Topical Delivery of Mesenchymal Stem Cells "Secretomes" in Wound Repair

Indah Julianto[1], Yuyun Rindastuti[2]

[1] Department of Dermato Venereology, Faculty of Medicine Sebelas Maret University - dr. Moewardi Hospital, Surakarta, Indonesia.
[2] Doctoral in Stem Cell Program, National South Korea University, South Korea

Correspondening Author:
Indah Julianto, MD. Department of Dermato Venereology, Faculty of Medicine, Sebelas Maret University - dr. Moewardi Hospital. Jl. Kol. Sutarto 132, Surakarta 57126, Indonesia. email: dr_inyuda@yahoo.com.

ABSTRAK

Penyembuhan luka merupakan kerja sama antara berbagai macam sel, faktor pertumbuhan dan protein matrik ekstrasel. Inti dari proses ini adalah mesenkimal stem cell (MSCs) endogen, yang mengkoordinasi perbaikan, dengan mengaktifkan sel host dan mensekresi berbagai macam faktor pertumbuhan dan protein matrik. MSCs adalah sel yang mampu memperbaharui dinya sendiri serta mampu melakukan transdiferensiasi pada galur sel-sel lain seprti, tulang, tulang rawan, tendo dan lemak. MSCs mengatur reaksi umun, inflamasi, dan mempunyai kemampuan yang tinggi untuk melindungi dan meregenerasi jaringan tubuh yang terluka, membuat sel tersebut mampu menatraktif untuk pengobatan berbagai macam penyakit. Manfaat efek MSCs eksogen telah dilaporkan pada berbagai penelitian dengan meggunakan hewan coba, untuk penyembuhan luka, dengan hasil yang memuaskan terutama pada luka kronis dengan menstimulasi penyembuhan luka secara cepat. Telah banyak produk yang digunakan untuk penyembuhan luka kronis, tetapi belum dapat menghasilkan penyembuhan secara maksimal. Dalam laporan ini, akan dilaporkan peranan MSCs eksogen pada luka kronis, dengan ilustrasi laporan ulkus kronis, serta didiskusikan peranan MSCs pada tahap-tahap penyembuhan luka.

Kata kunci: *mesenkimal stem cells, secretomes, regenerasi jaringan, ulkus kronis.*

ABSTRACT

Wound healing requires a coordinated interplay among cells, growth factors, and extracellular matrix proteins. Central to this process is the endogenous mesenchymal stem cell (MSC), which coordinates the repair response by recruiting other host cells and secreting growth factors and matrix proteins. MSCs are self-renewing multipotent stem cells that can differentiate into various lineages of mesenchymal origin such as bone, cartilage, tendon, and fat. In addition to multilineage differentiation capacity, MSCs regulate immune response and inflammation and possess powerful tissue protective and reparative mechanisms, making these cells attractive for treatment of different diseases. The beneficial effect of exogenous MSCs on wound healing was observed in a variety of animal models and in reported clinical cases. Specifically, they have been successfully used to treat chronic wounds and stimulate stalled healing processes. Recent studies revealed that human placental membranes are a rich source of MSCs for tissue regeneration and repair. This review provides a concise summary of current knowledge of biological properties of MSCs and describes the use of MSCs for wound healing. In particular, the scope of this review focuses on the role MSCs have in each phase of the wound-healing process, and clinical reports transplatation MSCs – secretomes in chronical ulcer.

Keywords: *mesenchymal stem cells, secretomes, tissue regeneration, chronical ulcer.*

INTRODUCTION

Nonhealing chronic wounds are a large and growing problem with an incidence of 5–7 million cases per year in the United States, and 50% of those wounds do not respond to current treatments. Accumulated data indicate that wound-care products should have a composition equivalent to that of the skin: a combination of particular growth factors and extra cellular matrix (ECM) proteins endogenous to the skin, together with viable epithelial cells, fibroblasts, and mesenchymal stem cells (MSCs). Recently, strategies consisting of bioengineered dressings and cell-based products have emerged for widespread clinical use; however, their performance is not optimal because chronic wounds persist as a serious unmet medical need. The presence of MSCs in normal skin and their critical role in wound healing suggest that the application of exogenous MSCs is a promising solution to treat nonhealing wounds.[1,2]

MSCs have been well characterized to be multipotent cells that can differentiate into multiple tissue-forming cell lineages, such as osteoblasts, adipocytes, chondrocytes, tenocytes, and myocytes. In addition, they can be readily expanded ex vivo for several passages without losing their self-renewal capacity. In addition to the multilineage differentiation capacity that is useful for regeneration, MSCs regulate immune and inflammatory responses. These functions provide therapeutic potential for treating conditions characterized by the presence of an inflammatory component. MSCs can also have a reparative effect through paracrine signaling by releasing biologically active molecules that affect cell migration, proliferation, and survival of the surrounding cells.

The involvement of MSCs in the wound-healing process is critical, in particular for difficult nonhealing wounds resulting from trauma, diabetes, vascular insufficiency, and numerous other conditions. MSCs have a role in the inflammatory, proliferative, and remodeling phases of wound healing, and their presence supports healthy physiologic functioning towards successful healing. As such, therapeutic application of MSCs has been shown to enhance and improve wound healing in clinical settings.1

CASE ILLUSTRATION

A patient, male, aged 33 years old, with a complaint an fistula in peri-anal (dextra) area. He has surgeries as many as 7 times during aperiode of 3 months, but the ulcers got worst, and there was no cure and even the pain followed. The **Figure 1** shows a tamponade supporting the deep and wide ulcer and was always replaced every 2 days in the hospital.

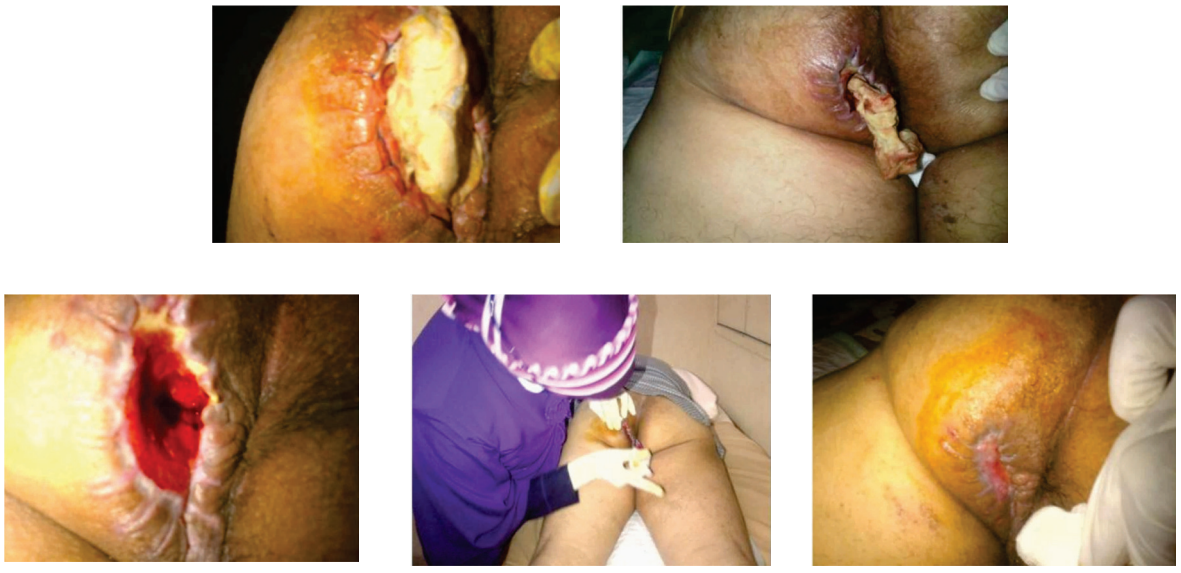

Figure 1. A tamponade supporting the deep and wide ulcer

The size of the wound was quite big and it did not heal, indeed. Intracutaneous injection and tropical application of antibiotc gel + MSCs-secretomes were provided around the ulcer followed by occlusived bandage.

After 4 days, fistula healed and it was confirm when author cheked by no 14 labeled needle insertion, it turned out some pain, giving a clue that there was some tissues growing.

DISCUSSION

MSCs are involved in all three phases of wound healing to varying degrees. They also influence the wound's ability to progress beyond the inflammatory phase and not regress to a chronic wound state. A significant component of the mechanism of action of MSCs is that they directly attenuate inflammatory response. Studies have shown that the addition of MSCs to an active immune response decreases secretion of the proinflammatory cytokines TNF-α and interferon-γ (IFN-γ) while simultaneously increasing the production of anti-inflammatory cytokines interleukin-10 (IL-10) and IL-4.[3,4] It is these anti-inflammatory properties of MSCs that make them particularly beneficial to chronic wound treatment, as they can restart healing in stalled wounds by advancing the wound past a chronic inflammatory state into the next stage of healing. Accumulated data indicate the importance of MSC anti-inflammatory and immunomodulative activities in wound healing.

At the present time it is recognized that MSCs have antimicrobial activity, which is critical for wound clearance from infection. MSC antimicrobial activity is mediated by two mechanisms: direct, via secretion of antimicrobial factors such as LL-37[5], and indirect, via secretion of immune-modulative factors, which will upregulate bacterial killing and phagocytosis by immune cells.[2]

MSCs in vivo can migrate to sites of injury in response to chemotactic signals modulating inflammation, repairing damaged tissue, and facilitating tissue regeneration . Differentiation and paracrine signaling have both been implicated as mechanisms by which MSCs improve tissue repair. MSC differentiation contributes by regenerating damaged tissue, whereas MSC paracrine signaling regulates the local cellular responses to injury. Current data suggest that the contribution of MSC differentiation is limited due to poor engraftment and survival of MSCs at the site of injury. MSC paracrine signaling is likely the primary mechanism for the beneficial effects of MSCs on wounds, that is, to reduce inflammation, promote angiogenesis, and induce cell migration and proliferation.[6]

Analyses of MSC-conditioned medium indicate that MSCs secrete many known mediators of tissue repair including growth factors, cytokines, and chemokines, specifically VEGF, PDGF, bFGF, EGF, keratinocyte growth factor (KGF), and TGF-β.[6,7] Studies indicate that many cell types, including epithelial cells, endothelial cells, keratinocytes, and fibroblasts, are responsive to MSC paracrine signaling, which regulates a number of different cellular responses including cell survival, proliferation, migration, and gene expression.[7]

MSC-conditioned medium acts as a chemoattractant for macrophages, endothelial cells, epidermal keratinocytes, and dermal fibroblasts in vitro. The presence of either MSCs or MSC-conditioned medium has been shown to promote dermal fibroblasts to accelerate wound closure. MSCs also secrete mitogens that stimulate proliferation of keratinocytes, dermal fibroblasts, and endothelial cells in vitro. Further investigation has shown that dermal fibroblasts secrete increased amounts of collagen type I and alter gene expression in response to either MSCs in coculture or MSC-conditioned medium. Overall, these data suggest that MSCs release soluble factors that stimulate proliferation and migration of the predominant cell types in the wound. In addition, the paracrine signaling of MSCs provides antiscarring properties through the secretion of VEGF and hepatocyte growth factor (HGF) and maintaining the proper balance between TGF-β1 and TGF-β3.[6,8]

Evidence of MSC Importance in Healing

In vivo studies have also demonstrated the advantages of using exogenous MSCs for the treatment of wounds. Several studies have shown that the administration of MSCs to either acute or diabetic wounds in rodents improves wound closure by accelerating epithelialization,

increasing granulation tissue formation, and increasing angiogenesis. Nakagawa et al.[9] suggested that MSCs, together with bFGF in a skin defect model, accelerate wound healing and showed that the human MSCs transdifferentiated into the epithelium in rats. Shumakov et al.[10] showed that the transplantation of MSCs on the surface of deep burn wounds in rats decreased inflammatory cell infiltration and accelerated the formation of new vessels and granulation tissue. The cells were also shown to produce bioactive substances that seemed to accelerate the regeneration process. Collectively, these data demonstrate that MSC treatment impacts all phases of wound repair, including inflammation, epithelialization, granulation tissue formation, and tissue remodeling.[9,10]

CONCLUSION

Wound healing is a complex process that requires the coordinated interplay of ECM, growth factors, and cells. MSCs, in particular, play an important role in mediating each phase of the wound-healing process—inflammatory, proliferative, and remodeling. During the inflammatory phase, MSCs coordinate the effects of inflammatory cells and inhibit the deleterious effects of inflammatory cytokines such as TNF and IFN-γ. In addition, MSCs support wound clearance from infection via direct secretion of antimicrobial factors and by stimulating phagocytosis by immune cells. The ability of MSCs to promote the transition from the inflammatory to the proliferative phase is particularly critical for treating chronic wounds where high levels of inflammation prevent healing. MSCs also contribute to the proliferative phase by expressing growth factors such as VEGF, bFGF, and KGF to promote granulation and epithelialization. Lastly, MSCs regulate remodeling of the healed wound by promoting organized ECM deposition. As such, the benefits of MSCs in wound healing have been demonstrated in several preclinical and clinical studies. Thus, multiple mechanisms are involved in MSC-mediated wound healing, including antiinflammatory and antimicrobial, immunomodulative, and tissue reparative activities.

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