of adipose-derived stem cells and their future perspectives. World J Stem Cells 2014; 6(1):65-8, DOI 10.4252/wjsc.v6.i1.65.
58. Priya N, Sarcar S, Majumdar AS, SundarRaj S. Explant culture: a simple, reproducible, efficient and economic technique for isolation of mesenchymal stromal cells from human adipose tissue and lipoaspirate. J Tissue Eng Regen Med 2014; 8(9):706-16, DOI 10.1002/term.1569.
59. Tobita M, Orbay H, Mizuno H. Adipose-derived stem cells: current findings and future perspectives. Discov Med 2011; 11(57):160-70.
60. Pikuła M, Marek-Trzonkowska N, Wardowska A, Renkielska A, Trzonkowski P. Adipose tissue-derived stem cells in clinical applications. Expert Opin Biol Ther 2013; 13(10):1357-70, DOI 10.1517/14712598.2013.823153.
61. Yu JM, Bunnell BA, Kang SK. Neural differentiation of human adipose tissue-derived stem cells. Methods Mol Biol 2011; 702:219-31, DOI 10.1007/978-1-61737-960-4_16.
62. Cao Y, Sun Z, Liao L, Meng Y, Han Q, Zhao RC. Human adipose tissue-derived stem cells differentiate into endothelial cells in vitro and improve postnatal neovascularization in vivo. Biochem Biophys Res Commun 2005; 332(2):370-9.
63. Salem SA, Hwie AN, Saim A, Chee Kong CH, Sagap I, Singh R et al. Human adipose tissue derived stem cells as a source of smooth muscle cells in the regeneration of muscular layer of urinary bladder wall. Malays J Med Sci 2013; 20(4):80-7.
64. Montarras D, Morgan J, Collins C, Relaix F, Zaffran S, Cumano A et al. Direct isolation of satellite cells for skeletal muscle regeneration. Science 2005; 309(5743):2064-7.
65. Archacka K, Kowalski K, Brzóska E. Czy komórki satelitowe są macierzyste? Postępy biochemii 2013; 59(2):205-218 Polish [Are satellite cells stem cells?].
66. Morgan JE, Partridge TA. Muscle satellite cells. Int J Biochem Cell Biol 2003; 35(8):1151-6.
67. Williams JT, Southerland SS, Souza J, Calcutt AF, Cartledge RG. Cells isolated from adult human skeletal muscle capable of differentiating into multiple mesodermal phenotypes. Am Surg 1999; 65(1):22-6.
68. Briggs R, King TJ. Transplantation of Living Nuclei From Blastula Cells into Enucleated Frogs' Eggs. Proc Natl Acad Sci USA 1952; 38(5):455-63.
69. Gurdon JB. The developmental capacity of nuclei taken from intestinal epithelium cells of feeding tadpoles. J Embryol Exp Morphol 1962; 10:622-40.
70. Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell 2006; 126(4):663-76.
71. Takahashi K, Tanabe K, Ohnuki M, Narita M, Ichisaka T, Tomoda K, Yamanaka S. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. Cell 2007; 131(5):861-72.
72. Yu J, Vodyanik MA, Smuga-Otto K, Antosiewicz-Bourget J, Frane JL, Tian S et al. Induced pluripotent stem cell lines derived from human somatic cells. Science 2007; 318(5858):1917-20.
73. Aasen T, Raya A, Barrero MJ, Garreta E, Consiglio A, Gonzalez F et al. Efficient and rapid generation of induced pluripotent stem cells from human keratinocytes. Nat Biotechnol 2008; 26(11):1276-84.
74. Seki T, Yuasa S, Oda M, Egashira T, Yae K, Kusumoto D et al. Generation of induced pluripotent stem cells from human terminally differentiated circulating T cells. Cell Stem Cell 2010; 7(1):11-4, DOI 10.1016/j.stem.2010.06.003.
75. Aoi T, Yae K, Nakagawa M, Ichisaka T, Okita K, Takahashi K et al. Generation of pluripotent stem cells from adult mouse liver and stomach cells. Science 2008; 321(5889):699-702.
76. Cox JL, Rizzino A. Induced pluripotent stem cells: what lies beyond the paradigm shift. Exp Biol Med (Maywood) 2010; 235(2):148-58, DOI 10.1258/ebm.2009.009267.
77. Shapiro AM, Lakey JR, Ryan EA, Korbutt GS, Toth E, Warnock GL et al. Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. N Engl J Med 2000; 343(4):230-8.
78. Ryan EA, Lakey JR, Paty BW, Imes S, Korbutt GS, Kneteman NM et al. Successful islet transplantation: continued insulin reserve provides long-term glycemic control. Diabetes 2002; 51(7):2148-57.
79. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993; 329(14):977-86.
80. Lumelsky N, Blondel O, Laeng P, Velasco I, Ravin R, McKay R. Differentiation of embryonic stem cells to insulin-secreting structures similar to pancreatic islets. Science 2001; 292(5520):1389-94.
81. Assady S, Maor G, Amit M, Itskovitz-Eldor J, Skorecki KL, Tzukerman M. Insulin production by human embryonic stem cells. Diabetes 2001; 50(8):1691-7.
82. Fujikawa T, Oh SH, Pi L, Hatch HM, Shupe T, Petersen BE. Teratoma formation leads to failure of treatment for type I diabetes using embryonic stem cell-derived insulin-producing cells. Am J Pathol 2005; 166(6):1781-91.
83. Tateishi K, He J, Taranova O, Liang G, D'Alessio AC, Zhang Y. Generation of insulin-secreting islet-like clusters from human skin fibroblasts. J Biol Chem 2008; 283(46):31601-7, DOI 10.1074/jbc.M806597200.
84. Shim JH, Kim J, Han J, An SY, Jang YJ, Son J et al. Pancreatic islet-like three-dimensional aggregates derived from human embryonic stem cells ameliorate hyperglycemia in streptozotocin-induced diabetic mice. Cell Transplant 2015; 24(10):2155-68, DOI 10.3727/096368914X685438.
85. Ahrén B, Holst JJ. The cephalic insulin response to meal ingestion in humans is dependent on both cholinergic and noncholinergic mechanisms and is important for postprandial glycemia. Diabetes 2001; 50(5):1030-8.
86. Ogawa N, List JF, Habener JF, Maki T. Cure of overt diabetes in NOD mice by transient treatment with anti-lymphocyte serum and exendin-4. Diabetes 2004; 53(7):1700-5.
87. Nicholls JG, Adams WB, Eugenin J, Geiser R, Lepre M, Luque JM, Wintzer M. Why does the central nervous system not regenerate after injury? Surv Ophthalmol 1999; 43 Suppl 1:S136-41.
88. Ingram V. Alzheimer's Disease. American Scientists 2003; 91(4):312-21.
89. Macphee GJA, Stewart DA. Parkinson's disease. Reviews in Clinical Gerontology 2001; 11(1):33-49.
90. Okano H, Sawamoto K. Neural stem cells: involvement in adult neurogenesis and CNS repair. Philos Trans R Soc Lond B Biol Sci 2008; 363(1500):2111-22.
91. Blurton-Jones M, Kitazawa M, Martinez-Coria H, Castello NA, Müller FJ, Loring JF et al. Neural stem cells improve cognition via BDNF in a transgenic model of Alzheimer disease. Proc Natl Acad Sci USA 2009; 106(32):13594-9, DOI 10.1073/pnas.0901402106.
92. Zhang Q, Wu HH, Wang Y, Gu GJ, Zhang W, Xia R. Neural stem cell transplantation decreases neuroinflammation in a transgenic mouse model of Alzheimer's disease. J Neurochem 2015; [Epub ahead of print], DOI 10.1111/jnc.13413.
93. Ager RR, Davis JL, Agazaryan A, Benavente F, Poon WW, LaFerla FM, Blurton-Jones M. Human neural stem cells improve cognition and promote synaptic growth in two complementary transgenic models of Alzheimer's disease and neuronal loss. Hippocampus 2015; 25(7):813-26, DOI 10.1002/hipo.22405.
94. Park HJ, Lee PH, Bang OY, Lee G, Ahn YH. Mesenchymal stem cells therapy exerts neuroprotection in a progressive animal model of Parkinson's disease. J Neurochem 2008; 107(1):141-51, DOI 10.1111/j.1471-4159.2008.05589.x.
95. Grealish S, Diguet E, Kirkeby A, Mattsson B, Heuer A, Bramoulle Y et al. Human ESC-derived dopamine neurons show similar preclinical efficacy and potency to fetal neurons when grafted in a rat model of Parkinson's disease. Cell Stem Cell 2014; 15(5):653-65, DOI 10.1016/j.stem.2014.09.017.
96. Wernig M, Zhao JP, Pruszak J, Hedlund E, Fu D, Soldner F et al. Neurons derived from reprogrammed fibroblasts functionally integrate into the fetal brain and improve symptoms of rats with Parkinson's disease. Proc Natl Acad Sci USA 2008; 105(15):5856-61, DOI 10.1073/pnas.0801677105.
97. Bai L, Lennon DP, Caplan AI, DeChant A, Hecker J, Kranso J et al. Hepatocyte growth factor mediates mesenchymal stem cell–induced recovery in multiple sclerosis models. Nat Neurosci 2012; 15(6):862-70, DOI 10.1038/nn.3109.
98. Burt RK, Loh Y, Cohen B, Stefoski D, Balabanov R, Katsamakis G et al. Autologous non-myeloablative haemopoietic stem cell transplantation in relapsing-remitting multiple sclerosis: a phase I/II study. Lancet Neurol 2009; 8(3):244-53, DOI 10.1016/S1474-4422(09)70017-1.

99. Burt RK, Balabanov R, Han X, Sharrack B, Morgan A, Quigley K et al. Association of nonmyeloablative hematopoietic stem cell transplantation with neurological disability in patients with relapsing-remitting multiple sclerosis. JAMA 2015; 313(3):275-84, DOI 10.1001/jama.2014.17986.
100. Connick P, Kolappan M, Crawley C, Webber DJ, Patani R, Michell AW et al. Autologous mesenchymal stem cells for the treatment of secondary progressive multiple sclerosis: an open-label phase 2a proof-of-concept study. Lancet Neurol 2012; 11(2):150-6, DOI 10.1016/S1474-4422(11)70305-2.
101. Cabanes C, Bonilla S, Tabares L, Martínez S. Neuroprotective effect of adult hematopoietic stem cells in a mouse model of motoneuron degeneration. Neurobiol Dis 2007; 26(2):408-18.
102. Vercelli A, Mereuta OM, Garbossa D, Muraca G, Mareschi K, Rustichelli D et al. Human mesenchymal stem cell transplantation extends survival, improves motor performance and decreases neuroinflammation in mouse model of amyotrophic lateral sclerosis. Neurobiol Dis 2008; 31(3):395-405, DOI 10.1016/j.nbd.2008.05.016.
103. Mazzini L, Mareschi K, Ferrero I, Miglioretti M, Stecco A, Servo S et al. Mesenchymal stromal cell transplantation in amyotrophic lateral sclerosis: a long-term safety study. Cytotherapy 2012; 14(1):56-60, DOI 10.3109/14653249.2011.613929.
104. Mazzini L, Gelati M, Profico DC, Sgaravizzi G, Projetti Pensi M, Muzi G et al. Human neural stem cell transplantation in ALS: initial results from a phase I trial. J Transl Med 2015; 13:17, DOI 10.1186/s12967-014-0371-2.
105. Alonso L, Fuchs E. Stem cells of the skin epithelium. Proc Natl Acad Sci USA 2003; 100 Suppl 1:11830-5.
106. Blanpain C, Fuchs E. Epidermal stem cells of the skin. Annu Rev Cell Dev Biol 2006; 22:339-73.
107. Pikuła M, Trzonkowski P. Biologia komórek macierzystych naskórka oraz ich znaczenie w medycynie. Postepy Hig Med Dosw 2009; 63:449-456 Polish [Biology of epidermal stem cells: Impact on medicine].
108. Barthel R, Aberdam D. Epidermal stem cells. J Eur Acad Dermatol Venereol 2005; 19(4):405-13.
109. Pikuła M, Imko-Walczuk B, Nowacka-Pikuła D, Okuniewska A, Langa P, Jaśkiewicz J, Trzonkowski P. Możliwości hodowli keratynocytów oraz komórek macierzystych naskórka i ich zastosowania w leczeniu trudno gojących się ran. Przegl Dermatol 2012; 99:222–229 Polish [The culture of keratinocytes and epidermal stem cells and their possible application in the treatment of chronic wounds].
110. Liu L, Yu Y, Hou Y, Chai J, Duan H, Chu W et al. Human umbilical cord mesenchymal stem cells transplantation promotes cutaneous wound healing of severe burned rats. PLoS One 2014; 9(2):e88348, DOI 10.1371/journal.pone.0088348.
111. Mirzaei H, Sahebkar A, Avan A, Jaafari MR, Salehi R, Salehi H et al. Application of mesenchymal stem cells in melanoma: a potential therapeutic strategy for delivery of targeted agents. Curr Med Chem 2015; [Epub ahead of print], DOI 10.2174/0929867323666151217122033.
112. Fukuoka H, Suga H. Hair Regeneration Treatment Using Adipose-Derived Stem Cell Conditioned Medium: Follow-up With Trichograms. Eplasty 2015; 15:e10.
113. Ibrahim ZA, Eltatawy RA, Ghaly NR, Abd El-Naby NM, Abou El Fetouh HM, Abd Elateef AE et al. Autologus bone marrow stem cells in atrophic acne scars: A pilot study. J Dermatolog Treat 2015; 26(3):260-5, DOI 10.3109/09546634.2014.946379.
114. Shabbir A, Cox A, Rodriguez-Menocal L, Salgado M, Van Badiavas E. Mesenchymal stem cell exosomes induce proliferation and migration of normal and chronic wound fibroblasts, and enhance angiogenesis in vitro. Stem Cells Dev 2015; 24(14):1635-47, DOI 10.1089/scd.2014.0316.
115. Falanga V, Iwamoto S, Chartier M, Yufit T, Butmarc J, Kouttab N et al. Autologous bone marrow-derived cultured mesenchymal stem cells delivered in a fibrin spray accelerate healing in murine and human cutaneous wounds. Tissue Eng 2007; 13(6):1299-312.
116. Yoshikawa T, Mitsuno H, Nonaka I, Sen Y, Kawanishi K, Inada Y et al. Wound therapy by marrow mesenchymal cell transplantation. Plast Reconstr Surg 2008; 121(3):860-77, DOI 10.1097/01.prs.0000299922.96006.24.
117. Caplice NM, Gersh BJ. Stem cells to repair the heart: a clinical perspective. Circ Res 2003; 10;92(1):6-8.
118. Fujita Y, Inokuma D, Abe R, Sasaki M, Nakamura H, Shimizu T, Shimizu H. Conversion from human haematopoietic stem cells to keratinocytes requires keratinocyte secretory factors. Clin Exp Dermatol 2012; 37(6):658-64, DOI 10.1111/j.1365-2230.2011.04312.x.
119. Roger VL, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, Brown TM et al; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics - 2011 update: a report from the American Heart Association. Circulation 2011; 123(4):e18-e209, DOI 10.1161/CIR.0b013e3182009701.
120. Walsh RA. Molecular and cellular biology of the normal, hypertrophied, and failing heart. w: O'Rouke RA, ed. The Heart, Arteries and Veins. 10th ed. New York: McGraw-Hill 2001; 115–118.
121. Jugdutt BI. Ventricular remodeling after infarction and the extracellular collagen matrix: when is enough enough? Circulation 2003; 108(11):1395-403.
122. Weber KT, Anversa P, Armstrong PW, Brilla CG, Burnett JC Jr, Cruickshank JM et al. Remodeling and reparation of the cardiovascular system. J Am Coll Cardiol 1992; 20(1):3-16.
123. Nag AC. Study of non-muscle cells of the adult mammalian heart: a fine structural analysis and distribution. Cytobios 1980; 28(109):41-61.
124. Rosenstrauch D, Poglajen G, Zidar N, Gregoric ID. Stem cell therapy for ischemic heart failure. Tex Heart Inst J 2005; 32(3):339-47.
125. Pfeffer MA, Braunwald E. Ventricular remodeling after myocardial infarction. Experimental observations and clinical implications. Circulation 1990; 81(4):1161-72.
126. Garry DJ, Martin CM. Cardiac regeneration: self-service at the pump. Circ Res 2004; 95(9):852-4.
127. Marchetti S, Gimond C, Iljin K, Bourcier C, Alitalo K, Pouysségur J, Pagès G. Endothelial cells genetically selected from differentiating mouse embryonic stem cells incorporate at sites of neovascularization in vivo. J Cell Sci 2002; 115(Pt 10):2075-85.
128. Vittet D, Prandini MH, Berthier R, Schweitzer A, Martin-Sisteron H, Uzan G, Dejana E. Embryonic stem cells differentiate in vitro to endothelial cells through successive maturation steps. Blood 1996; 1;88(9):3424-31.
129. Kehat I, Kenyagin-Karsenti D, Snir M, Segev H, Amit M, Gepstein A et al. Human embryonic stem cells can differentiate into myocytes with structural and functional properties of cardiomyocytes. J Clin Invest 2001; 108(3):407-14.
130. Menasché P, Hagège AA, Scorsin M, Pouzet B, Desnos M, Duboc D et al. Myoblast transplantation for heart failure. Lancet 2001; 357(9252):279-80.
131. Menasché P. Skeletal myoblasts for cardiac repair: Act II? J Am Coll Cardiol 2008; 52(23):1881-3, DOI 10.1016/j.jacc.2008.07.066.
132. Leobon B, Garcin I, Menasche P, Vilquin JT, Audinat E, Charpak S. Myoblasts transplanted into rat infarcted myocardium are functionally isolated from their host. Proc Natl Acad Sci USA 2003; 100(13):7808-11.
133. Orlic D, Kajstura J, Chimenti S, Limana F, Jakoniuk I, Quaini F et al. Mobilized bone marrow cells repair the infarcted heart, improving function and survival. Proc Natl Acad Sci USA 2001; 98(18):10344-9.
134. Perin EC, Dohmann HF, Borojevic R, Silva SA, Sousa AL, Mesquita CT et al. Transendocardial, autologous bone marrow cell transplantation for severe, chronic ischemic heart failure. Circulation 2003; 13;107(18):2294-302.
135. Chen SL, Fang WW, Ye F, Liu YH, Qian J, Shan SJ et al. Effect on left ventricular function of intracoronary transplantation of autologous bone marrow mesenchymal stem cell in patients with acute myocardial infarction. Am J Cardiol 2004; 94(1):92-5.
136. Beltrami AP, Barlucchi L, Torella D, Baker M, Limana F, Chimenti S et al. Adult cardiac stem cells are multipotent and support myocardial regeneration. Cell 2003; 114(6):763-76.
137. Messina E, De Angelis L, Frati G, Morrone S, Chimenti S, Fiordaliso F et al. Isolation and expansion of adult cardiac stem cells from human and murine heart. Circ Res 2004; 95(9):911-21.
138. Bolli R, Chugh AR, D'Amario D, Loughran JH, Stoddard MF, Ikram S et al. Cardiac stem cells in patients with ischaemic cardiomyopathy (SCIPIO): initial results of a randomised phase 1 trial. Lancet 2011; 378(9806):1847-57, DOI 10.1016/S0140-6736(11)61590-0.

prof. Agnieszka Pedrycz, M.D., Ph.D.
Institute of Histology and Embryology Medical Department of the University of Rzeszów
ul. Radziwiłłowska 11 20-080, Lublin
e-mail: apw4@wp.pl