Novel trends in application of stem cells in skin wound healing

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Abstract

The latest findings indicate the huge therapeutic potential of stem cells in regenerative medicine, including the healing of chronic wounds. Main stem cell types involved in wound healing process are: epidermal and dermal stem cells, mesenchymal stem cells (MSCs), endothelial progenitor cells (EPCs) and hematopoietic stem cells (HSCs).

In the therapy of chronic wounds, they can be administrated either topically or using different matrix like hydrogels, scaffolds, dermal substitutes and extracellular matrix (ECM) derivatives. Stem cells are proven to positively influence wound healing by different direct and indirect mechanisms including residing cells stimulation, biomolecules release, inflammation control and ECM remodelling. MSCs are especially worth mentioning as they can be easily derived from bone-marrow or adipose tissue.

Apart from traditional approach of administering living stem cells to wounds, new trends have emerged in recent years. Good healing results are obtained using stem cell secretome alone, for example exosomes or conditioned media. There are also attempts to improve healing potential of stem cells by their co-culture with other cell types as well as by their genetic modifications or pretreatment using different chemicals or cell media. Moreover, stem cells have been tested for novel therapeutic purposes like for example acute burns and have been used in experiments on large animal models including pigs and sheep.

In this review we discuss the role of stem cells in skin wound healing acceleration. In addition, we analyse possible new strategies of stem cells application in treatment of chronic wounds.

Key words: stem cells, wound, healing, mesenchymal

1. Introduction

A chronic wound is a loss of skin or other tissues that do not heal during the time normally needed to heal others wounds. Treatment of these wounds can be long-lasting, requires specific medical skills and constitute a great challenge for contemporary medicine. The problem affects an estimated twenty million people around the world. This number may significantly increase due to ageing population and escalating incidence of civilization diseases such as obesity and diabetes (Bumpus and Maier, 2013). Globally, by 2020 the wound care market is projected to surpass 22 billion USD per year (Tricco et al., 2015). Impaired wound healing increases the number of operative procedures, lengthens hospital stays and worsens a patient's susceptibility to infection (Butler et al., 2010). Thus, many scientists focus on determining different factors affecting the process of wound healing, among others those related to the use of certain drugs, improper diet and exposure to environmental pollution. It is also possible to identify specific diseases that increase the risk of developing non-healing ulcers and to determine the effect of hypoxia on the healing process (Burns et al., 2003).

The methods that are currently used in the treatment of chronic wounds are multifactorial and include several steps. First and foremost, direct causes are sought that have made the treatment process difficult and attempts are being made to eliminate them. If, despite this, healing is still very slow or does not progress, the specific methods are used to support the process. However, traditional wound care procedures using debridement, infection control and typical dressings have limited efficacy, especially for treatment of chronic wounds, which is still a challenging task for healthcare experts.

The development of biomedical engineering has increased the interest in working out new therapeutic approaches for wounds difficult to heal. These include for example gene therapy, cell therapy, biological dressings, growth factors delivery and engineered skin equivalents. Among these new treatment modalities, stem cell-based therapies have gained interest as a part of regenerative medicine.

Currently, a rising number of stem cell therapies has been tested in clinical and preclinical trials in the context of their impact on wound healing (Leavitt et al., 2016; Tsai et al., 2018). The use of stem cells in the treatment of chronic wounds is a novel approach that uses processes that naturally occur in wound healing such as the action of growth factors, stimulation of immune processes and regulation of the inflammatory process, as well as improving the blood supply to developing tissue, which speeds up epidermis growth (Kolle et al., 2013).

The aim of this review is to summarize mechanisms by which different stem cells influence wound healing process and to describe latest strategies used to improve their therapeutic potential in the context of non-healing wounds. Moreover, we will mention some clinical trials and experiments on animal models, that support the use of stem cells, especially mesenchymal stem cells (MSCs), in chronic wound treatment. Finally, we will discuss limits and benefits of stem cell therapy in comparison to traditional ones.

2. Adult stem cells related to wound healing process

Stem cells, due to their properties - differentiation into other cell types and the potential for unlimited proliferation - are one of the most popular issues of contemporary medicine and biological sciences. According to their ability to differentiate, they can be divided into toti-, pluri-, multi- and unipotent, while according to their source - into embryonic (isolated from the blastocyst), adult (isolated from the mature organism, also known as somatic stem cells) and obtained from the umbilical cord or placenta. Specific type of stem cells are induced pluripotent stem cells (iPSCs), which are generated directly from adult cells by introduction of several genes encoding transcription factors (Behr et al., 2010).

In the case of injury or minor burn, stem cells take their action and take part, along with the surrounding extracellular matrix (ECM) and growth factors, in regenerative processes. Apart from epidermal and dermal stem cells (found in the skin), MSCs as well as endothelial progenitor cells (EPCs) and hematopoietic stem cells (HSCs) deserve special attention, as they (directly or indirectly) affect wound healing process and can be potentially used for cell therapy. These three cell types are components of stromal vascular fraction (SVF) - the aqueous fraction derived from enzymatic digestion of lipoaspirate, which itself has been also used for regenerative wound therapy (Bora and Majumdar, 2017; Cervelli et al., 2011).

Main sources of stem cell populations involved in wound healing process are presented in Fig.1, whereas most important functions of stem cells, which positively influence this process are summarized in Fig.2.

2.1. Epidermal and dermal stem cells

Most of skin epidermal stem cells reside within hair follicle bulge, so superficial injuries heal rapidly, without leaving a scar. In this case, stem cell-derived daughter skin cells exit hair follicle and migrate to the basal layer and sebaceous gland of the epidermis. In deeper injuries the scar is formed, whereas epidermal appendages are not regenerated (Ito et al., 2005; Li et al., 2017; Taylor et al., 2000; Zhang and Fu, 2008). Hair follicle stem cells (HFSCs) and interfollicular stem cells (two types of epidermal stem cells) are main sources of new keratinocytes essential to reepithelialise the wound. Among them, only interfollicular stem cells reside in the basal layer of the interfollicular epidermis (Liang and Bickenbach, 2002; Zare et al., 2015). Dermal stem cells were characterized relatively late (in the beginning of XXI century). We can distinguish three main subtypes of these cells: neural crest stem cells, mesenchymal stem cell-like dermal stem cells and dermal hematopoietic cells. It is proven, that they show high plasticity an some immunosuppressive properties (Chen et al., 2015).

2.2.Mesenchymal stem cells (MSCs)

The term MSCs refers to multipotent progenitor cells capable of differentiating at least towards the osteoblastic, chondrocytic and adipocytic lineages under *in vitro* standard differentiation conditions. To be classified as MSCs, they must also express CD73, CD90 and CD105 markers, while not expressing CD14, D19, CD34, CD45, CD11b, CD79a and HLA-DR molecules (Dominici et al., 2006). These cells are similar to fibroblasts (Bae et al., 2009) and can be obtained from foetal tissues (umbilical cord, umbilical cord blood and placenta) and from a number of locations in the adult body, the most important of which are bone marrow and adipose tissue.

Bone marrow is a source of so called bone-marrow derived MSCs (BM-MSCs), whereas MSCs of adipose origin are known as adipose derived stem cells (ADSCs) (Aydemir et al., 2016; Leavitt et al., 2016). ADSCs are relatively easy to obtain in comparison to BM-MSCs due to minimization of patient discomfort and elimination of time consuming expansion steps in vitro - MSCs comprise barely 0,01% to 0,001% of all mononuclear cells in bone marrow (Li et al., 2016; Schneider et al., 2018). It was shown, that both ADSCs and BM-MSCs have identical transcriptomes that express genes specific for stem cells, e.g. Oct4, Sox2 and Rex1 (Izadpanah et al., 2006).

During wound healing, MSCs take part in all stages of this process and were proven to persist at the wound site even after the completion of healing (Pratheesh et al., 2017). They coordinate the inflammatory process, modulate fibrosis and reduce scarring, as they show strong immunomodulatory and immunoregulatory characteristics demonstrated by release of cytokines, chemokines and growth factors (Hu et al., 2014; Mester et al., 2017; Ren et al., 2008). It is reported, that human MSCs release over 30 biomolecules, that promote wound healing (Hwang et al., 2009). Thus, they not only coordinate inflammation, fibrosis and scarring, but also increase angiogenesis and granulation tissue formation (Maxson et al., 2012), show antimicrobial activity (Krasnodembskaya et al., 2010), neutralize reactive oxygen species (ROS) (Sato et al., 2007) and enhance dermal fibroblast function (Smith et al., 2010). Moreover, it was shown, that MSCs conditioned medium (via paracrine signalling) stimulates stem cells residing near the damaged tissue to repair the defect (Ho et al., 2018).

MSCs are used clinically both in the autologous system and as an allogenic transplant. This is possible due to the already mentioned immunomodulating properties of these cells, resulting in lack of immune system reaction to the transplantation of MSCs from a donor, as well as the lack of recognition (by allogeneic MSCs) of the recipient as a foreign organism.

Recently, more and more experiments have revealed detailed mechanisms of wound healing promotion by MSCs and their conditioned media. For example, it was shown *in vivo* and *in vitro*, that Ell3 (a transcription elongation factor) is one of the factors determining wound healing efficiency of ADSCs conditioned medium (Lee et al., 2017). SDF-1 produced by ADSCs is also very potent in wound healing acceleration, even in the case of healing impairments caused by glucocorticoids (Kato et al., 2017). On the other hand, keratinocyte migration and epithelial-mesenchymal transition (EMT)-like process taking place in these cells (crucial for re-epithelialization) were shown to be mediated by β_2-adrenergic receptor (β_2-AR), which is able to recognize soluble factors secreted by BM-MSCs (Huo et al., 2018). It was also shown on diabetic mice model, that BM-MSCs enhance wound healing among others by decreasing MMPs expression, resulting in improved collagen 1 content (Xu et al., 2017).

To conclude, wound repair promoting MSCs mechanisms of action are relatively well known. They are able to differentiate and transdifferentiate into tissue specific cells, to secrete a wide range of paracrine factors, to regulate immune response and local tissue microenvironment (Li and Fu, 2012).

2.3. Endothelial progenitor cells (EPCs)

Endothelial progenitor cells (EPCs) can be derived as a fraction of bone marrow mononuclear cells (BMMNCs) or peripheral blood mononuclear cells (PBMNCs). In the case of tissue injury they are recruited from bone marrow (circulate in the blood) and then, localize to sites of injury and distribute near endothelial cells thanks to the expression of endothelial and hematopoietic markers (Asahara et al., 1997; Lau et al., 2009). EPCs are known to be sensitive to hypoxia, as they respond to hypoxia-inducible factor 1 (HIF-1)-induced stromal cell-derived factor 1 (SDF-1) in conditions of oxygen deprivation (Ceradini et al., 2004). They also contribute to angiogenesis, which makes them a promising target for chronic wound treatment, especially those with ischemic pathologies, like for example diabetic ulcers (Capla et al., 2007; Grenier et al., 2007).

2.4. Hematopoietic stem cells (HSCs)

Hematopoietic stem cells (HSCs) constitute a relatively large fraction of BMMNCs (1%) (Li et al., 2016), but they can also be isolated from peripheral and umbilical cord blood. Potential of HSCs in skin regeneration results i.a. from their high plasticity (Kamolz et al., 2006) and participation in angiogenesis process (Sackstein, 2004). They also affect (positively) ECM during wound healing by secreting collagen and downregulating matrix metalloproteinases (MMPs) expression (Kanji et al., 2014). Moreover, they stimulate proliferation of keratinocytes and fibroblasts, which significantly accelerates wound closure (Kim et al., 2010). Differentiation of HSCs into macrophages is an important event during wound healing. It was shown, that this process is significantly impaired in diabetes, which is mediated by one of DNA methyltransferases (Yan et al., 2018).

3. Stem cells application in wound healing

In larger burns and chronic wounds, the number and function of stem cells may be impaired. For example, it was shown, that chronic wound environment inhibits ADSCs proliferation rate and changes expression of some genes crucial for wound healing in these cells (Koenen et al., 2015). Moreover, EPCs derived from diabetic patients (that often suffer from non-healing ulcers) demonstrated decreased adherence to human umbilical vein endothelial cells, impaired proliferation and less involvement in tubule formation in comparison to controls (Tepper et al., 2002). That is why a concept was created to support healing process by supplying missing stem cells to specific sites. In recent years, more and more studies have shown that stem cells (especially MSCs) can be useful for treating wounds that are difficult to heal. Different subtypes of MSCs are the subject of both *in vitro* and *in vivo* studies on this topic. There are also some clinical trials confirming the effectiveness of stem cell therapy in wound healing. Currently, most of them (both published and unpublished) focus on MSCs (~ 30%), EPCs (~ 25%) and BMMNCs (~ 20%). The most popular approach is the use of autologous stem cells (~ 90%) (Leavitt et al., 2016). MSCs used for experiments are mainly derived from bone marrow and adipose tissue (previously mentioned BM-MSCs and ADSCs), but beneficial effects on wound healing were also shown for example in case of umbilical cord blood and Wharton's Jelly derived MSCs (Jung et al., 2018; Pourfath et al., 2018).

The overview of some important animal model experiments and clinical trials using stem cells in the context of wound healing is presented in the Table 1.

3.1. Modes of stem cells delivery

One of the most important problems restricting the use of stem cell-based therapies is the mode of cell delivery to damaged tissues. The simplest techniques involve topical cell applications (for example as a spray), direct injections to the dermis or muscle as well as systemic delivery into circulation (Duscher et al., 2016). However, these methods have many limitations, for example difficulties in tissue targeting and high cell attrition rate (in the case of systemic delivery), low cell survival, additional tissue damages, lack of cell-ECM attachment and hostile wound environment (in the case of local administration). That is why bioscaffold-based stem cell delivery mode has recently gained much attention (Garg et al., 2014; Kean et al., 2013; Rustad et al., 2012), in which cells are transferred on a matrix (cellular or acellular) such as hydrogel, scaffold, dermal substitute or ECM derivative (Zare et al., 2015).

Polymer-based biomaterials are commonly used for stem cell delivery into the wound difficult to heal, as they show high biocompatibility, bioactivity and biodegradability (Kohane and Langer, 2008). They can be prepared using both natural polymers (e.g. collagen, fibrin, elastin, gelatin, silk, hyaluronic acid, chitosan) and synthetic ones (e.g. polyanhydrides, polyethylene glycol, poly(lactic-*co*-glycolic) acid). Some scaffolds (for example those with collagen) exhibit similar biological actions to cytokines regulating cell growth and immunity (Mashiko et al., 2018). Thermosensitive hydrogels are popular, as they effectively encapsulate the cells increasing the efficiency of their delivery to the wound (Kaisang et al., 2017; Lei et al., 2018). Some modifications of classical scaffolds are also made, which further promotes regenerative wound healing by improving biological activity of stem cells. Most often, these include the addition of fragments of natural proteins like laminin, fibrin, glycosaminoglycan and many others (Dash et al., 2018; Dawson et al., 2008; Ghasemi-Mobarakeh et al., 2015; Kohane and Langer, 2008). Moreover, addition of silver nanoparticles to the cellular dressing can be an interesting way to prevent bacterial colonization of wounds during healing process (Perez-Diaz et al., 2018).

Dermal substitutes (especially those derived from placental tissues) are also promising, as they include viable cells like fibroblasts, epithelial cells and MSCs, which actively produce tissue reparative paracrine factors. Among these substances there are not only growth factors, but also some anti-inflammatory and antimicrobial molecules, which accelerate the shift from the inflammatory to proliferative phase of wound healing (Bieback and Brinkmann, 2010; Maxson et al., 2012; Parolini et al., 2008). A completely different approach is represented by ECM derivative, so called acellular dermal matrix (ADM). It does not contain living cells, but preserves the ultrastructure and protein content characteristic for native ECM, which improves regenerative activity of stem cells, even those tested on diabetic wound mice model (Chu et al., 2018).

3.2. New therapeutic purposes of stem cells

Nowadays, stem cells are also tested for new therapeutic purposes, for example to treat corneal wounds and acute burns. ADSCs were administrated to mice in the form of eye drops, which resulted in earlier and better corneal repair (Zeppieri et al., 2017). In another study, two types of ADSCs (autologous and allogenic) were injected into burn full-thickness wounds created in male Wistar rats. It was shown, that only autologous cells enhanced wound healing, with injections 0,5 cm from the wound edge being more effective in comparison to injections in the wound centre (Chang et al., 2018).

3.3. Pretreatment and co-culture of stem cells

Various co-culture and preconditioning systems are being developed, which in some cases accelerates stem cell differentiation and their impact on wound healing process. One of the examples of this approach can be co-culturing ADSCs (on advanced collagen wound matrix) with primary keratinocytes and keratinocyte conditioned medium, which after fifteen days initiated ADSCs differentiation towards keratinocytes (Edwards et al., 2018). Furthermore, ADSCs preconditioned by endothelial cell medium showed increased angiogenic potential, both *in vivo* (on diabetic mice model) and *in vitro* as well as enhanced proliferation and endothelial differentiation (Fromer et al., 2018). Similarly, human ADSCs co-cultured with endothelial cells on collagen peptide bioscaffold accelerated wound closure on irradiated mice model (Mashiko et al., 2018). Unexpectedly, MSCs pretreated with S100A8/A9 (protein complex belonging to danger associated molecular patterns recognized by immune system) accelerated murine wound healing to the greater extent, than MSCs alone (Basu et al., 2018). Some other studies revealed, that treatment using MSCs combined with platelet rich plasma (PRP) – an increased concentration of platelets in small volume of plasma after centrifugation – increases wound healing rates by promoting re-epithelialization and regulating inflammatory processes (Mahmoudian-Sani et al., 2018; Roubelakis et al., 2014; Stessuk et al., 2016; Wang and Avila, 2007). Stem cells can be also pretreated by various chemicals like for example emu oil emulsified in egg lecithin and butylated hydroxytoluene. Such conditioning significantly increased the regenerative potential of ADSCs and even affected their cell cycle, which was proven by many different tests *in vitro* (Arezoumand et al., 2018). There were also attempts to activate stem cells with bioglass (type of silicate biomaterial) ionic products, which improved healing ability of urine-derived stem cells (USCs) by stimulation of paracrine effects between USCs and recipient cells as well as between fibroblasts and endothelial cells (Zhang et al., 2018b).

3.4. Genetic modifications of stem cells

There are also some studies, aim of which is to genetically modify stem cells in order to change their activity to solve a specific problem. For example, TGF-β_3 overexpressing BM-MSCs not only improved the course of wound healing process, but also reduced scar tissue formation, which may be useful in prevention of keloid formation (Li et al., 2018a). Another experiment held on murine epidermal stem cell culture revealed, that overexpression of Cd271 (p75 neurotrophin receptor) increased cell ability to differentiate, proliferate and migrate. The same study also proved, that Cd271 promotes burn wound healing on mice model (Zhang et al., 2018a). Human stem cells have also been subject to some genetic modifications. CA-Akt and v-myc expressing human ADSCs showed higher proliferation potential and higher vascular endothelial growth factor (VEGF) secretion level than control cells, which translated into acceleration of wound healing (Song et al., 2012). Other studies have demonstrated the possibility to maintain differentiation and proliferation potential of human MSCs isolated from placenta and bone marrow by overexpression of telomerase reverse transcriptase (TERT) genes (Abdallah et al., 2005; Zhang et al., 2006). Finally, genetic modifications of stem cells derived from patients with chronic wounds also seem very promising. For example, scientists from Austria and Italy successfully regenerated functional epidermis of 49-year-old woman suffering from junctional epidermolysis bullosa using her own epidermal stem cells modified with laminin subunit β3 (LAMB3) gene inserted by retroviral vector (Bauer et al., 2017).

3.5. Experiments on large animal models

Mouse or rat animal models are most commonly used to evaluate stem cells delivery effects on various aspects of wound healing. Nevertheless, some experiments on larger animals have been performed recently. It was shown, that Yorkshire pigs injected by ADSCs demonstrated improved healing parameters, which was proven by simple wound measurement as well as by using Real-Time PCR and Western Blotting for collagens, α-smooth muscle actin and CD31 expression assessment (James et al., 2018). Similar results were obtained on diabetic swine model using ADSCs alone, ADSCs differentiated into endothelial cells and various conditioned media (Irons et al., 2018). Moreover, it was shown on Bergamasca sheep model, that MSCs from peripheral blood improved wound healing in many aspects (macroscopic and biochemical), which was assessed 15 and 42 days after lesion creation (Martinello et al., 2018).

3.6. Stem cells secretome application for wound healing

Interestingly, the research group from Chile and Colombia showed on diabetic mice model, that better therapeutic effect (than with the MSCs themselves) is obtained with the use of their acellular derivative. It suggests, that the tissue repair must be initiated by some bioactive molecules present in stem cell conditioned medium (de Mayo et al., 2017). Thus, another interesting trend in modern regenerative medicine is to use stem cell secretome (such as conditioned media or purified exosomes) instead of cells themselves. This approach resolves some technical problems connected with living cells such as tumorigenicity, immune compatibility, infection transmission and complicated material storage. It was shown, that adipose tissue extracellular fraction (isolated from lipoaspirate) upregulated dermal and epidermal cell proliferation rate and enhanced migration of dermal fibroblasts (Bellei et al., 2018). What is more, MSCs-derived exosomes - extra-cellular nano-vesicles transferring active cargoes between the cells (Marote et al., 2016; Zhang and Grizzle, 2014) – are very promising as a novel therapy against delayed wound healing (Monsel et al., 2016; Pashoutan Sarvar et al., 2016; Sun et al., 2016). They can promote angiogenesis, cell migration, proliferation as well as re-epithelialization process by activating some signalling pathways (like STAT3, AKT, ERK and Wnt/β-catenin) resulting in growth factors expression upregulation (Goodarzi et al., 2018; Rani and Ritter, 2016). Furthermore, exosomes derived from iPSCs positively affected wound healing also on diabetic mice model – they accelerated wound closure and angiogenesis (*in vivo*) and increased migration and proliferation of fibroblasts isolated from these mice (Kobayashi et al., 2018). Similarly, ADSCs derived exosomes (particularly those from cells overexpressing Nrf-2 transcription factor) reduced the inflammation within the wound on diabetic mice model, which promoted the healing of diabetic foot ulcers. At the same time, they decreased glucose-induced senescence of EPCs (Li et al., 2018b).

4. Discussion

Human skin is the largest organ of the human body and its main function is to provide proper protection against external factors and the penetration of pathogens into the body. Its continuity is of the greatest importance and any damage may be a potential gateway to infection. Wounds created within the skin are the result of the impact of various damaging and irritating factors leading to disruption of the skin's continuity, while the process of their treatment is multistage and can be long-lasting. At each stage of wound healing, complications such as bacterial infection and hypertrophic scarring (keloid formation) may occur.

Wounds can be divided into acute and chronic depending on the duration and progress of the healing process.

In the case of acute wounds, it is assumed that the process of their healing passes through certain stages, so basically they can repair themselves in the specific period of time. Time necessary for first occurrence of features characteristic for the healing process should not take longer than 4 weeks - wounds that do not show healing after this time are likely not to heal for another 8 weeks (Cardinal et al., 2008). We can distinguish three stages of the normal healing process, which in some cases overlap in time: inflammation (with haemostasis at the beginning), proliferation and remodelling (Li et al., 2007). Wound closure occurs within about 2 weeks after the injury and depends on the depth of the wound. The most important cells involved in this process are myofibroblasts (arising from fibroblasts) which acquire the ability to contract, so it is possible to achieve a contraction of the wound (Demidova-Rice et al., 2012; Li et al., 2007).

Wounds in which proper healing is inhibited at one of its stages and do not show the characteristic features of its progression within 4 weeks after injury, are referred to as chronic wounds. Within these wounds, cells with altered phenotype can be noticed. In addition, not all of the wound areas are in the same stage of healing process. All these features make it difficult or impossible to properly heal the wound. There are several characteristics of cells present in the chronic wound. First of all, they show proliferative potential and morphological characteristics similar to senescent cells and express low levels of growth factors receptors, which is characteristic of hypoxic cells (Aydemir et al., 2016; Leavitt et al., 2016). At the same time, inflammatory mediators damage some growth factors and the ECM, whereas keratinocytes show poor migration capacity and produce fewer growth factors. An important characteristic is also the reduction in the production of laminin 332 (Demidova-Rice et al., 2012) as well as the decrease in fibroblasts mitogenic potential (Zare et al., 2015). These changes impair ECM deposition and the ability of fibroblasts to move and create granulation tissue.

Modern methods used in the treatment of chronic wounds include different types of dressings (gauze, occlusive, hydrogel etc.), application of growth factors, skin grafts and hyperbaric oxygen. Although they are well studied and easy to use, the have many disadvantages and limitations.

The simplest gauze dressings are not appropriate for use on exudate wounds, because they dry out and can cause further damage when replacing them. Similarly, occlusive dressings (which task is to maintain the inflammatory phase of the healing process by reducing the amount of oxygen and activating factors characteristic of cells in hypoxia) should only be used on wounds without exudate. Hydrocolloids should not be used on infected wounds, because they are impermeable to air, whereas hydrogel dressings maintain moisture and are easy to replace, but may cause excessive wound moistening. Alginates can be used to treat wounds with high exudate, however, they are not appropriate for dry wounds (Han and Ceilley, 2017; Wiegand et al., 2015).

Application of growth factors is quite promising, because it is clear, that in case of chronic wounds there are serious shortages of growth factors and cytokines, which may be one of the reasons for healing difficulties. Hence, attempts are made to supply these substances from the outside. The most well researched and approved for use by the Food and Drug Administration (FDA) in the USA is platelet-derived growth factor BB (PDGF-BB) mainly used in the treatment of neuropathic ulcers (Barrientos et al., 2014). However, the results of research conducted on this factor are not conclusive, because of its minor effects in pressure and venous ulcers. Research is also being carried out on other factors such as VEGF or TGF-β (which levels in chronic wounds are also reduced), but so far, effects of their use are not as positive as in case of PDGF-BB (Wu et al., 1999).

The most important advantage of skin grafts is the fact, that they contain biological element derived from human skin (taken from cadavers) or from the skin of animal in combination with the material serving as a scaffold for the cells. Cells used to create the transplant are usually human or animal fibroblasts and keratinocytes. Fibroblasts present in the transplant are the source of growth factors, cytokines and other substances that support wound healing. The disadvantage of this solution (when using animal cells) is a certain risk of rejection of the transplant as well as of the induction of allergic reaction. Moreover, these types of substitutes are very expensiv,e so they are used only in special cases (Kanji and Das, 2017).

Treatment with the hyperbaric oxygen is based on the administration of oxygen at a certain, usually high pressure, which is supposed to accelerate regeneration by proliferation of fibroblasts, to improve the immune system and to stimulate angiogenesis within the wound. Unfortunately, clinical trials in this field have also proved, that conducting this type of treatment causes many side effects such as myopia, oxygen poisoning as well as seizures and pneumothorax (Wu et al., 2010).

The use of stem cells in the treatment of chronic wounds has many advantages, which are absent in case of traditional approaches. Stem cell wound therapy is based primarily on their ability to produce substances, that promote regeneration processes such as cytokines and growth factors. Moreover, these cells support angiogenesis, have great proliferation ability and are well tolerated by the patient (in case of autologous therapy), because they come from his own body. Despite their origin from various tissues, they are able to transform into any other type of cells and to proliferate, accelerating the wound closure and additionally supporting the natural healing process. What is more, stem cells are relatively easy to use in therapy, because thanks to their good adherence to plastic materials, they can be administrated directly on the wound (as a covering material) or systemically through the blood (Yoshikawa et al., 2008). Stem cells also exhibit paracrine capacities and release many factors such as cytokines, chemokines and growth factors into the medium. When applied to the wound bed, they can stimulate local stem cells (present in the tissue adjacent to the wound) to proliferate and to initiate the healing process (Ho et al., 2018).

It is worth mentioning, that MSCs have some important advantages over other types of stem cells. They are multipotent, release a wide range of biologically active paracrine factors (which is well studied), have documented immunomodulatory properties and can be easily derived not only from bone marrow, but also from adipose tissue. That is why they constitute the main pool of stem cells used in the treatment of chronic wounds.

On the other hand, stem cell therapy for chronic wounds has some shortcomings and limitations. The potential risk of this therapy is the ability of stem cells to became malignant, which is especially true for the iPSCs. In MSCs (which are multipotent) this specific risk seems smaller. Another risk, as in any case of using biological material in therapy, is the probability of transmitting or causing specific diseases, for example opportunistic and disseminated infections. This mainly applies to the use of animal cells or allografts (Leavitt et al., 2016).

4.1.Conclusions

Chronic wounds still remain a great concern for many healthcare professionals, despite many current therapeutic options. Experiments on cell cultures, animal models and some clinical trials have proven, that adequately administered stem cells positively affect the biochemistry of healing process, which accelerates the overall time of wound closure. They not only differentiate and proliferate, but also can promote the cells *in vivo* for migration, immunomodulation and angiogenesis.

Especially MSCs and their secretions are promising therapeutics for use to accelerate wound healing, as they are easy to obtain and already well-studied. However, epidermal stem cells (including HFSCs), EPCs and HSCs also show some wound healing-promoting properties, for example influencing angiogenesis process, keratinocytes migration and ECM content.

Regenerative wound healing can be further enhanced by application of different stem cells modification and co-cultures, as well as by the use of appropriate scaffolds. More research is needed to find out (in detail) the mechanisms of action of stem cells in order to increase their therapeutic effectiveness and ensure the safety of their use in the treatment of patients.

Declaration of interest: none

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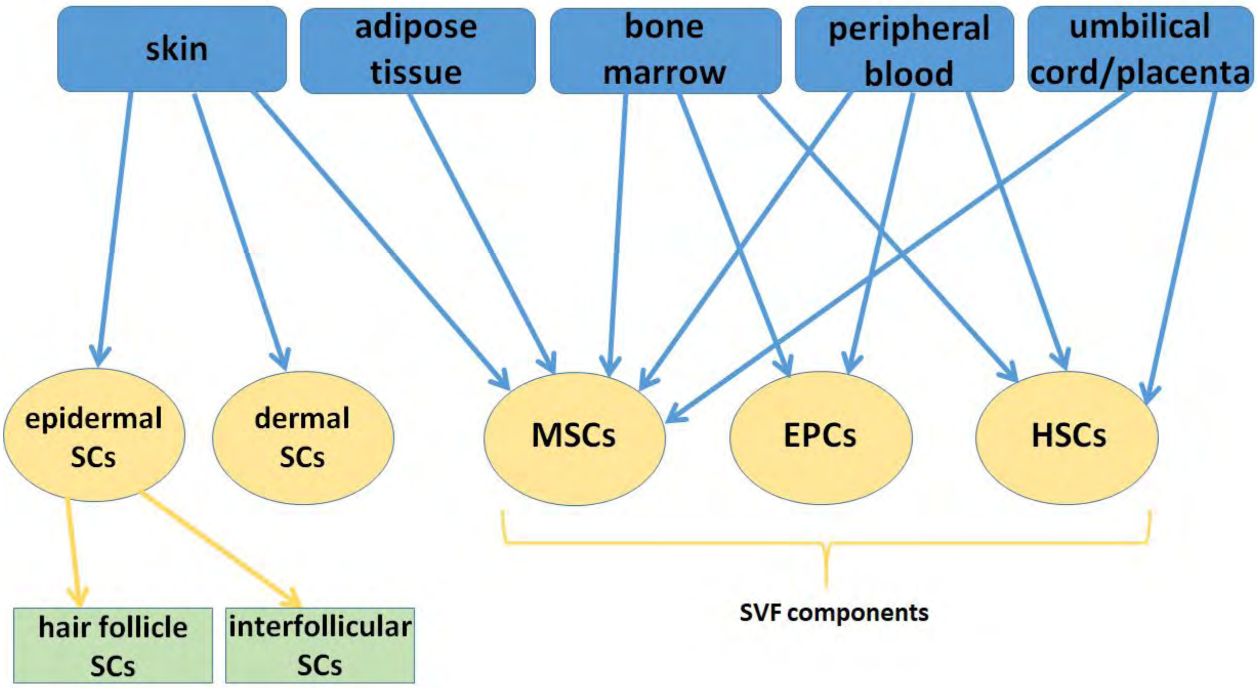

Fig.1. Main sources of stem cell populations crucial in wound healing process.
abbreviations: SCs, stem cells; MSCs, mesenchymal stem cells; EPCs, endothelial progenitor cells; HSCs, hematopoietic stem cells; SVF, stromal vascular fraction

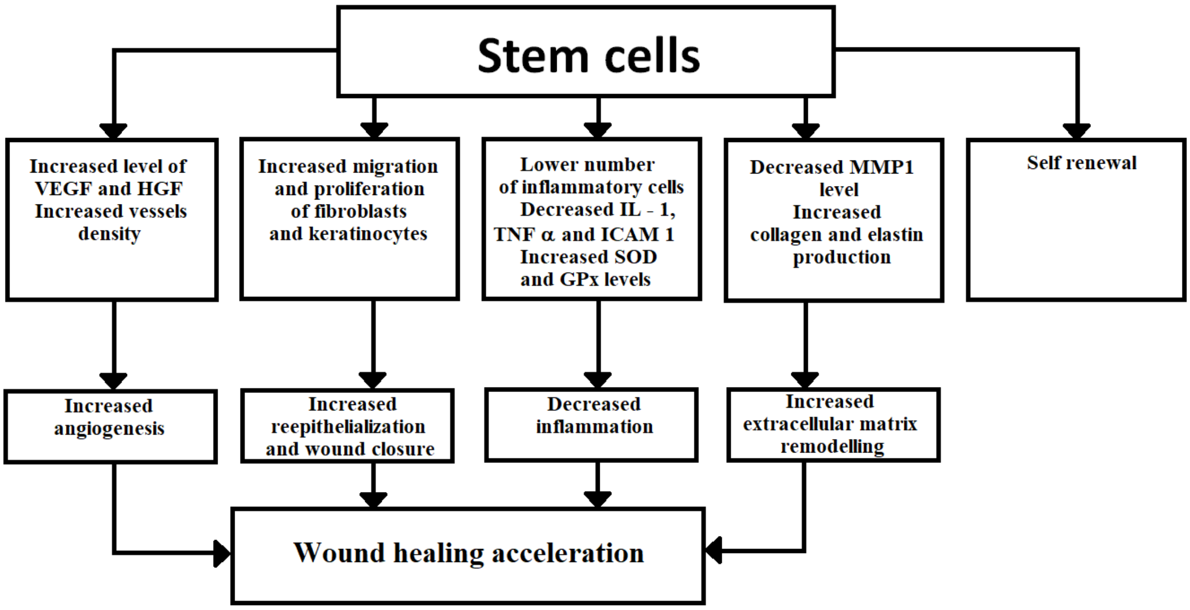

Fig.2. Stem cells functions, that improve wound healing process (Lee et al., 2017; Suma et al., 2015)

abbreviations: VEGF, Vascular Endothelial Growth Factor; HGF, Hepatocyte Growth Factor; IL – 1, Interleukin 1; ICAM 1, Intercellular Adhesion Molecule; SOD, Superoxide Dismutase; TNF-α, Tumor Necrosis Factor α; GPx; Glutathione Peroxidase; MMP1 – Matrix Metalloproteinase 1

Table 1. Stem cells in wound therapy clinical trials and animal models

Reference	Cell type	Route of administration	Therapeutic efficacy Potential functional forms Signaling pathway
(Jimenez et al., 2012)	Hair Follicle Stem Cells (HFSCs)	Direct application - Hair skin graft	Average reduction in ulcer size of 30.8%. Granulation tissue, wound border reactivation and less exudation was present in 7 of 10 patients. HFSC can became wound healing fibroblasts and continue the skin dermis repair.
(Ma et al., 2015)	Hair Follicle Dermal Sheath Mesenchymal Stem Cells (HF DS MSCs) - human/diabetic mouse	Direct injection – cell culture	Fully closure of the wound in 18 days. Stimulation of angiogenesis as well as proliferation and migration rates of human keratinocytes and fibroblasts promoting reepithelialization of the wound bed.
(Heidari et al., 2016)	Hair Follicle Stem Cells (HFSCs) rat	Intradermal injection	Improved wound closure after 1-3 days since implantation, Shorter inflammation period, thicker granulation tissue, extensive reepithelialization, functional erythrocyte containing vessels.
(Martinez et al., 2016)	Hair Follicle Stem Cells (HFSCs) autologous - Clinical trial	Direct application - Hair skin graft	Reduction in chronic ulcer area of 75.15%. Improved granulation tissue creation in all patients. Great proliferation/migration ability of HFSC promote the vascularization and innervation of the wound bed.
(Budamakuntla et al., 2017)	Hair Follicle Stem Cells (HFSCs) autologous – Clinical trial	Direct application - Hair skin graft	Improvement in the ulcer area of 48.8% and volume of the ulcer of 71.98%. Stem cells promote the reinnervation and capillary sprouting into the wound bed.
(Lee et al., 2012)	Adipose Derived Stem Cells (ADSCs) allogenic – Clinical trial	Intramuscular injection	Ischemic ulcer healing in 66.7% patients. Implantation increases the blood flow and collateral vessel formation.
(Marino et al., 2013)	Adipose Derived Stem Cells (ADSCs) autologous – Clinical trial	Direct injection	Reduction of diameter and depth of the ischemic ulcer. Complete healing in 6 of 10 cases. Cells proliferate and differentiate into different cell types.

(Bura et al., 2014)	Adipose Derived Stem Cells (ADSCs) autologous - Clinical trial	Intramuscular injection	Ischemic ulcer number and size became smaller. Display great angiogenic potential.
(Kinoshita et al., 2015)	Adipose Derived Stem Cells (ADSCs) autologous – diabetic mouse	Subcutaneous injection	Acceleration of healing process of the wound. Integration of the transplanted cells into the regenerating dermis and become vascular endothelial cells. ADSC ability of differentiation into different cell lines.
(Kuo et al., 2016)	Adipose Derived Stem Cells (ADSCs) autologous - rat	Subcutaneous injection	Diabetic ulcer healing improvement. Angiogenesis stimulation through VEGF secretion. Inflammation reaction improvement within wound bed.
(Irons et al., 2018)	Adipose Derived Stem Cells (ADSCs) autologous - pig	Direct injection	Significant increase in wound closure. Decrease of inflammatory cells number in the skin. Increased angiogenesis.
(Aboulhoda and Abd El Fattah, 2018)	Adipose Derived Stem Cells (ADSCs) allogenic - rat	Intradermal injection Intravenous injection	Complete wound closure after 14 days. ADSC injected intradermally showed the most spectacular effects by enhancing reepithelialization, decreasing inflammation and promoting granulation tissue reorganization.
(Guo et al., 2018)	Adipose Derived Stem Cells (ADSCs) – Bone Marrow Derived Stem Cells (BM-MSCs) human/diabetic mouse	Direct application – at the collagen scaffold	Acceleration of wound healing in both types of stem cells. Increased cellular proliferation, higher level of VEGF – A, increased angiogenesis for both cell types.
(Foubert et al., 2018)	Adipose Derived Stem Cells (ADSCs) autologous - pig	Intravenous injection	Significantly greater new epithelium creation on the day 5 to 52.8%. Fully epithelialization on the day 9. Reduction of inflammation, angiogenesis enhancement and promotion of epithelial cells proliferation.
(Dash et al., 2009)	Bone Marrow Derived Stem Cells (BM-MSCs) autologous - Clinical trial	Direct application	Diabetic wound contraction over 70%. Development of dermal cells (fibroblasts) and mature and immature inflammatory cells presence.
(Yoshikawa et al., 2008)	Bone Marrow Derived Stem Cells (BM-MSCs)	Direct application – cells onto a collagen sponge	Complete healing of the chronic ulcers different type in 90% of patients. Cells showed very high regenerative potential activating the healing process.

(Yoshikawa et al., 2008)	Bone Marrow Derived Stem Cells (BM-MSCs) autologous - Clinical trial	Direct application – cells onto a collagen sponge	Complete healing of the chronic ulcers different type in 90% of patients. Cells showed very high regenerative potential activating the healing process.
(Gupta et al., 2013)	Bone Marrow Derived Stem Cells (BM-MSCs) allogenic - Clinical trial	Intramuscular injection	Ischemic ulcer healing in 6 of 7 patients. Display great angiogenic potential.
(Das et al., 2013)	Bone Marrow Derived Stem Cells (BM-MSCs) allogenic - Clinical trial	Intraarterial injection	Ulcer healing from 70% size reduction to complete healing. Display great angiogenic potential.
(Aboulhoda and Abd El Fattah, 2018)	Bone Marrow Derived Stem Cells (BM-MSCs) allogenic – rat	Intradermal injection Intravenous injection	Complete wound closure after 14 days.
(Liubaviciute et al., 2018)	Mesenchymal Stromal Cells (MSCs) - mouse	Intradermal injection Intravenous injection	Had beneficial effect in wound healing Partially Modified Mesenchymal Stem Cells (PMSC) showed enhanced migration and increased survival at the site of injury, injected intravenously reinforced tissue regeneration
(Amini-Nik et al., 2018)	Burn Derived Mesenchymal Stromal Cells (BD-MSCs) – human/pig, mouse	Direct application	Cells cultured applied to the wound in pigs and mice. Increase epithelialization speed and area. Showed higher number of new blood vessels in the wound bed.
	Stem Cells from		Decreased wound area in all animals after 14 days. Decrease was slightly