Review Article **CODEN: AJPCFF** **ISSN: 2321 – 0915**

Asian Journal of Phytomedicine and Clinical Research

Journal home page: www.ajpcrjournal.com

https://doi.org/10.36673/AJPCR.2022.v10.i03.A13

WOUND HEALING: A COMPREHENSIVE REVIEW

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ABSTRACT

One of the body's most intricate processes is the healing of wounds. Several cell types with different roles during the phases of hemostasis, inflammation, growth, re-epithelialization and remodelling must be coordinated in both space and time. Phenotypic and functional variability within a few of these cell types have been discovered because to the development of single cell technologies. Rare stem cell subgroups that are unipotent in the undamaged state but become multipotent after skin injury have also been found to exist within the skin. Understanding the functions of each of these cell types and how they interact is crucial to comprehending the mechanisms of normal wound closure. The recruitment and activation of cells are directly impacted by changes in the microenvironment, which include modifications to mechanical pressures, oxygen levels, chemokines, extracellular matrix, and growth factor production. This results in conditions of poor wound healing. In order to create efficient therapeutic treatments for healing wounds, single cell technologies can be used to understand these cellular modifications in pathological states including chronic wounds and hypertrophic scarring. This review's goal is to outline the many cellular and molecular components of the skin's healing process.

KEYWORDS

Cell proliferation, Hedgehog proteins, Inflammation and Wound Healing.

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INTRODUCTION

Overview of wound healing

In terms of surface area, the skin is the biggest organ in the human body. It is a crucial component that protects internal organs against thermal shock, microbial infection, UV radiation, and mechanical harm. This makes it extremely prone to harm, which would have a substantial effect on both individual patients and the healthcare industry. Healthcare expenditures for non-healing wounds

alone in the United States total about $50 billion, scars from trauma and surgical incisions cost about $12 billion, and burns cost about $7.5 billion annually (Fife *et al*, 2012[1], Leavitt *et al*, 2016[2]). Diabetes patients, the elderly, and people with genetic diseases like sickle cell disease are particularly vulnerable to aberrant wound healing that can have long-term effects. Surprisingly, the actions in place haven't had a big impact on the situation. While there are many wound healing methods, their efficacy is only mediocre. Hence, there is a need for stronger wound healing therapies.

The complex synchronisation of numerous distinct cell types in orderly steps is necessary for skin restoration. The epidermis is the outer, impermeable layer of healthy skin that protects it from the elements. The sebaceous glands, sweat glands, and hair follicles are all located in the epidermis. The dermis gives the skin strength, nutrition, and immunity and is abundant in extracellular matrix (ECM), vascular and mechanoreceptors. The dermis is supported by subcutaneous adipose tissue, which serves as an energy store. Moreover, it provides the dermis with growth factors continuously.

Each layer also has resident immune cells that are constantly scanning the skin for injury in addition to these different cell types. Several cell types within these three layers must cooperate at specific phases to repair a wound in the skin. Hemostasis, inflammation, angiogenesis, growth, re-epithelialization, and remodelling are steps that take place in a chronological order but also overlap (Gurtner *et al*, 2008)[3]. As a result, skin restoration is one of the body's most intricate functions.

Constriction of the wounded blood arteries and activation of platelets to produce a fibrin clot are the first reactions to a lesion (Clark and Fibrin, 2003)[4]. Blood flow is stopped by the fibrin clot, which also acts as a scaffold for arriving inflammatory cells. As an immediate first line of defence against germs, neutrophils are drawn to the clot (Wilgus *et al*, 2013)[5]. Between 48-96 hours of damage, monocytes are drawn in and become tissue-activated macrophages at the wound site (Park and Barbul, 2007)[6]. To fight off self- and foreign-born antigens, the adaptive immune system, which consists of Langerhans cells, dermal dendritic cells and T cells, is also activated. Understanding the heterogeneity within these immune cell populations is of growing interest, particularly how particular subsets are involved in the removal of cellular debris as opposed to the resolution of infection (Davies *et al*, 2013, 1986)[7,8].

Angiogenesis takes place as the inflammatory phase concludes. Endothelial cell migration, proliferation, and branching are all components of angiogenesis, which creates new blood vessels. Endothelial cell proliferation is accompanied by activation of pericytes within the basal lamina, which operate as a scaffold and give the endothelial cells' structural integrity (Ansell, 2015)[9]. (Armulik *et al*, 2011)[10]. According to several studies, these mesenchymal stromal cells with greater plasticity are these activated pericytes (Crisan *et al*, 2008)[11]. Circulating progenitor cells from the bone marrow are also discovered to support the development of new blood vessels during wound healing in addition to the local cells (Asahara 1997[12], Ceradini *et al*, 2004[13], Kosaraju *et al*, 2016[14], Tepper *et al*, 2005[15]). Many cell types are involved in the development of new blood vessels, with the perivascular region housing the majority of this cellular diversity.

Local fibroblasts multiply and penetrate the clot to generate contractile granulation tissue as new blood vessels grow. Some of the fibroblasts in this area develop into myofibroblasts, which constrict the wound borders (Martin, 1997)[16]. Fibroblasts that are splitting lay down ECM and change the wound microenvironment from an inflammatory state to a growth state (Werner *et al*, 2007)[17]. Re-epithelialization takes place concurrently and involves the proliferation of terminally differentiated epidermal cells as well as unipotent epidermal stem cells derived from the basement membrane (Donati *et al*, 2017)[18]. Rebuilding of the skin appendages is also required for epidermal layer repair. Furthermore, sebum, sweat, and hair follicle tissue-resident stem cells have been identified that

can initiate local appendage repair (Clark, 2003[4], Fuchs, 2009[19]). In equilibrium, these epidermal stem cells are primarily unipotent, but in reaction to injury, they become extremely flexible and can give rise to several cell types, which can help to quickly rebuild the epidermis during wound healing.

Stromal vascular cells and their subgroups have been thoroughly defined within the subcutaneous adipose tissue (Rennert *et al*, 2016)[20]. These cells discharge cytokines and growth factors that are essential for neovascularization and wound healing. The subcutaneous tissue's inflammatory cells have also drawn interest, particularly in cases of obesity and type 2 diabetes where increased inflammation might affect how wounds heal.

Healing typically restores the skin's natural tensile strength and barrier function. However, adult wound healing creates a fibrotic scar that acts as a quick patch for the wound, in contrast to prenatal wound healing, which is a regenerative process that recreates the original skin architecture (Gurtner, 2008)[3]. The balance of fibrotic states of hypertrophic scarring and keloid development is shifted by excessive scarring (Walmsley *et al*, 2015)[21]. Growing data suggests that distinct cellular reactions to mechanical stress within the regenerating skin cause scarring (Wong *et al*, 2012)[22]. Chronic wounds can also result from deficiencies in the wound healing response (Jung *et al*, 2016)[23]. Patients with hemoglobinopathies, diabetes, vascular disease, and ageing all frequently get chronic wounds. Poor wound care causes recurrence, which can result in limb amputations and death.

It is crucial to remember that most of our current understanding of skin regeneration and the cellular architecture of healed wounds comes from the use of surgically created mouse skin injury models. Since it is simpler to produce defective wound conditions in mice, such as those seen in diseases like diabetes, age, and hemoglobinopathies, mouse models have been employed more frequently than porcine models of skin injury. Yet, unlike human or porcine skin, rat skin is elastic, lacks adhesion to underlying structures and closes by contraction triggered by the striated muscle or the panniculus carnosus (Galiano *et al*, 2004)[24]. In contrast, the human skin heals by producing granulation tissue and re-epithelializing. *Ex vivo* cultures of human skin, organotypic cultures, and debrided skin specimens have all been used more and more to study wound healing in human skin (Pastar *et al*, 2018)[25]. When using murine models for wound healing, silicone stents are applied around the excised skin to inhibit contraction and promote healing through the creation of granulation tissue and re-epithelialization (Galiano *et al*, 2004)[24].

The many cell types involved in wound healing will be discussed in detail, as well as the latest developments in single cell technologies that reveal phenotypic and functional heterogeneity within these cell types. The variations between mouse and human skin have been noted when pertinent. This review also discusses skin cell changes that result in unhealthy conditions including fibrosis and wounds that don't heal. Lastly, we discuss several approaches to wound healing and make recommendations for therapeutic interventions, such as the creation of cell-based therapies.

The fundamental process of wound healing

The continuum of normal tissue is breached by a wound, which causes a number of cellular and molecular repercussions. For many years, it has been understood that reducing tissue damage, removing nonviable tissue, increasing tissue perfusion and oxygenation, optimising adequate nutrition and creating a moist wound healing environment are the fundamental principles of effective wound healing (Pierce and Mustoe, 1995)[26].

The environment around the wound changes as a result of the person's changing health status, making wound healing a complex and dynamic process. Understanding the fundamental concepts of wound healing can be framed by knowing the physiology of the typical wound healing trajectory through the phases of hemostasis, inflammation, granulation, and maturation. Wounds recover in four stages, according to research on acute wounds in an animal model. It is considered that the same fundamental

stages must also be experienced by chronic wounds (Kerstein, 1997)[27]. The first two stages are sometimes combined by writers.

The stages of wound healing are

Hemostasis
Inflammation
Proliferation or Granulation
Remodeling or Maturation

Hemostasis

Utility technicians must enter a home to cap damaged gas or water lines once the cause of the damage has been eliminated and before any work can begin. In order to heal a wound, it is necessary to close any damaged blood arteries. The platelet cell serves as the utility worker closing off the broken blood channels during wound healing. In response to injury, the blood vessels themselves contract, but this spasm eventually relaxes. Although the platelets generate vasoconstrictor compounds to help with this process, their main function is to create a stable clot that seals the injured vessel. ADP (adenosine diphosphate), which leaks from injured tissues, causes platelets to clump together and attach to the exposed collagen (Mac Leod, 1981)[28]. Moreover, they produce substances that interact with and promote the intrinsic clotting cascade through thrombin generation, which in turn starts the process of forming fibrin from fibrinogen. The fibrin mesh helps the platelet aggregate become a reliable hemostatic stopper by fortifying it. Platelet-derived growth factor (PDGF), which is known as one of the initial factors secreted in initiating following processes, is one more cytokine that platelets secrete. Unless there are underlying clotting abnormalities, hemostasis happens shortly after the original injury (Mac Leod, 1981)[28].

Inflammation Phase

The traditional "rubor et tumour cum calore et dolore" clinical presentation of inflammation, the second stage of wound healing, includes erythema, swelling, and warmth that are frequently accompanied by pain. This phase often lasts up to days after the injury (Wahl and Wahl, 1992)[29]. In the wound healing analogy, clearing up the debris comes first after the utilities are turned off. Non-skilled labourers should apply for this position. The neutrophils or PMNs are the unskilled workers in a wound (polymorphonucleocytes). The blood vessels become leaky as a result of the inflammatory reaction, spilling plasma and PMNs into the surrounding tissue (Wahl and Wahl, 1992)[29]. The first line of defence against infection is provided by the neutrophils, which phagocytose waste and germs. Local mast cells assist them. The degradation products produced as a result of fibrin breakdown draw the subsequent implicated cell. Rebuilding a house is a difficult task that has to be overseen by a contractor or another person. The macrophage is the cell that functions as a "contractor" during wound healing. Bacteria can be phagocytosed by macrophages, which operate as an additional line of defence. Moreover, they release a number of chemotactic and growth factors, including interleukin-1 (IL-1), transforming growth factor beta (TGF-ß), epidermal growth factor (EGF), and fibroblast growth factor (FGF), which appears to influence the following stage (Kerstein, 1994)[30].

Proliferative Phase (Proliferation, Granulation and Contraction)

Depending on the size of the lesion, the granulation stage in acute wounds often lasts until day 21 following wounding. Clinically, it is distinguished by the presence of pebbled red tissue at the wound base and involves replacement of dermal tissues, and in deeper wounds, sub dermal tissues as well as wound contraction. In the wound healing comparison, the framers begin construction on the new home's framework after the construction site has been cleansed of waste and is being managed by the contractor. Now that the framework is in place, subcontractors may install new wiring and plumbing, and siding and roofers can complete the exterior of the house. The fibroblasts, which secrete the collagen framework on which subsequent skin regeneration occurs, are the "framer" cells. For wound contraction, specialised fibroblasts are responsible. The pericytes, which renew the capillaries' outer layers, and the endothelial cells,

which create the lining, are the "plumber" cells. Angiogenesis is the name of this process. The keratinocytes, also known as "roofer" and "sider" cells, are in charge of epithelialization. As the keratinocytes develop to create the protective outer layer, or stratum corneum, during the final stage of epithelializtion, contracture takes place (Kerstein, 1994)[30].

Remodeling or maturation phase

Interior finishing can start once the main framework of the house has been finished. Similar to how the dermal tissues are modified during wound repair in order to increase tensile strength. The fibroblast is the main cell taking part in this process. Remodeling can occur up to two years after wounding, which explains why wounds that appear to be healed might deteriorate suddenly and severely if the primary contributing variables are ignored (Kerstein, 1994)[30].

DISCUSSION

Due to its extensive surface area and simplicity of tissue separation, the skin is the perfect organ to research cellular heterogeneity and stem cell function in homeostasis, wound healing, and illness. By getting samples that would normally be discarded following various surgical operations, one can study human skin in equilibrium. The tissue from burn patients and trauma patients can be used to study acute wounds, while debrided samples from pressure ulcers, venous leg ulcers, diabetic foot ulcers, and sickle cell ulcers can be used to study chronic wounds. The mechanisms behind regular tissue repair and aberrations that take place in disease can then be determined by comparing the cellular and molecular signalling in homeostasis, acute wound healing, and chronic wound healing. A trustworthy cell atlas can be created by comparing the robustly discovered processes in the skin with those in other tissues and using the skin as a model system for other tissue types. It is generally known that the skin has both immune and nonimmune resident cell populations in its unharmed state. Also, it is understood that during wound healing, these resident cells are triggered at specific time intervals. The resident cells draw blood-borne bone marrow cells that play specific roles in wound healing. The mechanics behind these cellular processes are still unknown, though. The cellular milieu's intricacy raises a number of perplexing concerns. There may be variations of each resident cell subpopulation that react differently to various wound signals. It is uncertain if the subtypes have various sources, some of which have persisted since foetal development, or if they all originate from the same source in adult tissue. Cell-cell interactions, in particular how the resident cell types and subtypes interact with one another and with circulating cells in the wound environment, are a topic of debate. Additionally, the existence of circulating progenitor cells has been disputed. It's critical to comprehend how these cells contribute to wound healing and what happens to them when the healing process is complete. Also, it is taken into account how environmental variables including variations in mechanical stresses, oxygen availability and infection may impact cellular activity in wound healing. It's also possible that the skin contains unidentified stem cells and progenitor cells. Due to the variety of cell types present, each of which activates different signalling pathways, the entire wound cannot be examined using conventional population-averaging methods in order to provide a response to these issues. It may also be ineffective to isolate known cell types from wound tissue using immunostaining with surface markers, followed by population analyses, as the isolated cellular populations may contain different subsets with wildly divergent functions or may be made up of stem cells with anomalous functions. For instance, the early stage of angiogenesis and the late stage of inflammation in wound healing overlap.

Perspectives

The general steps of the wound healing process have been identified through experimental research over the previous two decades. All of the skin's cells, tissues, cytokines, chemokines, and growth factors are involved in the healing of wounds, which reveals that many cellular and extracellular players in wound repair have redundant and

pleiotropic activities and interactions. A deeper comprehension of this intricate network will clarify how skin cells interact with the morphing tissue milieu to define their phenotype during the entire tissue restoration process. The steps of tissue repair-repithelialization of the wound, granulation tissue creation, wound contraction, and scar formation-as well as the inflammatory phase, which lasts only a few days when cells are healthy, are well choreographed and proceed normally.

The inflammatory process is prolonged, the integrity of the skin is not restored, and an ulcer or pathological fibrosis develops when cells are defective, as in diabetes. In all stages of tissue repair, macrophages predominate over other types of cells. They have a crucial regulatory role, making them significant therapeutic targets for the future management of the wound healing process.

Table No.1: Cells for healing wounds (Broughton, 2006)[31]

Fibroblasts	- Release cytokines and growth factors - Chemo attractant - Synthesizes proteogylcans and and fibronectin to create matrix - Transforms to myofibroblasts to contract and close wound
Keratinocytes	- Directed by fibroblast release of KGF-1 and -2 - Proliferate, migrate and differentiate into epidermis - Stimulate neovascularization by secreting VEGF
Endothelial cells	- Involved in angiogenesis
Lymphocytes	-

Table No.2: Growth factors' function in wound healing (Broughton, 2006)[31]

S.No	Growth Factors	Role of Growth Factors in Wound Healing
1	PDGF	–Secreted by macrophages, monocytes, fibroblasts – Involved in chemotaxis and proliferation
2	VEGF	Receptors on endothelial cells, stimulation results in angiogenesis
3	EGF	– Released by platelets – Receptors on endothelial cells and fibroblasts – Involved in chemotaxis, angiogenesis and collagenase activity
4	TGF-α	– Produced by activated macrophages, platelets, keratinocytes – Involved in cell growth and chemotaxis
5	FGF	–Involved in cell proliferation, angiogenesis, collagen synthesis, wound contraction, epithelialization
6	KGF TGF-β	– Only found in damaged tissue – Involved in keratinocyte proliferation and motility – Stimulates monocytes to secrete other growth factors –Chemotactic for macrophages and fibroblasts –Stimulates fibroblast and epithelial cell proliferation – Potent stimulant for collagen synthesis – Involved in organization of extracellular matrix, –scar remodeling and wound contracture

Table No.3: Duration in Healing Phases

S.No	Phase of Healing	Days post injury	Cells involved in Phase
1	Hemostasis	Immediate	Platelets
2	Inflammation	Day 1 - 4	Neutrophils
3	Proliferation	Day 4 - 21	Macrophages
4	Granulation	-	Lymphocytes, Angiocytes, Neurocytes
5	Contracture	-	Fibroblasts, Keratinocytes
6	Remodeling	Day 21 – 2 yrs	Fibrocytes

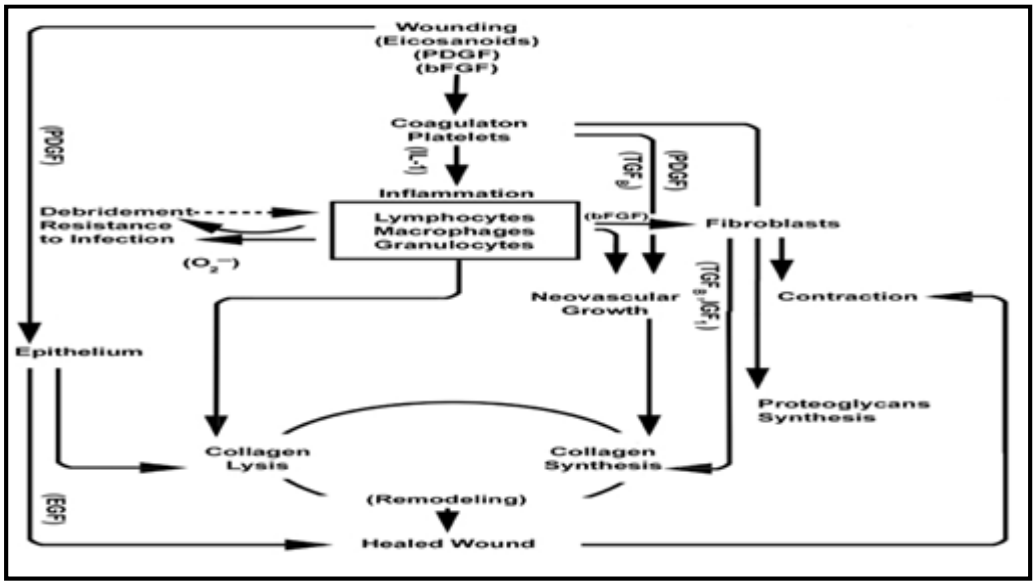

Figure No.1: Wound healing factors

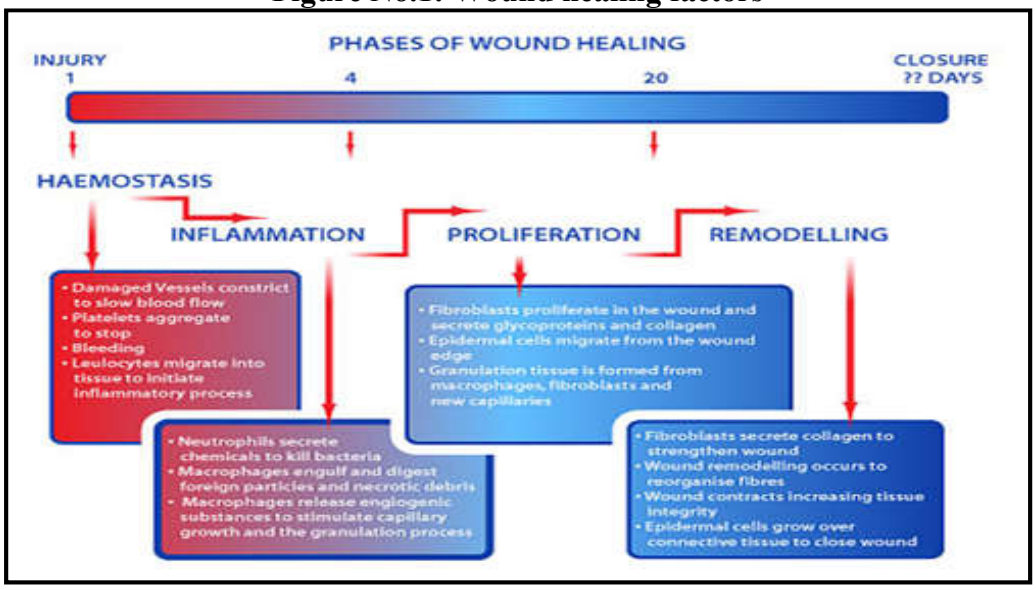

Figure No.2: Stages of wound recovery

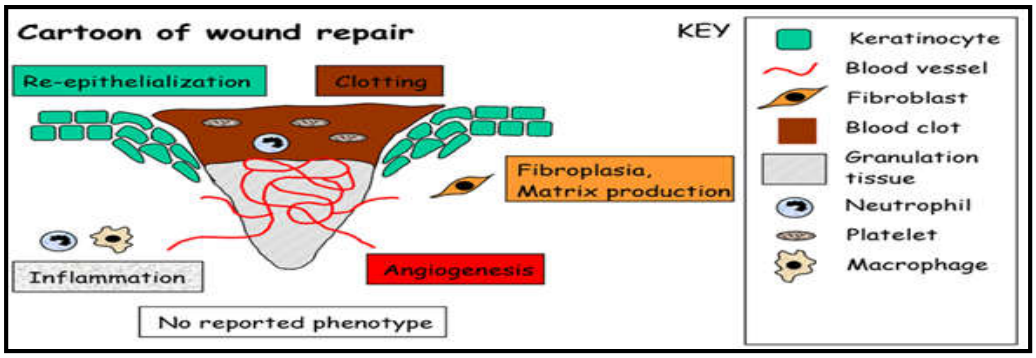

Figure No.3: Process of wound healing

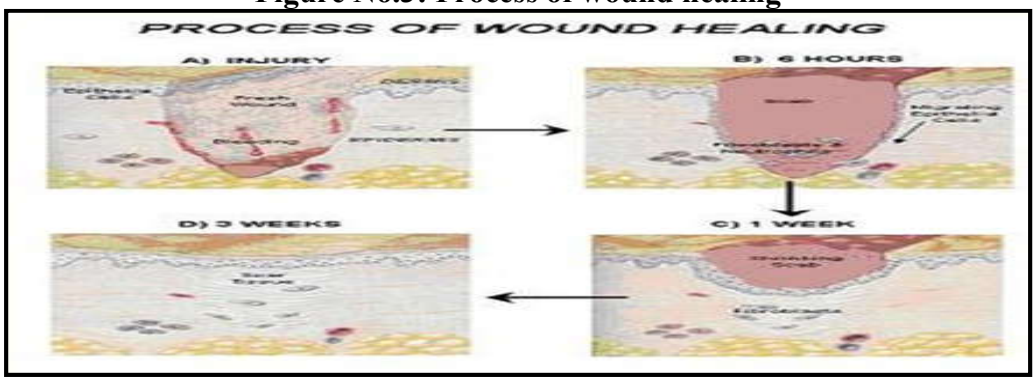

Figure No.4: Healing process for wounds

CONCLUSION

Both subsets of macrophages that are performing efferocytosis and those subsets that are releasing growth factors for new vessel creation are present in macrophages that have been isolated at this stage. Results from a population assay on this diverse group of macrophages would be biassed in favour of the bigger macrophage subset. Similar to this, it is hard to determine which subsets of fibroblasts preferentially develop into myofibroblasts, create adipocytes, or signal to epidermal cells if all fibroblasts are isolated and examined as a single group of cells. The development of efficient treatments for any skin damage will benefit from the identification of cell surface markers to isolate the most effective cells for wound healing.

ACKNOWLEDGEMENT

The authors wish to express their sincere gratitude to Central Laboratory Facility, Chhattisgarh Council of Science and Technology, Raipur, Chhattisgarh, India for providing necessary facilities to carry out this review article.

CONFLICT OF INTEREST

There are no disclosed conflicts of interest for the author.

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