Annals of Medicine and Surgery 20 (2017) 41–48

Contents lists available at ScienceDirect

Annals of Medicine and Surgery

journal homepage: www.annalsjournal.com

Review

The biological and clinical basis for the use of adipose-derived stem cells in the field of wound healing

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HIGHLIGHTS

- Worldwide, hard-to-heal wounds are a matter of economic and public concern.
- The emerging fields of regenerative medicine and stem cell-based therapies hold great promise for wound healing.
- ASCs can potentially give the support necessary for recovery of hard-to-heal wounds.
- ASCs can be easily harvested from adipose tissue by means of standard wet liposuction technique.
- ASCs have been widely studied in vitro and in vivo to demonstrate their potential and safety.

ARTICLE INFO

Article history:
Received 12 February 2017
Received in revised form
21 June 2017
Accepted 21 June 2017

Keywords:
Regenerative medicine
Tissue engineering
Adipose-derived stem cells
Wound healing

ABSTRACT

Worldwide, hard-to-heal lower limb wounds are estimated to affect 1.5–3% of the adult population with a treatment-related annual cost of $10 billion. Thus, chronic skin ulcers of the lower limb are a matter of economic and public concern. Over the years, multiple medical and surgical approaches have been proposed but they are still inadequate, and no effective therapy yet exists. Regenerative medicine and stem cell-based therapies hold great promise for wound healing. Recently, many plastic surgeons have studied the potential clinical application of adipose-derived stem cells (ASCs), which are a readily available adult stem cell population that can undergo multilineage differentiation and secrete growth factors that can enhance wound-healing processes by promoting angiogenesis, and hence increase local blood supply. ASCs have been widely studied *in vitro* and *in vivo* in animal models. However, there are few randomized clinical trials on humans, and these are still ongoing or recruiting patients. Moreover, there is no consensus on a common isolation protocol that is clinically feasible and which would ensure reproducible results. The authors aim to provide readers with an overview of the biological properties of ASCs as well as their clinical application, to help better understanding of present and future strategies for the treatment of hard-to-heal wounds by means of stem cell-based therapies.

Contents

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http://dx.doi.org/10.1016/j.amsu.2017.06.058

1. Introduction

A chronic wound can be defined as any wound that fails to heal within 30 days, even though there is no clear-cut definition regarding the chronicity of the wound.

As hard-to-heal wounds of the lower limb are estimated to affect 1.5–3% of the adult population and up to 5% of people aged over 65 years, they are a matter of economic and public concern [1,2]. Worldwide, the annual costs related to chronic wound treatment are about $10 billion, and they are expected to exceed $22 billion per year by 2020 [3,4]. Multiple medical and surgical approaches have been proposed for the treatment of chronic cutaneous ulcers. However, currently available treatments are still inadequate and are often mainly supportive, as truly effective therapies do not yet exist. The physiologically impaired healing response of the chronic wound is still poorly understood and thus a matter of debate. The emerging fields of regenerative medicine and stem cell-based therapies hold great promise for wound healing. Recently, many plastic surgeons have studied the potential clinical application of adipose-derived stem cells (ASCs), which represent a readily available adult stem cell population that has gathered a lot of attention in the field of regenerative medicine [5].

ASCs can undergo multilineage differentiation and to secrete growth factors that can enhance wound-healing processes by promoting angiogenesis, and hence increase local blood supply [6]. As a result, hard-to-heal wounds can potentially receive the support necessary for recovery. Although ASCs have been widely studied *in vitro* and *in vivo* in animal models, which have demonstrated their potential and safety, randomized clinical trials on humans are either ongoing or recruiting patients, and are still very few [6]. Moreover, there is no consensus on a common isolation protocol feasible for clinical application that could ensure reproducibility of results. In this review, the authors aim to provide readers with an overview of the biological properties of ASCs as well as their clinical application, to help better understanding of present and future strategies for the treatment of hard-to-heal wounds by means of stem cell-based therapies.

2. Regenerative medicine and cell-based therapy

Tissue engineering and regenerative medicine are multidisciplinary sciences, involving physicians, engineers, and scientists, which have evolved in parallel with recent biotechnological advances and may provide novel tools for reconstructive surgery. Tissue engineering combines the use of biomaterials, growth factors, and stem cells to repair failing organs. In particular, stem cell therapies hold high therapeutic promise based on the possibility of *ex vivo/in vivo* stimulation of stem cell expansion and differentiation into functional progeny that may repair and even replace damaged tissues or organs [7,8].

Ideally, a stem cell for regenerative medical applications should meet the following criteria:

1. Can be found in large quantities (millions to billions of cells).
2. Can be harvested using a minimally invasive procedure.
3. Can be differentiated along multiple cell lineage pathways in a controllable and reproducible manner.
4. Can be safely and effectively transplanted to either an autologous or allogeneic host.
5. Can be manufactured in accordance with current Good Manufacturing Practice guidelines [9,10].

Several different types of stem cells have been considered for clinical applications. Embryonic stem cells (ESCs), pluripotent-amniotic epithelial cells, umbilical cord mesenchymal stem cells, and induced-pluripotent stem cells (iPSCs) are very promising since all show nearly unlimited potential to differentiate *in vitro* and *in vivo* into specific progenitor cells or mature and specialized cell lineages of all three embryonic germ layers [11–17]. However, the clinical use of these cells is limited by ethical, legal, and political considerations, as well as by scientific and clinical issues of safety and efficacy. One of the main issues that hampers successful and safe clinical use of ESCs is the possibility of immune rejection, and *in vivo* formation of teratoma or teratocarcinoma [12,13,15,18,19]. iPSCs have a low reprogramming efficiency and thus require the introduction of exogenous transcription factors using viral vectors, or require other significant *ex vivo* manipulations, which mean that iPSCs are not currently feasible for practical clinical use [20–22].

Tissue-specific stem cells derived from adults offer an alternative approach that circumvents many of these concerns [23].

3. Mesenchymal stem cells

Mesenchymal stem cells (MSCs) are a well-characterized population of tissue-resident adult stem cells identified in most tissues/organs within specific cell niches, where they colocalize with