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Review Article

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STEM CELL THERAPY IN SKIN REGENERATION

Kasturi Nag* and Kishori S. Tarfe

Department of Biotechnology, Smt. Chandibai Himathmal Mansukhani College, Ulhasnagar, Thane, Maharashtra, India.

402 D Wing Shivam Sankul Society, Anant Nagar, Gaondevi. Badlapur (E), 421503, Maharashtra, India.

***Corresponding Author: Kasturi Nag**

402 D Wing Shivam Sankul Society, Anant Nagar, Gaondevi. Badlapur (E), 421503, Maharashtra, India.

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ABSTRACT

Skin is the largest organ on your body, made up of several different components, including water, protein, lipids, and different minerals and chemicals. Skin wounds are among the most common injuries in animals and humans. The skin offers a perfect model system for studying the wound healing cascade, which involves a finely tuned interplay between several cell types, pathways and processes. Vertebrate skin is composed of an epidermis and dermis. After a deep skin injury in mammals, the wound heals, but the dermis cannot regenerate. Cell-based therapies as alternative or adjunct devices to standard skin grafting have demonstrated therapeutic potentials at cellular, molecular and tissue regenerative levels in severe burn wound healing. Cell therapy may be utilized to deliver various types of living cells that are critically needed for skin regeneration. Stem cell-based therapy might not only accelerate earlier wound closure and skin regeneration but also prevent wound contracture and scar formation. Treatments for chronic non-healing wounds are expensive because reiterative treatments are needed. Regenerative medicine and in particular mesenchymal stem cells approach is emerging as new potential clinical application in wound healing. Mesenchymal stem cells (MSCs) are multipotent stem cells derived from adult stem cells. Primary MSCs can be obtained from diverse sources, including bone marrow, adipose tissue, and umbilical cord blood. Recently, MSCs have been recognized as therapeutic agents for skin regeneration and rejuvenation. The aim of this review is, therefore, to present a critical synthesis of our current understanding of the role of stem cells in skin regeneration.

KEYWORDS: Stem cell therapy, Skin regeneration, Mesenchymal stem cells, Regenerative medicine, Wound healing, Bone marrow, Adipose tissue, Umbilical cord blood.

INTRODUCTION

Comprising 10% of the total body mass, the skin is the largest organ of vertebrates and is crucial for defence as well as survival. Each injury induces loss of the integrity of the skin resulting in functional imbalance, possibly accompanied by disability or even death.[1]

After a skin injury, skin regeneration and wound healing of the epidermis and dermis are crucial to lowering the risk of infections associated with high mortality.[2] Therefore, in wound treatment, skin substitutes play an important role and provide temporary or permanent wound coverage if autologous, allo- or xenografting therapy is unavailable. Cellularized skin substitutes aim to mimic skin and are being developed having great potential once they are commercially available. Many acellular skin substitutes are widely used. Integra® is one of the most recognized scaffolds worldwide and is approved for acute as well as chronic wounds. It is a synthetic skin replacement which is used to reconstruct wounds after elective planned surgery, or after trauma.[3]

The percentage success for regenerative medicine is closely related to the biological sources used, such as stem cells, scaffolds, growth factors, and grafts. The main role of regenerative medicine is to replace damaged tissue while maintaining its original function or, alternatively, to stimulate regeneration of the tissue itself, respecting the original histological hierarchy.

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)

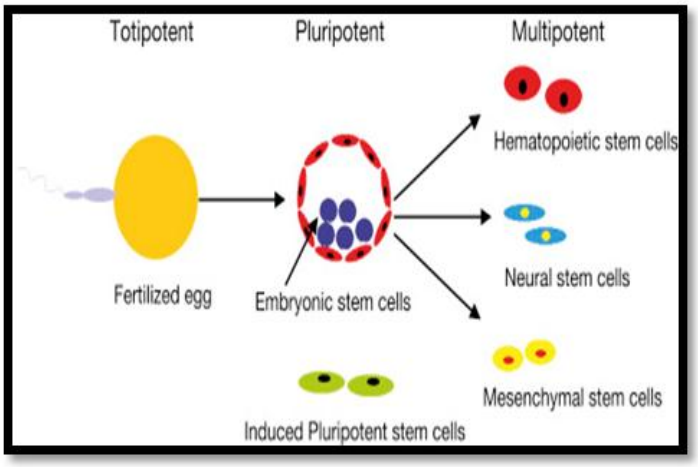

Fig. 1: Overview of the stem cell classification.

The aim of stem cell therapy is to replace a damaged or aged tissue, restoring healthy, functioning cells. In practice, stem cell therapies are based mainly on the use of mesenchymal stem cells (MSCs), which are multipotent cells with unique biological properties. Several in vitro and preclinical studies have reported that MSCs might be promising in cell therapy because of their ability to differentiate into several cell types and secrete bioactive molecules capable of stimulating recovery of injured cells through a paracrine effect of inflammation inhibition. MSCs also show a lack of immunogenicity and can exert immunomodulatory functions. The use of MSCs has been evaluated under different conditions, such as ischemic cardiovascular diseases, critical limb ischemia, bone and cartilage regeneration, and neural diseases.[4-5]

The aim of this review is to summarize mechanisms of MSCs influence skin regeneration process and to describe latest strategies used to improve their therapeutic potential in the context of skin regeneration.

Mesenchymal stem cells

MSCs are stromal cells that possess the capacity to self-renew and also exhibit multilineage differentiation. MSCs can be isolated from a variety of tissues, such as umbilical cord, endometrial polyps, menses, blood, bone marrow, adipose tissue, etc. This is because the ease of harvest and quantity obtained make these sources most practical for experimental and possible clinical applications. Recently, many MSCs have been derived from new sources, such as menstrual blood and endometrium.

1. MSCs from Menstruation: About 400 cycles of menstruation take place in a woman's reproductive years. Most MSCs from menstrual blood have the ability to differentiate to muscle, especially cardiac muscle cells.
2. MSCs from Endometrium: Endometrium from human uterus is a highly regenerative tissue undergoing more than 400 cycles of shedding, growth, and differentiation during a woman's reproductive years. Stem or progenitor cells may play a major role in endometrial regeneration.
3. MSCs from Endometrial polyps: Endometrial polyps are localized hyperplastic overgrowths of endometrial glands and stroma around a vascular core that forms sessile pedunculated projection from the surface of the endometrium. Endometrial polyps cause intermenstrual bleeding, irregular bleeding, and menorrhagia which can be determined by hysteroscopy. As endometrial polyps are benign overgrowths of endometrial tissue they may be a rich source of MSCs.
4. MSCs from Fallopian Tubes: The human fallopian tubes share the same embryologic origin as the uterus, they have the capacity to undergo dynamic endocrine-induced changes during the menstrual cycle, including cell growth and regeneration. MSCs derived from human fallopian tube can differentiate into adipogenic, chondrogenic, oestogenic, and myogenic lineages.
5. MSCs from Human Cruciate Ligaments: MSCs from human anterior and posterior cruciate ligaments (ACL & PCL) can differentiate into chondrocytes, adipocytes, and osteocytes. This ligaments can easily be obtained from patients following total knee or cruciate ligament reconstructive surgery.
6. MSCs from Umbilical Cord Matrix: MSCs from Wharton's jelly (WJC) can differentiate into neuronal and glial cells in-vitro and proved that umbilical cord Wharton's jelly could be a rich source of primitive cells.[6]

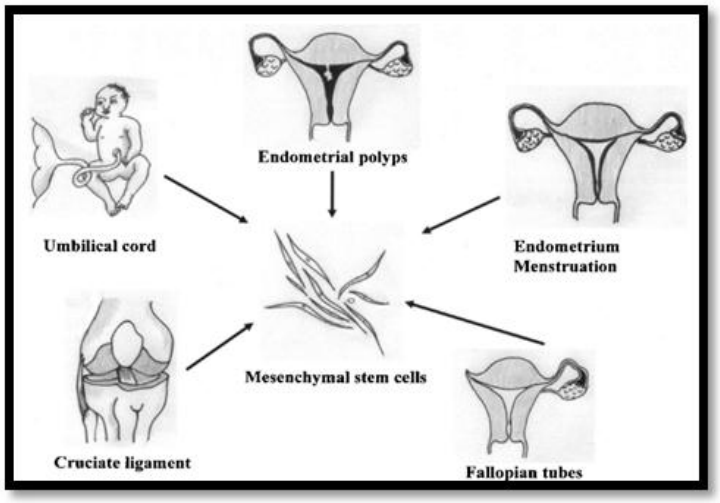

Fig. 2: Various sources of MSCs.

MSCs derived from two major sources are the Bone marrow and Adipose tissue.

Bone marrow MSCs are isolated from bone marrow aspirates, involving a painful process where bone marrow is syringe extracted from the back of the pelvic bone. Only about 0.001% of bone marrow mononuclear cells in the aspirate are MSCs, and efforts to increase cell number through cell culture expansion are complicated to apply to the clinic given the time needed and difficulty in maintaining stem cell phenotype in the lab.

While bone marrow MSCs can be difficult to obtain, adipose derived stem cells (ASCs) are much more abundant and are easily isolated from subcutaneous fat tissue and lipoaspirates. In addition, these adipose tissues are generally discarded from plastic surgery clinics, making excellent use of otherwise disposed tissue. ASCs have been widely explored for skin application given its common mesoderm layer origins.[7]

Stem cell delivery methods

Regarding treatment, cell delivery methods are a very important aspect that is often neglected.

Stem cells can be applied in several ways such as systemically, which does not allow local specific treatment and is less efficient as local injections; topical, which is an excellent alternative in cases of skin wounds and bioscaffolds, which are the most promising delivery method.

Bioscaffolds

They are 3D-printed with biocompatible materials generating 3D patterns, which enable the incorporation of cells (in this case stem cells) or biomolecules that remain viable. They are composed of natural organic materials, synthetic organic materials or even inorganic porous materials, allowing stem cells to be seeded in controlled spaces, protected and promoting their self-renewal and survival. The advantages of this method are due to the ability to produce an identical scaffold with homogeneous distribution, which can incorporate an identical and well-defined dose, being easy to apply.[8]

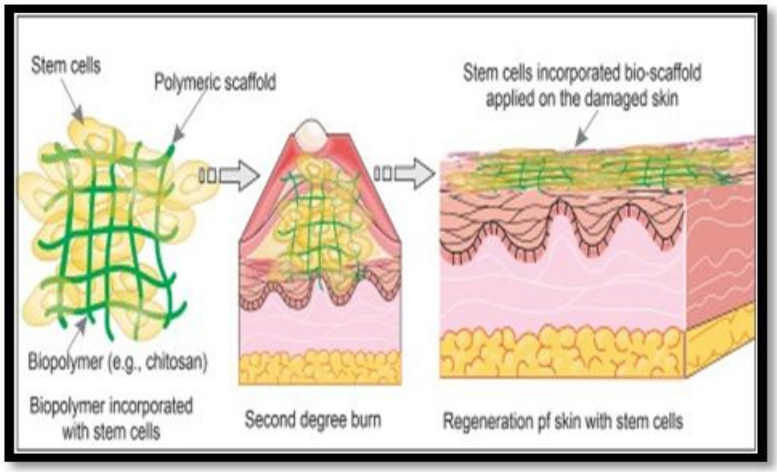

Fig. 3: Bioscaffolds used in regeneration of skin with stem cells.

Delivery of exogenous mesenchymal stem cells to wound/ischemic sites

Most therapeutic applications of MSCs to wound/ ischemic targets dictate that exogenous (for example, culture-expanded) populations be delivered using either systemic or direct/topical approaches. Systemic delivery mimics the route of endogenous MSCs via the circulatory system with final homing to target sites. During vascular transit, MSCs risk being taken out of circulation, on either a temporary or a permanent basis, in organs such as the lungs, spleen, and liver. This may either delay their transit or reduce the numbers of cells that finally appear at target sites. Upon reaching their target site (or sites), MSCs must exit the vasculature to enter the connective tissue stromal region where their principal functions occur.

Direct/topical delivery of exogenous mesenchymal stem cells

For direct/topical delivery to succeed, a highly concentrated population of cells must be either placed onto the surface of the wound or injected immediately adjacent to the wound. The timing of this administration may also be important in that applied MSCs must functionally interact with wound cells at critical stages of the healing process.

Because of its exposed nature, skin has been a target for direct/topical delivery in both preclinical and clinical studies.[9]

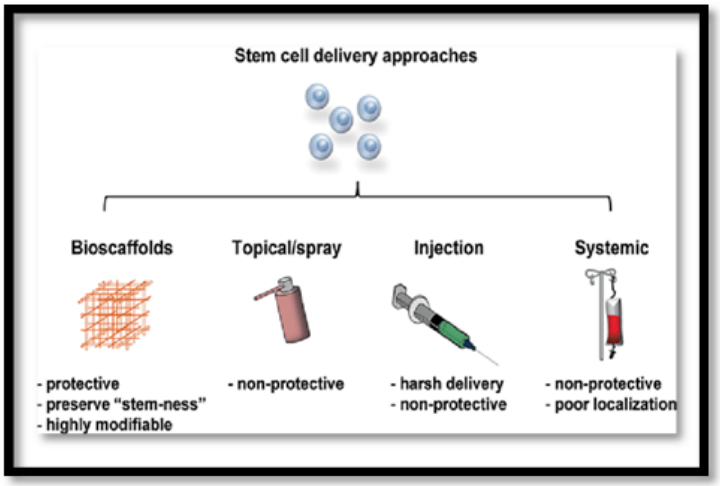

Fig. 4: Stem cell delivery methods.

Homing of MSCs

The lingering problem in the field of cell-based therapies is the delivery of the cells to the site of injury, a process termed "homing." Homing is the process by which cells migrate to, engraft in the tissue in which they can exert local functional effects. Homing involves a cascade of events initiated by shear resistant adhesive interactions between flowing cells and the vascular endothelium at the target tissue. This process is mediated by homing receptors expressed on circulating cells that engage relevant endothelial coreceptors, resulting in cell tethering and rolling contacts on the endothelial surface.[10]

Migration and homing to the tissue of injury is influenced by multiple factors including age and passage number of the cells, culture conditions, and the delivery method.

Age, Passage Number, and Dosage of MSCs.

It has been shown that with higher passage number, the engraftment efficiency of MSCs decreased. Rombouts et al. had performed a time course experiment, where they showed that freshly isolated MSCs had a better efficiency of homing compared to cultured cells.[11,12] The culture of MSCs for 24hr decreased the homing efficiency to 10% from 55–65% and to near 0% when cultured for 48hr. It is well documented that with age, the ability of an organism to repair and heal goes down which is in part due to decreased potency of resident stem/progenitor cell.

Source and Culture Conditions of MSCs.

MSCs can and have been isolated from multiple different tissues with differences in the phenotype of the cells isolated. These differences are likely in part due to differences in the native microenvironment from where they are isolated. This presents a challenge for the use of MSCs for therapeutic purposes.[12]

Delivery method

The efficacy, bioavailability, and functionality of a pharmacological drug are dependent on the method via which it is being administered. In order to enhance efficacy and availability, the method of administration of MSCs should hence facilitate homing of MSCs to the desired tissue. Intravenous infusion is one of the major routes of administration of MSC. When MSCs are infused systemically, they are trapped into capillary beds

of various tissues, especially the lungs. Therefore, intra-arterial injection of MSCs has been assessed.[12]

Preparations of host tissue

Researchers also considered the preparations of host tissue environments to increase the adaptability of cells to harsh environments. Physical methods can be used for host tissue preconditioning.

Combined with MSC therapy, extracorporeal shock wave (ECSW) can significantly reduce the muscle damage, fibrosis, and collagen deposition in a rat model of ischemic muscle injury, proving to have therapeutic effects on tissue regeneration.[13]

CONCLUSIONS

Stem cells function as the human body's building blocks that have to make ''choices.'' Numerous studies have begun to disclose their inner unlimited capacities, and unlike what was previously thought, they can be driven toward trans-differentiation and give rise to unexpected relevant cell lineages. Specifically in skin regeneration, the use of stem cells can contribute in an active way to revolutionize and overcome some of the limitations of the current approaches.[14] In recent years, Charles-de-Sá et al. (2015) observed the histological and structural modifications in aged facial skin after the injection of expanded AD-MSCs, collected from fat removed by liposuction.[110] Treatment with AD-MSCs caused an increase in elastic fibers in the superficial layer of the dermis and modified the collagen and reticular fiber networks, which became more arranged.[15-16] Therapeutic advantages of the MSCs are attributed to the release of some effective and useful mediators, rather than a direct participation in differentiation into the skin cells. Therefore, depending on the specific purpose of a clinical study, each MSC source can have a unique effect and advantage. Some of the main effective indices are the cost of administration, stem cells yield, invasiveness rate of cell harvesting, expanse potency of cells in culture media, and even the differentiation potency of each MSCs source. The high cell yield from adipose tissue by lipoaspiration method and its low invasive procedure as compared with bone marrow aspiration from the iliac crest made AD-MSCs an exclusively attractive stem cell source for the research and clinical studies.[17] Guenou et al. showed that human embryonic stem cells growing in induction medium containing BMP4 (bone morphogenetic protein-4) and ascorbic acid could differentiate between basal keratinocytes, which were subsequently used to reconstitute the epidermis composed of multiple layers of differentiated cells.[18]

Zebra fish (*Danio rerio*) are a model of quick scar-free skin regeneration. Zebra fish have the ability to regenerate a full-thickness injury at a rate of 250 mm/hr., whereas re-epithelialization in a human wound injury is 0.001 mm/hr. Zebra fish are useful for the in vivo tracking of skin cells, along with epithelial cellular responses, involved in scar-free skin regeneration. The skin of zebra fish follows the three general phases of wound healing, similar to that seen in mammalian skin. Fibroblast growth factor (FGF) is crucial for later epidermal remodelling and granulation tissue formation. A recent study demonstrated the behaviour of epidermal cells in the scar-free regeneration of smooth skin in zebra fish. Two types of epithelial cell were found to be involved at the site of injury. The first type initially covered the wound but disappeared within a few days as a result of cellular apoptosis, whereas the second type of epithelial cells was recruited to the vicinity of the skin that contains the stem cells that actively participate in scar free skin regeneration. In addition, existing stem cells in the basal layer had a key role in scar-free skin regeneration. This study provides clues about the role of the autonomous proliferation of stem cells in the basal layer for scar-free skin regeneration.[19]

Luo et al.,[20] examining the effect of human umbilical cord blood MSCs on severe combined immunodeficient (SCID) mice, reported that, in addition to significantly enhancing wound-healing rate, MSCs increased the thickness of the regenerated epidermis, increased the dermal ridges and amount of cells in regenerated skin, and produced healing tissue with more regular alignment of fibers.[21]

Future perspective

Future directions for research in this field might focus on optimization of MSC function in chronic wound contexts, both in delivery systems and scaffold designs as well as improving cell survival via independent technologies or in combination with these delivery systems. MSC therapy also holds promise in improving wound healing outcomes in other wound care settings, such as surgical wounds or burns.[22] The use of adult stem cells, especially mesenchymal stem cells (MSCs), is becoming more realistic in burn treatment. MSCs can be isolated from bone marrow and other tissues, such as adipose tissue, umbilical cord blood and skin tissue. Furthermore, BMSCs have the potential to differentiate into epidermal cells and fibroblasts in vitro, and combined with a scaffold can accelerate the skin wound repair significantly in vivo, demonstrating the clinical feasibility of BMSCs acting as the seed cells in skin tissue engineering. Stem cells from umbilical cord blood are able to differentiate into keratinocytes under in vitro conditions.[23] Regenerative medicine has made significant progress over the last several years with regards to further understanding stem cell biology and the different applications of stem cells for the treatment of clinical problems. The field of plastic surgery is no exception, and stem cells have been reported to be effective in treating a variety of defects including bony and soft tissue defects, as well as non-healing wounds complicated by radiation and ischemia. Aesthetic procedures such as skin rejuvenation have also shown positive outcomes with stem cell treatments. Importantly, these studies have noted minimal complications from these cell-based therapies. Adult stem cells (ADSCs)

have proven to be particularly useful as their ease of isolation and efficient ex vivo culture makes them favourable candidates for clinical applications.[24]

Studies in recent years have reported various stem cells for chronic wound healing, e.g. skin-derived precursor cells (SKPs), epidermal stem cell (EpSCs), amnion derived mesenchymal stem cells (AMSCs), synovium mesenchymal stem cells (SMSCs), bone marrow-derived stem cells (BMSCs) and adipose-derived stem cells (ASCs). These are effective in cell proliferation, promoting angiogenesis, granulation and immunomodulation. However, the researchers in agreement on the use of the MSCs due to their advantages. Mesenchymal stem cells (MSCs) have been a subject of an increased interest due to their ability in skin regeneration has been extensively studied.[25]

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