*Cytotherapy*, 2016; ■■: ■■–■■

International Society for Cellular Therapy
ISCT®

# Will stem cells bring hope to pathological skin scar treatment?

QIANKUN LI[1], CUIPING ZHANG[2] & XIAOBING FU[1,2]

[1]*Wound Healing and Cell Biology Laboratory, Institute of Basic Medical Science, Chinese PLA General Hospital, Beijing, China, and* [2]*Stem Cell and Tissue Regeneration Laboratory, The First Affiliated Hospital, General Hospital of PLA, Beijing, China*

**Abstract**

Pathological skin scars, such as keloids, aesthetically and psychosocially affect patients. The quest for scar reduction and the increasing recognition of patient satisfaction has led to the continued exploration of scar treatment. Stem cells are a promising source for tissue repair and regeneration. The multi-potency and secretory functions of these cells could offer possible treatments for pathological scars and have been examined in recent studies. Here, we analyze the factors that influence the formation of pathological skin scars, summarize recent research on pathological scar treatment with stem cells and elaborate on the possible mechanisms of this treatment. Additionally, other effects of stem cell treatments are also presented while evaluating potential side effects of stem cell–based pathological scar treatments. Thus, this review may provide meaningful guidance in the clinic for scar treatments with stem cells.

**Key Words:** *paracrine signaling, pathological scar, stem cells*

## Introduction

Skin wound healing is a complicated pathophysiological process and is generally divided into inflammation, proliferation and reshaping phases [1]. The skin repair process results in the formation of a scar composed of excess extracellular matrix (ECM) in the place of the normal dermal tissue [2]. Pathological scars, which are present in severe scarring disorders, affect patients both aesthetically and psychosocially [3]. However, current scar management therapies are ineffective and have unsatisfactory effects, including skin ulcers from uneven pressure therapies, side effects from long-term corticosteroid uses, pain and hyperpigmentation or hypopigmentation after cryotherapy and laser therapy and the unproven safety of gene therapy. Therefore, the restoration of pathological scars in cutaneous wound healing remains a challenge. Stem cells are extremely valuable cells for tissue regeneration because of their capabilities of self-renewal and differentiation into specific functional cell types [4]. Recently, with in-depth study of stem cell biology and regenerative medicine, therapeutic approaches that use stem cells have highlighted their potential to inhibit scar formation. Enormous efforts have been made into the study of skin fibrosis in basic and clinical research, and stem cell–mediated scar blocking and resolution are possible in human and animal studies. However, some research has shown that stem cell paracrine signaling could enhance fibrosis and upregulate many profibrotic gene markers. In this review, we focus on several stem cell advances in pathological scar studies, summarize specific mechanisms through which stem cells participate in skin fibrosis and discuss how to develop their antifibrotic potential in pathological skin scar treatments.

## The formation of pathological skin scars

A pathological skin scar is an aberrant fibro-metabolic disease resulting from a trauma, infection, burn or other surgical procedure [5,6]; the two main forms are hypertrophic scar (HS) and keloids. Both types of scar are characterized by excessive proliferation of wound fibroblasts [7,8] and pathological accumulation of ECM [9,10]. However, an HS has collagen arranged in parallel spindles that do not extend past the boundaries of the original wound, but keloids have collagen arranged haphazardly and extend beyond the wound. Keloid scars are considered abnormal, benign fibroproliferative tumors because of their invasive growth into the surrounding skin and high recurrence rates [11].

Correspondence: **Cuiping Zhang**, MD, Stem Cell and Tissue Regeneration Laboratory, The First Affiliated Hospital, General Hospital of PLA, 51 Fu Cheng Road, Beijing 100048, China. E-mail: zcp666666@sohu.com; **Xiaobing Fu**, MD, Wound Healing and Cell Biology Laboratory, Institute of Basic Medical Science, Chinese PLA General Hospital, 28 Fu Xing Road, Beijing, 100853, China. E-mail: fuxiaobing@vip.sina.com.

*(Received 6 January 2016; accepted 10 May 2016)*

ISSN 1465-3249 
http://dx.doi.org/10.1016/j.jcyt.2016.05.008

The pathomechanism of a pathological scar is still an attractive focus in trauma surgery. Considerable scientific effort has been undertaken to understand the mechanism of cutaneous scar formation after wound healing. When skin tissue is injured, inflammation, proliferation and reshaping phases will follow. Fibrosis begins as a normal tissue regeneration process, and the balance between collagen synthesis and degradation is maintained [12]. However, in many cases, a prolonged inflammatory phase can influence wound healing and initiate scar formation [13]. Aberrant proliferation or apoptosis of myofibroblasts or fibrocytes, synthesis or degradation of collagen, and many cytokines constitute the biological foundations of pathological scars. Previous studies have identified that an HS results from the combined regulation of chronic inflammation, mechanical force and fibroblast activation. Indeed, scarring is a process that includes a series of responses to wound healing driven by multiple factors, such as inflammatory reactions, hypoxia and oxidative stress, leading to transforming growth factor-β1 (TGF-β1) pathway activation. Exaggerated inflammation is one of the major players in the cutaneous wound-healing process involving hypertrophic scar formation. In particular, TGF-β1 plays a pivotal role in the pathophysiology of multiple fibrotic conditions [14,15]. It binds to its receptors and activates signaling cascades. With elevated TGF-β1 levels, the signaling pathway leads to the proliferation of phenotypically profibrotic cells, such as myofibroblasts. In particular, it stimulates the epithelial-to-mesenchymal and endothelial-to-mesenchymal transitions, which are partially responsible for excessive ECM synthesis of in the tissue and produce the visual scar appearance [16]. Increased reactive oxygen species (ROS) from skin injuries along with chronic inflammation results in HS or keloids. During rescue and injury treatments, cytotoxic compounds used to sterilize the wound also increase ROS, such as superoxide, hydrogen peroxide and alkyl peroxides. The ROS usually secreted by neutrophils support collagen deposition during wound healing [17]. Prolonged ROS exposure leads to enhanced fibrogenesis and accumulation of fibrotic skin. Previous studies have found that the plasminogen activator inhibitor-1 (PAI-1) plays a pivotal role in keloid pathogenesis [18–20] through aberrant cell signaling pathways [21]. PAI-1 overexpression in keloid fibroblasts can cause collagen accumulation. Other related-fibrotic factors, such as TGF-β, connective tissue growth factor (CTGF) and vascular endothelial growth factor-A (VEGF-A) [22,23] have been proposed as profibrotic markers.

Pathological scarring has an incidence of 4.5% to 16% [24,25]. The main clinical challenges are scar-related cosmetic and functional dysfunctions, such as a rough appearance, uncomfortable itching and skin malfunction. The tensile strength of scar tissue is also limited to approximately 80% relative to normal skin [26]. As a result, weakened cutaneous scars are susceptible to reinjury. Moreover, considerable numbers of patients suffer from a psychosocial disturbance, which varies from mild to severe [27]. All these clinical challenges may decrease patient quality of life. Generally speaking, a typical scar matures in 18–24 months, and this time span helps scars settle and fade. Adult human skin is limited in its ability to completely repair itself to a state like the surrounding epidermis after injury. Because of its high frequency and intractability, many studies have searched for satisfactory treatments. Currently, surgery remains the most common modality, and other therapeutic strategies, such as injectable fillers, radiotherapy (up to 4500 rads), lasers and cold therapy, combined with other agents (silicone gel, steroids, vitamins, imiquimod cream and antimitotic drugs) are also used [28]. Although many approaches have been attempted, no ideal treatment has emerged to completely remove skin scars in adults, and these scars remain as remnants of most skin injuries. Thus, additional efficacious therapies are needed for these disorders, and stem cells could serve as a potential candidate.

Additionally, the formation of skin scars is similar to the development of other tissue fibrosis, such as the heart, lung and kidney, which is the result of body repair. When tissues get damaged, fibroblasts secrete collagen to repair the mesenchyma. Normal tissues are replaced by scar tissues just like skin scars. Persistent fibrosis of the skin tissue results in scar formation, whereas other organ fibrosis is represented as interstitial tissue sclerosis. Therefore, the effective effects of stem cells on other tissue fibrosis can give tips to stem cell treatments of skin scars.

## Effects of different stem cell types on pathological fibrosis

With the rapid development of stem cell treatments and their availability and potential for cell banking, an immense interest exists for stem cells as an attractive candidate for clinical applications [29,30]. Gimble *et al.* suggested the ideal stem cell criteria for regenerative medicine applications [31,32], including abundant quantities (from millions to billions of cells) with minimally invasive procedures for harvesting, differentiation capacity through multiple cell lineage pathways in a regulated and reproducible manner and safe and effective autologous or allogeneic transplantation. Moreover, these cells can be manufactured in accordance with current Good Manufacturing Practice guidelines Stem cells can be divided into embryonic stem cells (ESCs) and adult stem cells, according to their emergence during embryogenesis. The most