



Beta-Glucans: A Biomimetic Approach for Reducing Chronicity in Delayed Wound Healing

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Abstract

The challenge which grows over time in the chronic wound healing is a self-care wound dressing. These wounds have unfavourable impact on patients wellbeing and also challenging to the health economy. The wound healing requires a complex series of physiological and immunological processes with adequate nutrition. Any derangement of immune signals at any stage can lead to impaired wound healing which alters the key transition point that lies between the inflammatory and proliferation phase that destroys the components of Extracellular matrix. The Extracellular matrix is responsible for regulating the growth factors and its receptors that are important for wound healing. To boost up the growth factor signalling and accelerating the chronic wound healing, a new biomimetic approach of mimicking the role of extracellular matrix helps in the development of instructive wound dressing. Thus this review deals in discussing the tremendous activity of the Natural polysaccharide called β -glucan on wound healing signalling which may help in mimicking the role of extracellular matrix.

Introduction

The thriving ubiquity of diabetes, obesity, aging population and change in life style continues to increase the frequency of the chronic wounds. Chronic skin wounds are one of the serious issue that is reaching epidemic proportions which are estimated to affect 20-60 million people worldwide by 2026¹. Unlike acute wounds, which heal after a certain period of time, chronic skin wounds heal slowly or not at all heal. These wounds can lead to long term hospitalization which is highest burden to the healthcare sector as there is a mortality of the patients as they have shown to cause loss of mobility and ability to perform daily tasks, limb amputation and poor quality of life. The effect of non-healing wounds on mortality has even been comparable to or worse than that of few common cancers like prostate, breast and colon cancer².

Chronic wounds

The healing process starts from the hemostasis stage that is connected with forming a temporary matrix, secreting cytokines and other growth factors, and interaction of the latter ones with Extracellular Matrix(ECM), which initiates the repairing process, preparing the wound bed to the next stage of the healing process. In a healthy person with no underlying inhibitory factors an acute wound should heal within 3 weeks with the remodeling occurs over the next year or so. If a wound does not follow the normal path of healing, one of the phase of healing may be hindered and lengthened which makes the wound to becomes chronic³. Chronic wounds are

thus defined as wounds, which have “failed to proceed through an orderly and timely process to produce anatomic and functional integrity, or proceeded through the repair process without establishing a sustained anatomic and functional result”⁴. Conventionally, a period of 6-8 weeks has been accepted by various authorities as the cut off time, beyond which the wound is labeled as chronic/non-healing³.

Chronic wounds and ECM breakdown

There are number of causes of delayed healing such as ischemia, wound infection, persistence of foreign body or bacterial proteins, chronic irritation, trauma and so on⁵. Ischemia is one of the key factor that makes the chronic wound to develop and makes it severe in the old age patients when it occurs repetitively. Ischemia decreases the blood supply to tissues leading to decreased oxygen and nutrients in the affected area causing inflammation in the tissues that triggers the cells to release factors such as chemokines, interleukins, leukotrienes and complement system that attract neutrophils⁶. During the response against pathogens, neutrophils tend to release inflammatory cytokines and various other enzymes. Myeloperoxidase is one of the essential enzyme produced by neutrophils which in turn kills the bacteria by developing the reactive oxygen species (ROS)⁷. The increase in these enzymes and ROS production of neutrophils and other leukocytes damage cells that are essential for the proliferation phase by preventing proliferation and wound closure thereby causing damages in DNA, lipids, proteins, ECM and cytokines that normally aid the healing process⁸. Neutrophils remain extended in chronic wounds than that of acute wounds contributing to the elevated level of inflammatory cytokines and ROS. Also the wound fluid from chronic wounds has high amount of proteases and ROS which inhibit healing by inhibiting cell growth and breaking down growth factors and proteins in the ECM⁹.

ECM and therapeutic approaches for chronic wound healing

The therapeutic approaches observed based on the accurate knowledge about the pathophysiology of a chronic wound have broadly focused on developing methods to decrease the ECM degradation, restoration of a healthy ECM and production of artificial ECM to activate chronic wound healing process¹⁰. Thus development of biomimetic material is a favourable approach for chronic wound healing¹¹. Every tissue inside the body has a unique set of cells and ECM proteins arranged into a distinctive architecture, thus requiring the properties of bioengineering materials to be designed in an organ-specific way¹². The lengthed inflammation and higher level of Matrix Metalloproteinases (MMPs) at the wound site causes significant degradation of ECM that delays wound healing process leading to

chronicity (Figures 1&2). Thus the development of therapeutic dressing to control and positively regulate MMPs balance helps in achieving faster healing. The design of biomaterial matrices has the challenge to mimic the function of ECM that helps in fibroblast migration at wound site¹³. Recently, natural polymers have highly attracted the scientific community interest. By knowing the biocompatibility and biodegradable, nature of the naturally occurring polymers helps in highest level of biomimicry, replicating the biological and physicochemical features of the native ECM. By looking into our natural surroundings and by re-using some of the discarded natural resources, several functional biomaterials can be easily identified and implemented for promising wound healing applications, with a reduced impact on the environment. Nature itself can be better inspiration to develop economical, reduced energy consumption and fully biodegradable materials, providing great environmental sustainability. The increase interest in the use of either protein-based or polysaccharide-derived dressings provides striking and reflects the growing approach of giving back what we borrowed from Nature¹⁴. Naturally derived polymers provide a versatile, multitasking and tunable platform to design appropriate extracellular environments that actively contrast the onset of infection and inflammations, while promoting tissue regeneration and scar remodeling.

Beta glucans as a naturally derived polymer

Natural polysaccharides are abundant in nature which are useful in many applications due to their unique properties. One of the most predominant class of polysaccharides is the β -glucans which are carbohydrate polymers that are found in the cell walls of many organisms such as bacteria, fungi, yeasts and some cereals like barley and oat¹⁵. All β -glucans comprises of glucose polymer linked by 1-3 linear glycosidic chain core of varying length and branching structures¹⁶. These branches that are derived from the glycosidic chain core are highly different with two main group of branching such as 1-4 or 1-6 glycosidic chains¹⁷. Also, different types of β -glucans exhibit distinct molecular weight, solubility and viscosity causing diverse physiological functions¹⁸. It is also most known for its powerful immune stimulant, antagonist of both benign and malignant tumors, anti-biotic properties and lower blood pressure or cholesterol levels¹⁹. Since beta-glucan enhances the production of growth factor that are essential for skin, promotes collagen biosynthesis and maintains skins moisture and elasticity²⁰, we discussed the activity of various β -glucans on wound healing to make it evident for boosting the wound healing process of chronic wounds.

β -glucans also exhibited *in vitro* antimicrobial activity directly against a broad range of bacterial species, including *E.coli*, *Paeruginosa* and *S.aureus* or indirectly by enhancing phagocytic activity and resistance towards the microbes²¹.

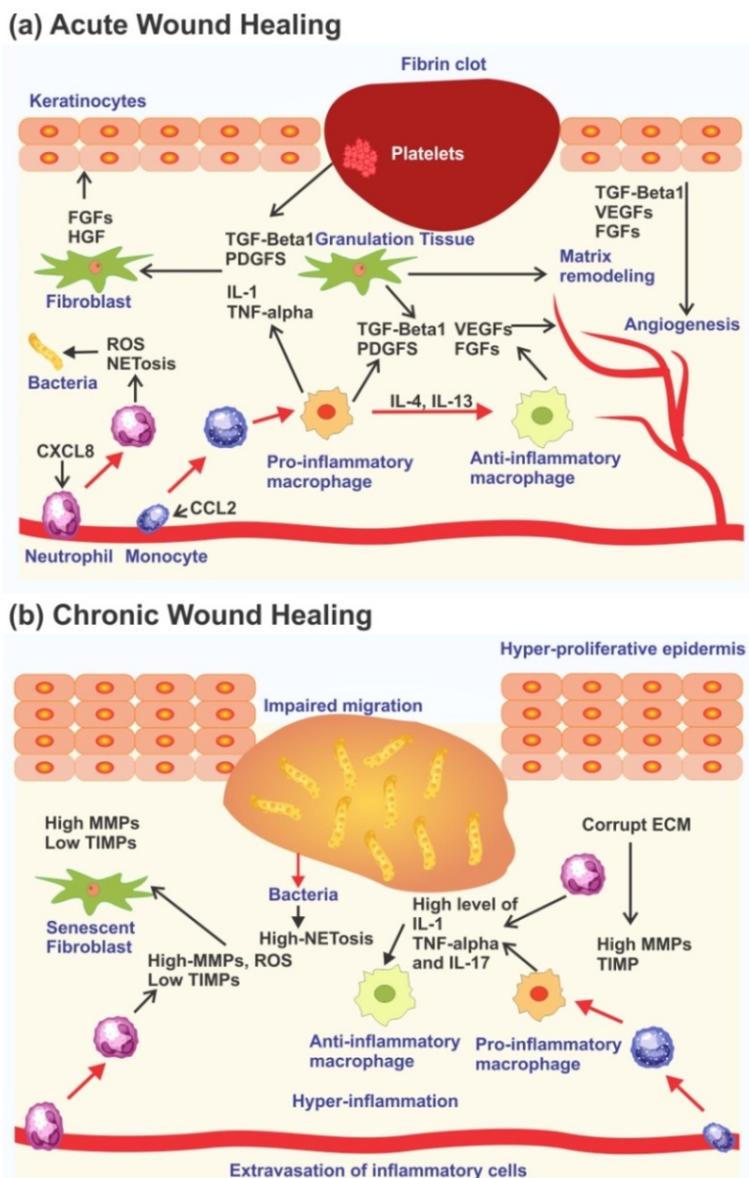


Figure.1: Acute and Chronic Wound Healing Process

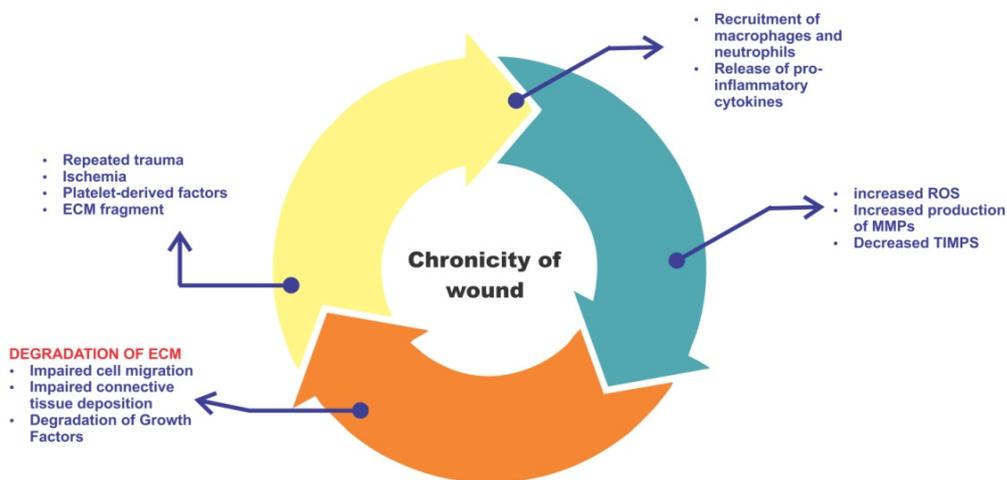


Figure. 2: Inflammation cycle that contribute to the chronicity

In another study it was confirmed that the oat β -glucan showed antimicrobial activity against *E.coli* and *B.subtilis*²². β -glucan have a broad spectrum of effects on different cell types that can evident their proficiency on wound healing²⁰. The ability of β -glucan to stimulate wound healing was first described by Leibovich and Danon in 1980²³, who observed faster re-epithilisation and increased macrophage activity and fewer polymorphonuclear neutrophils in the wound bed during inflammatory stage of repair. Various clinical trials reported that the topical application of fungal beta glucan accelerated healing in chronic ulcers²⁴⁻²⁸. β -glucan also activates macrophages that can remove cellular debris resulting from oxidative stress, thereby speeding up the recovery of damages tissue²⁹. Fuste³⁰ also confirmed that the barley β -glucan induced an early response in Human dermal fibroblast (HDF) cells favouring movement versus proliferation, and accelerated wound closure *in vivo*. According to Van den Berg³¹ et al., β -glucan have immuno-

stimulatory capacity in temporary wound and show enhanced wound healing in burns. Curdlan enhanced migration, proliferation and wound closure of human keratinocytes in a dectin-1 dependent manner both *in vitro* and in *ex vivo*. Numerous studies that are evident for the wound healing property of different type of β -glucan (Table 1).

Conclusion

Wound healing is a repair and restoration of tissues through the series of stages that involves different cells and signalling molecules to regulate the cellular response and the dynamic remodelling of the extracellular matrix. Chronic wounds contain elevated levels of inflammatory cells, giving rise to more amount of proteases that degrades the ECM components, growth factors and receptors which are essential for wound healing. To restore and regulate the chronic wound healing cascade, a new approach of

Table 1: β -glucan types from various source and their respective wound healing activity

Name of the β -glucan	Target cell type/ animal model	Inference
Baker's yeast Glucan	HDF	increased the nuclear factor-1 binding capacity and enhanced collagen biosynthesis ²⁵
	Porcine keratinocytes	enhanced the keratinocyte proliferation ²⁶
	3T3 fibroblast	nanofibrous membranes enhanced the adhesion and proliferation of fibroblasts and keratinocytes ²⁷
	Venous ulcer biopsy	enhanced the healing in venous ulcer ²⁸
Barley Glucan	Adult Human dermal fibroblast (HDFa) / Mice	induces an early response in HDF cell favouring movement versus proliferation ³⁰ .
Oat Glucan	Rats	increased anti microbial activity, reduction of cholesterol and blood pressure ²²
Xyloglucan	Wister rats	exerted good healing effect in rats with severe wound ³²
	NHEK, HaCaT and NHDF	promoted skin regeneration ³³
Laminarin	Human corneal epithelial cells	enhanced the epithelial migration ³⁴
Paramylon	Mice	accompanied with a modest increase of inflammatory cytokines ³⁵
	HEK 293 T cells	acts as a bioactive supplement by boosting the cell proliferation capacity ³⁶
Curdlan	Human Keratinocytes	stimulated the cell proliferation and migration in a Dectin-1 dependent manner ³¹
	Swiss 3T3 fibroblast & wister rats	Nanofibrous dressing of PVA/curdlan incorporated with Ag has fast healing of wound in rats ³⁷
β -(1,3-1,6)-D-Glucan from <i>Aureobasidium pullulans</i>	BALB / nude mouse	Membrane containing 50% β -glucan and Poly-(lactic co glycolic acid), accelerated the wound interactions ³⁸
	ddY mouse	Beta-glucan and chitosan complex enhanced the wound repair by activation macrophages and cytokine release ³⁹
	Human dermal fibroblasts	enhanced the dermal fibroblast migration and proliferation that modulated the effect of transforming growth factors ⁴⁰
	Human dermal fibroblasts, adipose tissue derived stem cells	boosted up the cellular response, migration and proliferation of both the cells ⁴¹
Schizophyllan (SPG)	L292 Fibroblast	SPG based nanofibrous scaffolds showed cell proliferation and cell migration ⁴²
		PVA/SPG-AgNPs nanofibers showed anti-microbial activity thereby helping in reducing the infection in the wound ⁴³
Lichenan	NHEK and HaCaT keratinocytes	stimulated human keratinocytes by specific mechanism into the terminal differentiation ⁴⁴

mimicking the extracellular matrix was discussed with a help of immuno modulatory polysaccharide called β -glucans. Various *in vivo* and *in vitro* studies discussed are evident to confirm the wound healing activity of beta-glucans from various sources. Also the β -glucans induces the proliferation and migration of keratinocytes and fibroblasts through specific receptors such as Dectin-1, CR3 or TLRs. These data also confirmed that β -glucans directly or indirectly modulate the activity of diverse cells and growth factors that are central to the reparative process. Thus β -glucans may interact with the innate immune system by regulating the macrophages and release the cytokine to produce growth factors/receptors thereby providing a temporary ECM for chronic wound healing.

Conflict of Interest statement

The authors declared that they have no conflicts of interest to this work.

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