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Review Article

MODELSOF RAT SKIN WOUND HEALING: AN OVERVIEW

RATNANJALI PANDEY*, RAMESH KUMAR GUPTA

Department of Pharmacology, Hygia Institute of Pharmaceutical Education and Research, Lucknow, Uttar Pradesh, India.
Email: ratnanjalipandey1998@gmail.com

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ABSTRACT

Wounds have developed into one of the earliest types of human pain, with two histories that go back to before the existence of humans. The growth of medical research led to an abundance of new ideas and opened the doors for creating a separate field solely dedicated to treating wounds. The underlying cause, the site of the injury, the mechanism of injury-producing symptoms, the depth and tissue loss of the wound, or the clinical presentation can all be used to categorize wounds. According to studies utilizing animal models, there are four stages of acute wound healing. It is a given that chronic wounds must go through similar underlying mechanisms. Hemostasis, inflammation, proliferation or granulation, and remodeling or maturation are adequate stages of wound healing. There has been a substantial change in how we understand and apply information. This study investigated every aspect of wound healing, including every pathway and model for wound healing.

Keywords: Skin, Wound healing, Models of wound healing.

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INTRODUCTION

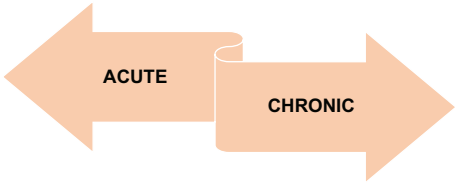
Skin

The primary organ, the skin, is complicated and versatile, with many distinct types of cells that may perform a range of functions. The basement membrane, which joins the epidermis and dermis, or outer and inner layers of the skin, securely keeps them together. Fat and loose connective tissue supports the dermis [1]. The different components of the skin produce a variety of cytokines, neurotransmitters, neuroendocrine hormones, and their accompanying receptors, allowing the skin to communicate with and control itself. These neuroimmunoendocrine mechanisms and the central regulatory systems have strong connections [1].

Wound

A wound is described as damage or destruction to the typical anatomical structure and function [3]. Wounds can be caused by pathological processes that begin either externally or inside the concerned organ. They could develop from a disease process or have an unintended or deliberate cause. Unaffected by the wound's origin or form, the tissue is damaged, and the surrounding environment is disturbed. Physiological response to the noxious element results in bleeding, vascular constriction with coagulation, complement activation, and inflammatory response [3,4].

Wound types

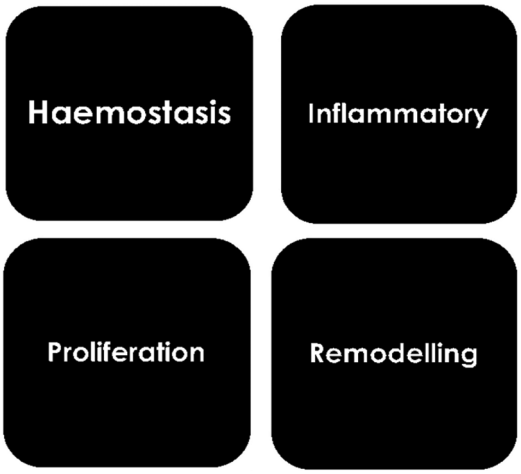


The term "acute wound" refers to a cell injury that "often continues through an orderly and timely reparative process that ends in sustained restoration of anatomic and functional integrity."

A chronic wound is one that "proceeds through the healing process without creating a sustained anatomic and functional result" or "fails to go through an orderly and timely reparative process to attain anatomic and functional integrity" [5].

WOUND HEALING

All of the body's tissues and organs are capable of suffering from wounds and repairing them. The crucial yet challenging process of both human and animal wound healing includes several overlapping but sequential phases, including the hemostasis/inflammation phase, proliferation phase, and remodeling phase [6,7].



HEMOSTASIS

Several factors can trigger hemostasis to proceed. Skin cells that have been damaged initiate the extrinsic coagulation cascade by generating clotting factors. The intrinsic clotting cascade and platelet-mediated vasoconstriction are started by platelet aggregation and the release of collagen from the injured skin. Vasoconstriction stops additional blood loss, while a fibrin clot temporarily closes the wound and prevents the spread of infection [8].

INFLAMMATORY

Inflammation happens during the second stage of wound recovery. Activated platelets and their cytokines, injured tissue cells and capillaries, and hemostasis by-products, among other mediators, mediate the inflammatory response. Neutrophils come to the injury site shortly after it occurs to control any potential germs that may be there [9]. In addition, neutrophils stimulate nearby fibroblasts and epithelial cells to start the lesion's healing process. Despite other white blood cells such as monocytes, lymphocytes, and plasma cells traveling to the injury site, neutrophils predominate for the first few days before declining until the lesion gets infected. Usually, until the infection is under control when there is an infection, neutrophil infiltration persists [10].

PROLIFERATIVE

The initial inflammatory responses to an injury serve as the building blocks for the later growth of a new functional barrier. At this point, cellular activity is the dominant form of healing. The major activities at this stage include re-epithelialization, angiogenesis, and strengthening of the injured dermal tissue. A permeability barrier is also created (i.e., fibroplasia) [11].

REMODELING

The final step of wound healing, known as the remodeling phase, is capable of producing new epithelium and creating the final layer of scar tissue. During the proliferative and remodeling phases, the creation of granulation tissue starts at the same time as the extracellular matrix is being produced. During this period, time may pass for up to 2 years, or perhaps longer. The delicate balance between synthesis and degradation, which encourages optimal healing, is carefully monitored by regulatory mechanisms while an acute wound remodels. With the maturation of the intracellular matrix, collagen bundle diameter rises while hyaluronic acid and fibronectin are simultaneously broken down [12,13].

MODELS OF WOUND HEALING

When the healing process is prominently slowed down in certain circumstances, chronic wounds develop [14]. Poorly understood mechanisms lead to slow wound healing and insufficient cutaneal regeneration. Emerging research suggests that stem cells may be able to promote skin regeneration and wound healing. Various wound healing models that aim to represent human wound healing concerns have been produced [15].

DIABETIC MODEL

A high-fat diet or the intravenous administration of a drug like alloxan or streptozotocin was both used to cause diabetes (STZ). Furthermore, transgenic dB/dB mice were employed in various researches as a model for diabetes. Full-thickness excisional wounds are created on the dorsal surfaces of pigs, rabbits' ear pinnae, and rodents' dorsal surfaces. The stages of the chronic healing process were imitated using diabetic models. We believe that this approach is sufficient for investigating the healing of small, acute wounds in diabetic animals, but it is inappropriate for researching the healing of bigger, chronic skin ulcers due to the highly different etiologies of the wounds. Furthermore, wounds frequently appeared 1–2 weeks after the diagnosis of hyperglycemia; therefore, diabetes' long-term effects had not yet manifested. Since the causes of the wounds are fundamentally different, we feel that this model is adequate for studying the healing of smaller, acute wounds in diabetic animals but are insufficient for studying the healing of larger, chronic skin ulcers. In addition, the long-term effects of diabetes had not yet appeared, because wounds typically occurred 1–2 weeks after the diagnosis of hyperglycemia [16].

SKINFOLD CHAMBER MODEL

Algire *et al*. created this concept for the 1st time in 1943. The animal's dorsal skin was sandwiched between two coordinating plates. An observation area with a diameter of around 1 cm is located in the center. An ear chamber was positioned beneath the ears and holes were created into the cartilage. This model allows for the investigation of the pathophysiology of microvascular circulation using microscopic and real-time imaging techniques. The disadvantages of this design include the possibility of an animal feeling pain and discomfort when wearing such a device. Other variants with lighter chambers were consequently created [17].

TAPE STRIPPING

A 2 cm^2 area of the mice's dorsal side was covered with adhesive tape seven to 10 times. When the stratum corneum is separated using an adhesive bandage, this is the smallest partial thickness skin wound. The epidermal layer in this model is largely unaffected. However, the stratum corneum layers being removed temporarily reduces the skin's permeability, which may be measured with a specialized probe that measures transepidermal water loss (TEWL). Most studies on skin barrier function use this simple, extremely painless model. In addition to assessing the impact of adhesive wound dressings on the skin barrier, it enables examination of the re-epithelization process component of acute wound healing. In addition to assessing the impact of sticky wound dressings on the skin barrier, it also enables measurement of the re-epithelization process component of acute wound healing. The fact that it only treats small wounds is a drawback. This kind of wound is unexpected since it depends on how sticky the tape is, how much force is used to apply it, and how quickly it is applied. The number of tape strips used and how they are eliminated both have an impact on the wound [18].

BURN WOUND MODEL

Using a metal comb or stainless-steel bar heated to 80–110°C for 20 s, contact burns were applied. *Staphylococcus aureus* was frequently discovered in the wound infection. One of its many advantages was the simple and inexpensive way to burn pigs with a hot comb. It was simple to explore how ischemic tissue quickly transforms into full-thickness necrosis and how burn wounds progress because the comb burn model caused inconsistent harm [19]. A flaw in the gadget was the extremely small surface area that burnt. A steel bar was used as a modification to the comb method to control the burn's depth by pulling on the skin to result in a contact burn. A non-invasive model for controlled burn wound infection has been the infected burn model. It is considered to be a crucial model for evaluating the outcomes of novel antibiotics. By introducing bacterial biofilm, this paradigm could be changed, allowing researchers to examine the impact of various bacterial species on the pathophysiology of the wound. These models can be used to research hypertrophic scarring and evaluate the medical benefits of novel medications [20].

DEAD SPACE MODEL

A polypropylene tube was inserted through the dorsal paravertebral lumbar skin of rats and mice to create dead space wounds. On pigs, incisional wounds with dead space were created by removing a portion of the back muscle. Although it is not beneficial for investigating epithelization, this model can be utilized to examine granuloma tissue because interstitial fluid gathers there and provides information about the wound area [21].

SKIN AGING MODEL

Rodents to age the skin, UVB was introduced to mice for 12 weeks. To evaluate anti-aging medications, this model is adequate. In addition to the high mortality rate from radiation and the requirement for specialized equipment, one of the disadvantages of this model is that rat skin differs from human skin [22].

BLISTER WOUND MODEL

To assess epidermal regeneration and the effects of various chemicals and medications, this model can be applied to both animals and humans.

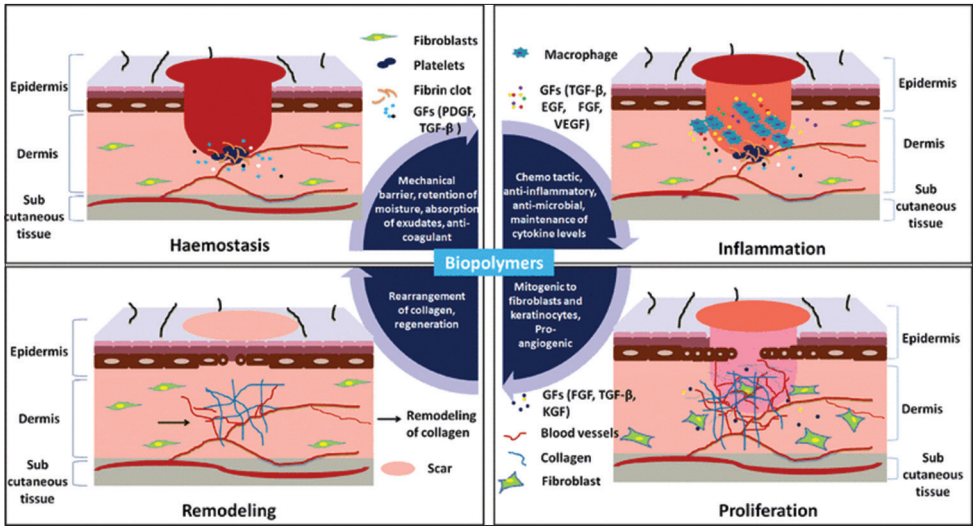


Fig. 1: Physiology of wound

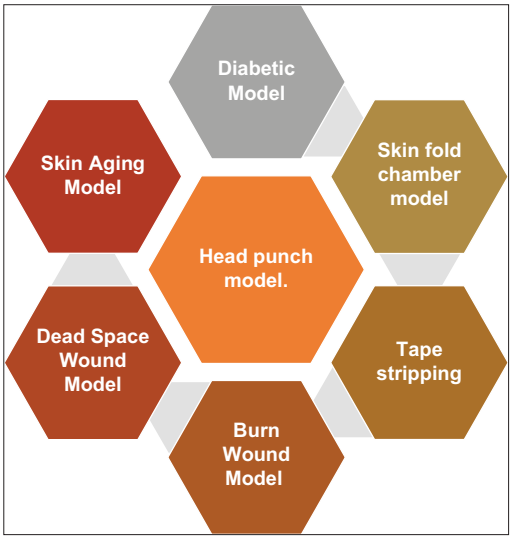


Fig. 2: Models of wound

Blisters, which are blisters, are created by various suction techniques and are small, homogenous epidermal blebs. Transdermal invasion is thereby prevented. It is common for many blisters to form in the same anatomical region or elsewhere on the body. The acanthotic epidermis of the hairless hamster has fully healed 120 h after the suction blisters first appeared. By applying a 20 cm Hg vacuum to a person's midvolar forearms, blisters can be raised. Under these circumstances, normal human skin will start to blister in 35–55 min. The blisters on the roof can, then, be removed using a scalpel blade. Through this process, identical superficial wounds with a consistent depth and equal dimension are produced [12]. This model can be used to conduct a variety of experiments, such as assays for molecular weight or the absorption of medications or substances in various solutions. These findings provide a rapid technique for the short-term distribution of drugs containing peptides and proteins that would otherwise be weakly absorbed [13]. It can be used to passively diffusely test a wide range of medications. In occlusive and semi-occlusive conditions, the absorption impact can be evaluated. TEWL measurements taken every day can be utilized to determine how effective the epidermis is in acting as a barrier [24].

BACK PUNCH MODEL

A full-thickness circular cut is made on the mouse's back to make the easiest back punch model, which is then bandaged. It is simple to inflict two wounds, so the animal can act as its own controller. This model is likely the most popular mouse wound healing model overall. The biggest weakness in this model is how quickly wound healing takes place in the loose skin of the mouse trunk, which might also account for up to 90% of wound healing after an excisional wound. This large contribution to wound contraction makes it difficult to quantify re-epithelialization and granulation tissue formation. The human skin's fascia is linked to it and immobile [25].

TUBE FLAP MODEL

This technique produces a vascularly impaired flap for studying wound healing in challenging environments, much like the TRAM flap model. Angiogenesis, re-epithelialization, wound healing under ischemia, and tensile strength can all be assessed using this model. To create this model, paramedian bi-pedicled skin flaps along the back are first lifted. A cylindrical tube is then used to re-approximate the skin beneath the flap to prevent neovascularization. Wounds could be incised or excised along the tube flap for experimental purposes. The downside of this model is the possibility of ischemia fluctuation [25].

PRESSURE-RELATED WOUNDS

These wounds are expensive for the healthcare system; therefore, any model that can duplicate them would be helpful. In the past, numerous forms of research have used models such as rats, rabbits, guinea pigs, dogs, and pigs. Recently, a number of mouse "pressure" models have been created. By placing a barrier over the muscle and below the wound, one method is to "stretch" the wound. Another inventive option is to apply pressure to the skin with a stainless-steel plate underneath it and a magnet on top. The plate can also be placed underneath the muscle to create a "pressure sore" that resembles the deep wounds of patients. The level of padding used to protect the medial malleolus will affect how much pressure is applied to it and how it will be a serious injury [26].

EXCISIONAL WOUND MODEL

The most prevalent kind of wound model used to study wound healing is one that involves excision. Since it heals differently than human wounds – through constriction of the panniculus carnosus, it is regarded as the least effective type of wound model [27]. Some researchers used a silicon splint in the form of a donut to address the issue of muscular contraction. A whole-thickness wound through the panniculus carnosus was supported by this splint. Because the blood vessels are still present and assist in the healing process, this method focuses on acute wound healing rather than chronic wound healing [28].

INCISIONAL WOUND MODEL

In this model, the animal's skin is cut after anesthesia with anesthetic ether has been administered. On each side of the depilated rat's back, 1.5 cm from the midline, a paravertebral incision measuring 6 cm long was created through the skin and cutaneous muscles. The skin should be held together after the incision has been made and stitched tightly and constantly at intervals of 0.5 cm using suture threads (No. 000) and a curved needle (No. 11). The sutures are to be taken out on day 9, after the wounds have fully healed, and on day 10, using a steady and constant water flow method, the tensile strength of the healed wound will be assessed [29].

PARA BIOSIS MODEL

To permit sharing of blood circulation, Bert initially developed this model in the 1860s. The flank skin of two animals was surgically linked, while the ears of rabbits were joined. The circulating factors that play a significant part in numerous skin and tissue restoration stages were studied as a result of this model. The study of metabolic diseases, cancer metastasis, and immunology all benefit greatly from this paradigm. This model's drawbacks include a higher risk of surgical and post-operative death [30].

MAGNETIC IR INJURY MODEL

We have promoted a multifactorial unified hypothesis for the conceptualization of chronic wounds that take into account cellular aging, local bacterial burden, local tissue hypoxia, and IR injury. The local conditions that are probably present in the skin that has been exposed to IR damage are simulated by this imperfect model. The use of this model is beneficial for researching the pathophysiology of and treatment options for persistent wounds like pressure sores. The mouse's flank, beneath the panniculus carnosus, must have a disc-shaped magnet implanted to create this model. The region of the implanted magnet can subsequently be covered with an external magnet to replicate compressive and ischemia conditions after a few days of recuperation following this small procedure. A reperfusion interval follows the removal of the magnet. It is possible to accurately reproduce practically any ratio of cycles and time intervals. By altering the magnet cycling protocol, the quantity of recurring IR injury that results in wounding and necrosis might be calibrated by the experimental goals [25].

HEAD PUNCH MODEL

Sharp scissors are used to excise a wound down to the crown of the skull and score it with a trephine to create the head punch model. Wound desiccation is avoided by applying a semiocclusive bandage. Depending on the size of the initial wound, full recovery normally takes 8 days. The head punch model's strikes hardly close the wounds due to the skull's splinting effect. Therefore, the main healing mechanisms for such wounds are the development of granulation tissue and re-epithelialization. The two main factors influencing the healing of excisional wounds in people are usefully simulated by this model. Both the dermal and epidermal repair processes can be evaluated using the data collected from these lesions. This model shares many similarities with the rabbit ear dermal ulcer model, in which we have observed to be extremely useful [31].

CONCLUSION

Every pathology includes significant wounds. They are classified based on a variety of variables, including etiologies. The tissue is harmed by some wounds, and the environment is also affected. The wound-healing process can be influenced, and difficulties can be decreased, by management techniques. The biochemical pathways underlying the wound healing process can be studied using wound healing models, which are an effective tool. These mice offer significant possibilities for additional fruitful research. Research into wound healing should benefit from efforts that make use of the right models in a multidisciplinary manner, as well as from the growing availability of genetically modified mice. The researcher must evaluate each model's benefits and shortcomings in the experiment's objectives.

CONFLICTS OF INTEREST

The authors claim to have no conflicting interests.

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