ADIPOSE-DERIVED STEM CELLS – ORIGIN, TISSUE AND CELLULAR SPECIFICITY, AND APPLICATION IN REGENERATIVE MEDICINE

KOMÓRKI MACIERZYSTE POCHODZENIA TŁUSZCZOWEGO – POCHODZENIE, CHARAKTERYSTYKA ORAZ ZASTOSOWANIA W MEDYCYNIE REGENERACYJNEJ

Zuzanna DORNA[1], Michał JAWORSKI[1], Rafał SIBIAK[2,3], Maurycy JANKOWSKI[4], Katarzyna STEFAŃSKA[2], Grzegorz WĄSIATYCZ[5], Wojciech PIEŃKOWSKI[6], Marlena DUDEK-MAKUCH[7], Dominik LANGER[8], Renata DAWID-PAĆ[9], Marta CYKOWIAK[10], Magdalena KOWALÓWKA[11], Bartosz KEMPISTY[2,4,5]

[1]Student's Scientific Society, Poznań University of Medical Sciences, Poznań
[2]Department of Histology and Embryology, Poznań University of Medical Sciences, Poznań
[3]Department of Reproduction, Chair of Obstetrics, Gynecology, and Gynecologic Oncology, Poznań University of Medical Sciences, Poznań
[4]Department of Anatomy, Poznań University of Medical Sciences
[5]Department of Veterinary Surgery, Nicolaus Copernicus University, Toruń
[6]Division of Perinatology and Women's Diseases, Poznań University of Medical Sciences, Poznań
[7]Department of Pharmacognosy, Poznań University of Medical Sciences
[8]Department of Pharmaceutical Genetics and Microbiology, Poznań University of Medical Sciences, Poznań
[9]Department of Natural Raw Materials in Medicine and Cosmetology, Poznań University of Medical Sciences, Poznań
[10]Department of Pharmaceutical Biochemistry, Poznań University of Medical Sciences, Poznań
[11]Department of Bromatology, Poznań University of Medical Sciences, Poznań

Summary: The application of stem cells in medicine is still a relatively new topic associated with scientists' great interest. It is a source of hope for the patients suffering from various medical conditions, which are resistant to widely used healing paths. In recent years, the attention was drawn to multipotent adipose-derived stem cells (ADSCs). They are distinguished by their proliferative and secretive abilities, as well as accessibility. In addition, they are characterised by relative ease of harvesting and culture. Their unique qualities make them seem like a great opportunity in the field of regenerative medicine, which is a dynamically developing field associated with many types of research. ADSCs have the potential to be used in the treatment of chronic, non-healing wounds, as well as in diseases such as diabetes mellitus. Their use is also taken under consideration in treatment bone and cartilage defects, as well as in aesthetic medicine, including hair regeneration therapy on patients afflicted by alopecia in androgenetic alopecia or female pattern hair loss. Due to their regenerative properties, they are also perceived as a promising possibility in treatment of neurodegenerative diseases. The knowledge acquired during such research might be a base of the creation of novel alternative therapies in many other fields of medicine.

Keywords: Adipose-derived stem cells, ADSCs, stem cells, adipose tissue, regenerative medicine, tissue engineering

Streszczenie: Wykorzystanie komórek macierzystych w medycynie jest wciąż stosunkowo nowym zagadnieniem, które wzbudza duże zainteresowanie naukowców. Jest także źródłem nadziei dla chorych cierpiących na różne dolegliwości, którzy nie reagują na standardowe metody leczenia. W ostatnich latach, zwrócono uwagę na multipotencjalne komórki macierzyste pochodzące z tkanki tłuszczowej (ADSCs). Wyróżniają się one swoimi szczególnymi właściwościami proliferacyjnymi i sekrecyjnymi, a także szeroką dostępnością. Co więcej, łatwo je pozyskać oraz hodować in vitro. Wyżej wymienione cechy sprawiają, że wydają się one wyjątkową okazją na poczynienie postępów w dziedzinie medycyny regeneracyjnej, która jest obiektem wielu badań i dynamicznie się rozwija. ADSCs mogą potencjalnie zostać wykorzystane w leczeniu przewlekłych, niegojących się ran w chorobach takich jak cukrzyca. Rozważa się także nad ich użytecznością w regeneracji uszkodzeń tkanki kostnej oraz chrzęstnej. Mogą być także zastosowane w medycynie estetycznej w terapiach zapobiegających utracie włosów w łysieniu androgenowym, a także łysieniu typu kobiecego. Ze względu na swoje cechy, komórki te bierze się pod uwagę także jako obiecującą możliwość w leczeniu szeregu chorób neurodegeneracyjnych. Uzyskana z tych doniesień wiedza, może być podstawą do tworzenia różnych, nowoczesnych, alternatywnych metod leczenia, także w wielu innych dziedzinach medycyny.

Słowa kluczowe: inżynieria tkankowa, komórki macierzyste tkanki tłuszczowej, medycyna regeneracyjna, tkanka tłuszczowa

INTRODUCTION

Adipose tissue, a type of loose connective tissue, partakes in energy storage and protects the body against mechanical trauma. It is also a significant endocrine organ that secretes many hormones, e.g. leptin, adiponectin, resistin, or estradiol [4]. It consists of two cellular components: adipocytes and a stromal vascular fraction (SVF). In turn, SVF comprises various cells such as preadipocytes, endothelial cells, fibroblasts, mesenchymal stem cells (MSCs), vascular smooth muscle cells, lymphocytes, macrophages, and adipose-derived stem cells (ADSCs). The adipose tissue's specific cellular composition differs depending on the tissue's anatomical location or type. A higher amount of ADSCs can be obtained from subcutaneous than from visceral fat [7, 16]. ADSCs are considered a promising stem cell lineage because of ease of access to adipose tissue and the relatively low-invasive way of isolation. Fat can be easily harvested via liposuction in the form of lipoaspirate; less often, the surgical option can also be chosen. The most common subcutaneous adipose tissue source utilized in medical research and clinical therapies is the abdomen, thigh, and arm [34].

Adipose-derived stem cells have recently become an object of comprehensive, in-depth research due to their beneficial cellular and secretive properties combined with their ubiquitous availability and relatively simple mode of harvesting. They are a population of multipotent adult stem cells originating from mesenchymal stem cells, localized in the adipose tissue's stromal vascular fraction. Their exceptional proliferative capacity and ability to differentiate into cells of three developmental germ layers provide a number of opportunities to apply them in various treatment protocols. Moreover, ADSCs are characterized by a valuable secretome, combining many angiogenic and immunomodulating factors which might accelerate healing and regeneration [36, 17]. They are also considered the most accessible source of stem cells in the human body due to their emplacement in adipose tissue, making their collection a minimally invasive, relatively safe, and mostly painless procedure. Furthermore, they are capable of maintaining their phenotype in culture for an extended periods of time. The combination of all of the above features explains the discussion that unleashes around the subject of ADSCs and their potential application and beneficial impact in many areas of research [42].

THE ORIGIN OF ADIPOSE-DERIVED STEM CELLS

Stem cells are unspecialized human cells with self-renewal capacity and the ability to differentiate into multiple cell lineages [37]. Different groups of stem cells vary in potency, which defines the number of cell types they can differentiate into [30]. Totipotent cells derived from morula are of the greatest potency. They can create both embryonic and extra-embryonic structures that subsequently give rise to all three germ layers and the placental cells [6]. The inner cell mass (ICM), one of the components forming blastocyst that develops 4 days post-fertilization, is the source of pluripotent cells capable of differentiation into all human organism cells. They are known as human embryonic stem cells (hESCs), having the ability to form germ layers – cellular units built of multipotent progenitor cells. Each germ layer, endoderm, mesoderm, or ectoderm, is responsible for the creation of specified tissue later in the process of human development [5,30]. In turn, adult or somatic stem cells are located in every tissue of a mature organism. Their potency is limited, and the time necessary for the cell to proliferate is elongated. Multipotent stem cells partake in the process of healing, regeneration, and replacement of the adult cells [14]. Mesoderm, one of the three germ layers, is a source of mesenchymal stem cells, as well as hematopoietic stem cells (HSCs). MSCs located in the bone marrow stroma give rise to muscle, cartilage, bone, and adipose tissues [15]. MSCs also partake in angiogenesis, but cannot differentiate into HSCs [22]. MSCs give rise to adipose-derived stem cells (ADSCs), the population of stem cells located in the adipose tissue [1].

ADIPOSE-DERIVED STEM CELL CHARACTERISTICS

Among many types of adult stem cells, ADSCs are particularly valued not only for their common availability but also higher proliferation potential and ability to maintain their phenotype in culture for a longer period of time [42]. Another feature that speaks in their favor is the lack of ethical controversies, which surround embryonic stem cells application in clinical use. The International Federation for Adipose Therapeutics and Science (IFATS) and the International Society for Cellular Therapy (ISCT) set three criteria, which are essential to determine ADSC identity. The first necessary condition, which has to be demonstrated by the cell, is its ability to adhere to plastic. Secondly, they display the expression of mesenchymal phenotypic markers CD73, CD90, and CD105, while lacking the surface marker expression of CD11b, CD14, CD19, CD45, and HLA-DR. The last indicator is the cell's ability to differentiate into preadipocytes, osteoblasts, and chondrocytes [18]. Moreover, ADSCs are responsive to inducers of non-mesenchymal cell lineages differentiation, giving rise not only to cells of mesodermal derivation but also those of the other two germ layers [2]. They can differentiate toward subpopulations such as smooth and cardiac muscle cells, keratinocytes, hepatocytes, endothelial cells, neurons, beta islet cells, macrophages, or melanocytes [2, 8, 34].

ADSCs gained attention not only for their multipotency but also secretome, which is rich in cytokines, extracellular proteins, and RNAs. Paracrinally released factors beneficially contribute to surrounding tissues through their immunomodulating properties and stimulating effect on the process of angiogenesis.

All of these features combined imply that ADSCs could be a promising and easily accessible source of stem cells in further research and clinical trials. Furthermore, the profile of these cells could be useful in the development of regenerative medicine and should be a subject of precise study [12, 20].

APPLICATION OF ADSCs IN THE REGENERATIVE MEDICINE

Large full-thickness skin defects and non-healing wounds are still a challenge for modern medicine. They might be caused by a number of reasons: from trauma, burns, and congenital defects, to of tumour resection and chronic ischemia due to diabetes mellitus or immobilization. Initially, cultured epidermal autografts (CEA) were developed, but to no satisfying avail [21]. The addition of fibroblasts produced extracellular matrix (ECM) proteins such as collagen, fibronectin, or elastin was expected to improve the process of healing. However, CEA application is limited to nonextensive cases because of their tendency to contract, recurring wound opening, and fragility [27]. Klar et al. developed dermo-epidermal skin substitutes (DESS), which for now are believed to be the most promising prospect in regenerative medicine. They consist of both epidermal and dermal layers, which guarantees resemblance to natural skin structure and provides the best cosmetic effect among other skin grafts. It is even possible to add the patient's melanocytes to obtain suitable skin color and prevent them from the harmful influence of UV radiation. Other opportunities for people suffering from traumatic wounds are treatments based on ADSCs. ADSCs support tissue repair with their proliferating and immunomodulating abilities. They are also capable of secreting VEGF, fibroblast growth factors, and anti- or proinflammatory factors. Autologous fat grafts are created by processing lipoaspirates harvested via liposuction of subcutaneous adipose tissue. The treatment is applied to soft tissues in the form of an injection enriched by cultured ADSCs. This method is valued for being minimally invasive, low risk, and sufficiently positive outcome, but it is worth mentioning that it usually has to be performed several times to obtain the expected effect [21, 35]. Zhang et al. report on clinical trials on ADSCs-NCSS, new collagen sponge scaffolds combined with extracted ADSCs, repair potential of which in full-skin defects was tested on nude mice with satisfying heal rates compared to other methods of treatment used in this trial [41]. Furthermore, Qiu et al. presented their results on the utilization of exosomes derived from adipose-derived stem cells (ADSCs-Exos), a cell-free substance obtained from extracellular vesicles secreted by ADSCs [3]. The authors bring attention to the beneficial effects of the ADSCs-Exos on skin regeneration and acceleration of the process of vascularization, without any major side effects [3, 25].

The application of ADSCs is also a subject of study in hair regeneration therapy. Their secretive properties were taken under consideration in the treatment of hair loss in conditions such as androgenetic alopecia or female pattern hair loss. ADSCs excrete various cytokines that have the ability to stimulate the process of angiogenesis, increasing the blood supply of the hair follicle and inducing hair growth. Moreover, a lot of attention was drawn to the conditioned medium of ADSCs (ADSC-CM), which turned out to be capable of reducing oxidative stress, enhancing collagen synthesis, or suppressing cell apoptosis and inflammation [13]. ADSC-CM is a cell-free nourishing suspension, rich in ADSC-derived cytokines and growth factors. Basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), keratinocyte growth factor (KGF), and insulin-like growth factor I (IGF-I) modulate hair growth by promoting cell proliferation, angiogenesis, and fibroblast migration [9,38]. The results of research on ADSC-CM applications seem to be very promising. This therapeutic approach is considered relatively safe and inexpensive; however, the effects vary depending on the case and its severity. Alopecia affecting a significant part of the scalp, advanced age, or long history of the disease are the factors that may limit treatment efficacy due to fibrosis of hair follicles. It is worth noticing that the process of hair regrowth is time-consuming, so the outcome of the procedure is not immediate [13, 28].

Bone tissue engineering is another dynamically developing field of regenerative medicine. At present, for the patients suffering from trauma, bone structure defects, infections, and tumours, treatment options are limited to autologous and allogeneic bone grafts and artificial bone substitutes. Bone grafts are perceived as an effective method, but their utilization is associated with iatrogenic damage made to the donor's bone tissue [32]. The results of artificial bone substitutes' application show difficulties in stimulating osteoinduction, affecting the efficacy of this procedure. Conclusions made during ADSC investigation suggested that these stem cells might be a useful tool in the field of bone regenerative medicine. Research conducted on animal models seems to confirm those assumptions, indicating the impact of paracrine factor secretes such as VEGF in the process of bone remodeling [7, 19]. Probst et al., in their study, explored the potential of exploitation of cell-scaffold assemblies. There was evidence that the interaction between ADSCs and biomaterials resembling bone structure facilitated the formation of extracellular matrix and improved osteogenesis. The focus of the research were the maxillofacial bone defects, but the obtained outcomes could be transferred to clinical use in other bone disease or damage [33]. Chang et al. reported that ADSCs are also capable of modulating bone erosion and suppressing osteoclastogenesis. The results of their in vitro academic work show that ADSCs decrease the formation of osteoclasts in mice and humans. Furthermore, the acquired knowledge might also be a base for the creation of novel alternative healing paths in diseases such as rheumatoid arthritis and osteoarthritis [11].

Treatments based on ADSCs are also studied in the subject of cartilage tissue engineering in medical conditions such as cartilage lesions, which are hard to regenerate. The mechanism of the methods is analogical to those listed above and utilizes the unique abilities of ADSCs. The application of both scaffold-free and scaffold-based procedures is taken under consideration [24]. However, it is worth mentioning that sometimes in vivo trials of cartilage implantation of ADSCs derivation end unsuccessfully. This is due to the formation of ossification as a result of increased vascularisation. Xie et al. conducted research on thrombospondin-1 use in the inhibition of ossification to a satisfying outcome, improving the knowledge about cartilage defects treatment [39]. The utilization of ADSCs in the form of intra-articular injections consisting of adipose SVF and platelet-rich plasma is also discussed as a tool in reducing the ailments of patients suffering from medical conditions such as osteoarthritis or chondromalacia [31]. Numata et al. compared the effectiveness of local administration of ADSCs with intra-articular injections in a rabbit model, ruling greater efficiency of the first one of the listed [29].

Furthermore, Alzheimer's, Parkinson's, Huntington's disease, and amyotrophic lateral sclerosis (ALS) have been scientist's objects of interest for years. Although much research was conducted, no effective treatment that inhibits the progression of these diseases was discovered. Due to their regenerative properties, ADSCs are perceived as a chance for patients suffering from neurodegenerative disorders. Stem cells derived from the adipose tissue have the ability to be induced to differentiate into neuronal cells. Secretion of angiogenic factors, as well as stimulation of the immune system, might also mitigate symptoms and limit neuronal damage. Other mechanisms that were taken under consideration are the capacity to reduce gliosis, the process that occurs in some of the mentioned diseases, as well as the expression of neurotrophic factors [40]. Ma et al., in their study, created ADSCs-derived extracellular vesicles (ADSCs-derived EVs) containing molecules such as cytokines, growth factors, and miRNA, and applied them to mice with Alzheimer's disease. The research showed that nasally administrated ADSCs-derived EVs have the potential in the treatment by promoting neurogenesis and their neuroprotective properties by inhibiting the formation of amyloid plaques [26]. In the murine model, EVs have also prevented memory loss [23,26]. Chan et al. brought up progress in knowledge on use of ADSCs in less common diseases such as Huntington's or Parkinson's disease, as well as ALS. It is believed that neurotrophic factors produced by ADSCs such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), VEGF, and insulin-like growth factor (IGF-1) can alleviate disease symptoms. Additionally, ADSC-CM seems to be able to confer protection from 6-OHDA (6-hydroxydopamine), which directly damages neurons of substantia nigra in Parkinson's disease. In research on rats, it was proven that the application of ADSC-CM could reduce neurotoxicity and ROS influence caused by 6-OHDA. It was also reported that administration of ADSC could delay and alleviate symptoms in Huntington's disease through their secretive properties. All of the above reports are expected to be a chance for a method of alternative treatment for patients suffering from these medical conditions in the future. However, any such advancements will require further investigation [10].

CONCLUSIONS

ADSCs emerged as a promising tool in tissue engineering. While the available reports seem to be satisfactory, further in-depth research appears to be essential. Increasing the knowledge on ADSCs physiology and their potential applications seems to be crucial in elaborating novel forms of treatment in the field of regenerative medicine. Understanding these exceptional stem cells' functioning might give new opportunities to achieve satisfying effects in treatment of medical conditions which are still a challenge for the modern science.

REFERENCES

[1] Almalki SG, Agrawal DK. Key transcription factors in the differentiation of mesenchymal stem cells. *Differentiation.* 2016; **92**: 1-11.

[2] Argentati C, Morena F, Bazzucchi M, Armentano I, Emiliani C, Martino S. Adipose Stem Cell Translational Applications : From Bench-to-Bedside. *Int J Mol Sci.* 2018; **19**: 3475.

[3] Qiu H, Liu S, Wu K et al. Prospective application of exosomes derived from adipose-derived stem cells in skin wound healing : A review. *J Cosmet Dermatol.* 2020; **19**: 574-581.

[4] Frigolet ME, Gutierrez-Aguilar R. The colors of adipose tissue. *Gac Med Mex.* 2020; **156**: 142-149.

[5] Bacakova L, Zarubova J, Travnickova M et al. Stem cells: their source, potency and use in regenerative therapies with focus on adipose-derived stem cells – a review. *Biotechnol. Adv.* 2018; **36**: 1111-26.

[6] Baker CL, Pera MF. Capturing Totipotent Stem Cells. *Cell Stem Cell* 2018; **22**: 25-34.

[7] Barba M, Di Taranto G, Lattanzi W. Adipose-derived stem cell therapies for bone regeneration. *Expert Opin. Biol. Ther.* 2017; **17**: 677-89.

[8] Bellei B, Migliano E, Tedesco M, Caputo S, Picardo M. Maximizing non-enzymatic methods for harvesting adipose- derived stem from lipoaspirate : technical considerations and clinical implications for regenerative surgery. *Sci. Rep.* 2017; **7** : 10015.

[9] Cai Y, Li J, Jia C, He Y, Deng C. Therapeutic applications of adipose cell- free derivatives : a review. *Stem Cell Res Ther.* 2020; **11**: 312.

[10] Chan T, Chen JY, Ho L et al. Review ADSC Therapy in Neurodegenerative *Disorders. Cell Transplant.* 2014; **23**: 549-57.

[11] Chang Q. Adipose-derived mesenchymal stromal cells suppress osteoclastogenesis and bone erosion in collagen-induced arthritis. *Scand J Immunol.* 2020; **92**: e12877.

[12] Dubey NK, Mishra VK, Dubey R, Deng YH, Tsai FC, Deng WP. Revisiting the advances in isolation, characterization and secretome of adipose-derived stromal/stem cells. *Int. J. Mol. Sci.* 2018; **19**: 1-23.

[13] Fukuoka H, Narita K, Suga H. Hair Regeneration Therapy: Application of Adipose-Derived Stem Cells. *Curr. Stem Cell Res. Ther.* 2017; **12**: 531-4.

[14] Goodell MA, Nguyen H, Shroyer N. Somatic stem cell heterogeneity : diversity in the blood , skin and intestinal stem cell compartments. *Nat. Publ. Gr.* 2015; **16**: 299-309.

[15] Hall BK. Germ layers, the neural crest and emergent organization in development and evolution. *Genesis.* 2018; **56**: e23103.

[16] Han S, Sun HM, Hwang K, Kim S. Adipose-Derived Stromal Vascular Fraction Cells : Update on Clinical Utility and Efficacy. 2015; **25**: 145-52.

[17] Hong P, Yang H, Wu Y, Li K, Tang Z. The functions and clinical application potential of exosomes derived from adipose mesenchymal stem cells : a comprehensive review. *Stem Cell Res Ther.* 2019; **10**: 242.

[18] Id PP, Id FL, Siragusa G, Cifone MG, Cinque B, Giuliani M. Methods of Isolation , Characterization and Expansion of Human Adipose-Derived Stem Cells (ASCs): An Overview. *Int J Mol Sci.* 2018; **19**: 1897.

[19] Journal AI, Jin Q, Yuan K, Lin W, Niu C, Ma R. Comparative characterization of mesenchymal stem cells from human dental pulp and adipose tissue for bone regeneration potential. *Artif. Cells, Nanomedicine, Biotechnol.* 2019; **47**: 1577-84.

[20] Kapur SK, Katz AJ. AC. Review of the adipose derived stem cell secretome *Biochimie.* 2013; **95**: 2222-8.

[21] Klar AS, Zimoch J, Biedermann T. Skin Tissue Engineering: Application of Adipose-Derived Stem Cells. *Biomed Res. Int.* 2017; **2017**: 9747010.

[22] Lagarkova MA. Such Various Stem Cells. *Biochemistry (Mosc).* 2019; **84**: 187-9.

[23] Lee M, Ban J, Yang S, Im W, Kim M. The exosome of adipose-derived stem cells reduces β -amyloid pathology and apoptosis of neuronal cells derived from the transgenic mouse model of Alzheimer’s disease. *Brain Res.* 2018; **1691**: 87-93.

[24] Li X, Wang M, Jing X et al. Bone Marrow- and Adipose Tissue-Derived Mesenchymal Stem Cells: Characterization, Differentiation, and Applications in Cartilage Tissue Engineering. 2018; **28**: 285-310.

[25] Li X, Xie X, Lian W et al. Exosomes from adipose-derived stem cells overexpressing Nrf2 accelerate cutaneous wound healing by promoting vascularization in a diabetic foot ulcer rat model. *Exp. Mol. Med.* 2018; **50**: 1-14.

[26] Ma X, Huang M, Zheng M et al. ADSCs-derived extracellular vesicles alleviate neuronal damage , promote neurogenesis and rescue memory loss in mice with Alzheimer’s disease. *J Control Release.* 2020; **327**: 688-702.

[27] Mazini L, Rochette L, Admou B, Amal S, Malka G. Hopes and Limits of Adipose-Derived Stem Cells (ADSCs) and Mesenchymal Stem Cells (MSCs) in Wound Healing. I*nt J Mol Sci.* 2020; **21**: 1306.

[28] Narita K, Fukuoka H, Sekiyama T, Suga H, Harii K. Sequential Scalp Assessment in Hair Regeneration Therapy Using an Adipose-Derived Stem Cell-Conditioned Medium. *Dermatol. Surg.* 2020; **46**: 819-25.

[29] Numata H, Nakase J, Ph D et al. Effectiveness of Adhering Adipose-Derived Stem Cells to Defective Cartilage in Promoting Cartilage Regeneration in a Rabbit Model. *Arthroscopy.* 2019; **35**: 2619-2626.

[30] Ota KI. Fuel Cells: Past, Present and Future. *IEEJ Trans. Fundam. Mater.* 2008; **128**: 329-332.

[31] Pak J, Lee JH, Kartolo WA, Lee SH. Cartilage Regeneration in Human with Adipose Tissue-Derived Stem Cells : Current Status in Clinical Implications. *Biomed Res Int.* 2016; **2016**: 4702674.

[32] Park S, Heo H, Lee K, Kim H, Pyo S. Improved Bone Regeneration With Multiporous PLGA Scaffold and BMP-2-Transduced Human Adipose-Derived Stem Cells by Cell-Permeable Peptide. *Implant Dent.* 2017; **26**: 4-11.

[33] Probst FA, Fliefel R, Burian E et al. Bone regeneration of minipig mandibular defect by adipose derived mesenchymal stem cells seeded tri-calcium phosphate- poly(D , L-lactide-co-glycolide) scaffolds. *Sci Rep.* 2020; **10**: 2062.

[34] Si Z, Wang X, Sun C et al. Adipose-derived stem cells: Sources, potency, and implications for regenerative therapies. *Biomed. Pharmacother.* 2019; **114**: 108765.

[35] Smith OJ, Jell G, Mosahebi A. The use of fat grafting and platelet-rich plasma for wound healing : A review of the current evidence. *Int Wound J.* 2019; **16**: 275-285.

[36] Smith RJP, Reid AJ. The potential of adipose-derived stem cell subpopulations in regenerative medicine. *Regen. Med.* 2018; **13**: 357-60.

[37] Wang X. Stem cells in tissues, organoids, and cancers. *Cell. Mol. Life Sci.* 2019; **76**: 4043-70.
[38] Xiao S, Deng Y, Mo X, Liu Z, Wang D, Deng C. Promotion of Hair Growth by Conditioned Medium from Extracellular Matrix/Stromal Vascular Fraction Gel in C57BL/6 Mice. *Stem Cells Int.* 2020; **2020**: 9054514.
[39] Xie A, Xue J, Shen G, Nie L. Thrombospondin-1 inhibits ossification of tissue engineered cartilage constructed by ADSCs. *Am J Transl Res.* 2017; **9**: 3487-3498.
[40] Yeh D, Chan T, Harn H et al. Adipose tissue-derived stem cells in neural regenerative medicine. *Cell Transplant.* 2015; **24**: 487-92.
[41] Zhang A, Jiang TAO, Li Q, Jin P, Tan Q. Experimental research on ADSCs-NCSS in wound repair. *Exp Ther Med.* 2018; **16**: 4429-4436.
[42] Zhang J, Liu Y, Chen Y et al. Adipose-Derived Stem Cells: Current Applications and Future Directions in the Regeneration of Multiple Tissues. *Stem Cells Int.* 2020; **2020**: 8810813.

Editor − Maciej Zabel

Received: 17.03.2021
Accepted: 02.04.2021
Bartosz Kempisty Ph.D.
Department of Histology and Embryology, Department of Anatomy
Poznań University of Medical Sciences
6 Święcickiego St., 60-781 Poznań, Poland
tel./fax: +48 61 8546567 / +48 61 8546568
e-mail: bkempisty@ump.edu.pl