International Journal of Science and Research Archive
eISSN: 2582-8185
Cross Ref DOI: 10.30574/ijsra
Journal homepage: https://ijsra.net/

(REVIEW ARTICLE)

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Skin Necrosis: Pathophysiology and innovations in tissue regeneration

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International Journal of Science and Research Archive, 2024, 13(02), 3106-3114

Publication history: Received on 06 November 2024; revised on 18 December 2024; accepted on 20 December 2024

Article DOI: https://doi.org/10.30574/ijsra.2024.13.2.2514

Abstract

Skin, the largest organ in the human body, serves as a crucial barrier against environmental threats. However, larger skin defects or compromised wound healing can result in persistent wounds, sometimes requiring skin substitutes. Skin tissue engineering aims to create materials that can replace skin functions temporarily or permanently. The skin comprises several tissue types, including epithelial, connective, muscular, nervous, and vascular tissues. Keratinocytes, for instance, undergo a specialized process to form the cornified layer, which differentiates from apoptosis, a type of programmed cell death. Pathogenic processes often involve necrosis, a form of tissue death caused by insufficient blood supply, infections, or trauma. There are various types of necrosis, including coagulation, liquefactive, gangrenous, caseous, fat, and fibrinoid necrosis, each defined by the tissue changes and underlying causes. Necrosis can result from external factors like mechanical trauma, thermal damage, or ischemia, and internal factors such as infection or certain diseases. Necrosis is linked to autoimmune conditions, vascular diseases, and toxic exposures. Risk factors include age, alcohol abuse, infections, and conditions like diabetes and HIV. Treatment for necrosis involves removing dead tissue (debridement), managing infections, and restoring blood flow, often requiring surgery or amputation. Additional treatments like antibiotics, hyperbaric oxygen therapy, and wound dressings support healing. Alternative approaches, including homeopathy and Ayurveda, focus on stimulating natural healing processes through herbs and detoxification.

Keywords: Necrosis; Bromelain; Wound Healing; Skin Substitutes

1. Introduction

The skin, the largest organ in the body, acts as a vital barrier to keep the body safe from the outside world. Despite the tremendous capacity of human skin for self-regeneration, skin defects larger than a specific diameter do not heal on their own and need to be replaced with skin. Furthermore, some patients have compromised wound healing, resulting in persistent wounds that may eventually require amputation or even death [1]. The goal of the rapidly expanding discipline of skin tissue engineering is to create skin substitutes for use in the clinical setting. These skin substitutes are a diverse collection of materials for wound dressings that, depending on the characteristics of the product, can be applied to the wound site to temporarily or permanently replace the functions of the skin [2].

The study of cells and organs is the most frequently included in the word. Tissue is a collection of related cells and their byproducts that share a common function and are specialized in the same way. Organs are constructed using tissues as building blocks. Epithelial, connective, muscular, nervous, and vascular tissues are the five main tissue types that differ in structure and function [3].

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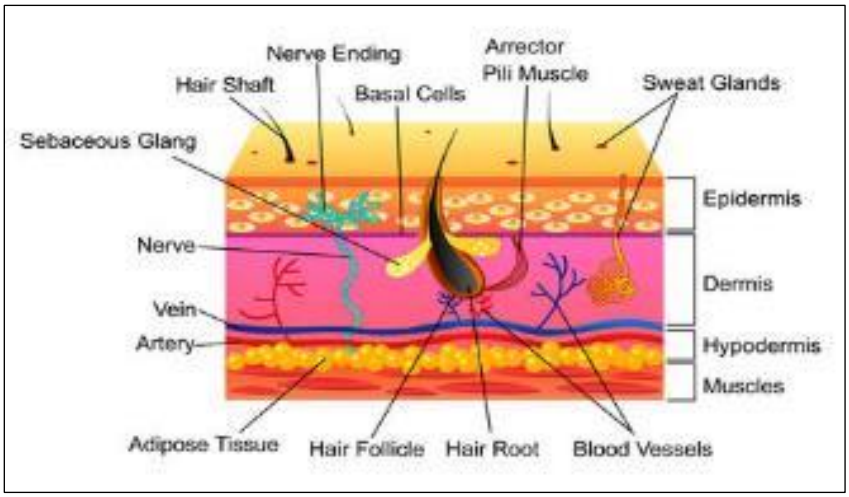

Figure 1 structure of skin

Keratinocytes must undergo a systematic process of cell death to produce cornfield envelopes in the outermost layer of the epidermis. Despite the similarities between this process and apoptosis, these two events can be differentiated from one another, both morphologically and biochemically [4].

The majority of pathogenic processes are based on cell death, which is a crucial component of the plan for controlling healthy tissues. It is possible to identify two main effector pathways involved in cell death. The first, known as necrosis, is linked to triggers such as complement injury, lytic viral infection, and hypoxia, and entails unrepaired damage to the cell membrane. The second process, known as apoptosis, is characterized by noticeable alterations in the nucleus. This kind of mortality happens throughout development, under physiological conditions, in T and natural killer (NK) cell death as well as in reactions to hormonal cues [5].

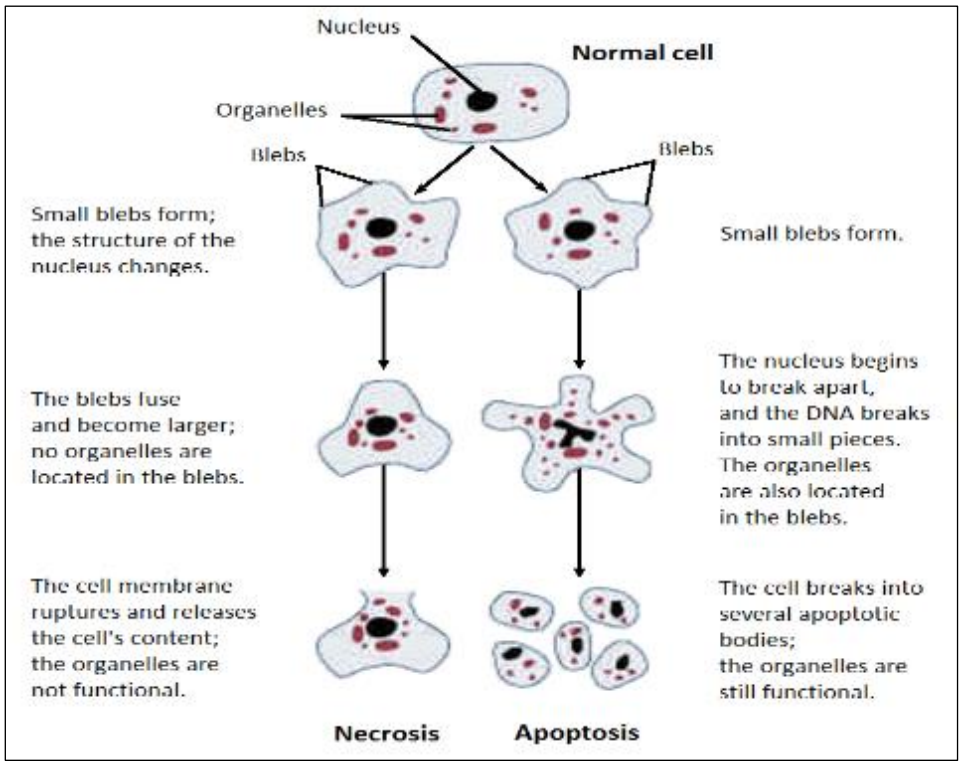

Figure 2 Identification of cell death

When a cell undergoes apoptosis, it is either destroyed by nearby cells or professional phagocytes drawn to the area. Although neutrophils are widely accepted to carry out efferocytosis, their role in eliminating apoptotic cells is thought to be less significant than that of macrophages. Therefore, this neutrophil talent remained unknown for a long period of time. It has been demonstrated In the last ten years that neutrophils play a major role in the removal of apoptotic neutrophils during inflammation, which accumulate in high quantities near the site of tissue damage. [6]

Death of bodily tissues is known as necrosis. When the tissue does not receive enough blood due to conditions such as injury, infection, or chemical exposure, necrotic tissue develops. It is impossible to undo the damage that results. A broad area of necrosis is referred to as "gangrene" [7].

2. Type of necrosis

Since necrosis can affect different parts of the body, such as bone, skin, organs, and other tissues, there are various varieties of necrosis.

2.1. Coagulation necrosis

Light microscopy can be used to study coagulative necrosis, which is defined by the development of a gelatinous (gel-like) material in dead tissues while preserving the tissue architecture. Protein denaturation leads to coagulation, which converts albumin into a solid, opaque state. This necrotic pattern is commonly observed in hypoxic (low-oxygen) conditions, such as infarction. The kidneys, heart, and adrenal glands are among the tissues most commonly affected by coagulative necrosis. This type of necrosis is most frequently caused by severe ischemia [8].

2.2. Liquefactive necrosis

In contrast to coagulative necrosis, liquefactive necrosis (also known as colliquative necrosis) is characterized by the breakdown of dead cells into viscous liquid substances. This is typical of illnesses caused by bacteria or occasionally by fungi because they can induce inflammation. Commonly referred to as pus, necrotic liquid masses are often creamy yellow in color due to the presence of dead leukocytes. Because the brain has minimal connective tissue, hypoxic infarcts manifest as this type of necrosis. Cells can be easily broken down by their own enzymes because the brain has many lipids and digestive enzymes, but little connective tissue. [9]

2.3. Gangrenous necrosis

One type of coagulative necrosis that resembles mummified tissue is gangrenous narcosis. This is typical of ischemia of the stomach and lower limbs. This type of necrosis can result from gas or dry gangrene. Wet gangrene or liquefactive necrosis develops if the dead tissues become infected and overlaid. [10]

2.4. Caseous necrosis

Caseous necrosis is usually caused by mycobacteria (such as tuberculosis), fungi, and certain external substances and is a mix of coagulative and liquefactive necrosis. Similar to clumped cheese, necrotic tissue is white and friable in color. Granular particles remain after dead cells break down but are not fully broken down. Amorphous granular debris encased in a characteristic inflammatory boundary is visible on microscopic inspection. This pattern of necrosis is present in certain granulomas. [11]

2.5. Fat necrosis

The impact of active lipases on fatty tissues, such as the pancreas, causes specialized necrosis of fat tissue known as fat necrosis. By separating triglyceride esters into fatty acids by fat saponification, pancreatic enzymes liquefy the membrane and cause acute pancreatitis, a condition in which the enzymes leak into the peritoneal cavity. A chalky white material may form from the binding of calcium, magnesium, or sodium to these lesions. The calcium deposits are substantial enough to be seen on radiographic examinations and can be recognizable under a microscope. Calcium deposits were visible to the unaided eye as coarse white particles. [12]

2.6. Fibrinoid Necrosis

Necrosis inside the blood vessels is known as fibrinoid necrosis. It is frequently induced by immunological responses that harm blood vessels. Typically it is impossible to observe fibrinoid necrotic tissue with the naked eye. Under a microscope, blood vessel walls exhibit inflammation and the accumulation of a material known as fibrinoid. Fibrinoid necrosis, a unique type of necrosis, is typically caused by vascular injury mediated by the immune system. It is identified

by antigen-antibody complexes, also known as immunological complexes, which are deposited alongside fibrin in arterial walls. [13]

3. Causes of necrosis

3.1. External factors

Mechanical trauma (physical harm to the body that results in cellular disintegration), electric shock, blood vessel damage (which may interfere with the flow of blood to related tissues), and ischemia are examples of external stressors. Necrosis is frequently caused by thermal impact (very high or low temperatures), which disturbs cells, particularly bone cells. [14]

3.2. Internal factors

The following internal elements contribute to necrosis: damage and paralysis of nerve cells and trophoneurotic illnesses (diseases that arise from abnormal nerve action in a region of an organ that leads to a lack of nutrition). Fat necrosis is mostly caused by pancreatic enzymes called lipases. [15]

3.3. Injury

Traumatic injuries have the potential to harm blood vessels and stop blood flow to nearby tissues and bone. Traumatic injuries that cause necrosis can occur from vehicle accidents to falling off a ladder. Necrosis is frequently caused by frostbite, a condition in which the cold severely damages the tissues. If the treatment is delayed, the frostbitten region turns black and dies (gangrene). These necrotic tissues are usually removed via surgical amputation because they cannot be repaired. [16]

Necrosis can also result from the following injuries: Electrical burn, Radiation exposure, chemical burns, traumatic brain damage, and bone fractures

3.4. Infarction

Tissue death from infarction occurs when there is insufficient blood flow to the affected area. A blood clot, such as deep vein thrombosis (DVT), which develops in a blood vessel and stops blood flow to the surrounding area, is frequently the cause of necrosis caused by an infarction. The cells will hunger for oxygen and eventually perish if blood flow is not promptly restored. Although DVT can occur anywhere in the body, it typically affects the legs. If a blood vessel is completely blocked, tissue loss may occur underneath the blockage location. [17]

3.5. Infection

Necrosis can be caused by a broad range of bacterial, viral, fungal, or parasitic illnesses. Necrosis can result even from a small cut or scrape that becomes infected. Necrosis is more frequently caused by the illness type than by others. The most prevalent necrotizing infection is believed to be caused by a bacterium known as Group Streptococcus. [18]

Necrotic tissue can be caused by the following bacteria.[19]

- Species of the genus *Enterococcus*
- *Staphylococcus aureus*
- *Clostridium perfringens*
- Anaerobic, gram-negative bacteria such as *Escherichia coli* and *Bacteroides fragilis*

Viruses that can lead to necrosis include

- Human immunodeficiency virus (HIV) [20]
- Herpes simplex virus type-1 (HSV-1) [21]
- West Nile virus [22]
- Vaccinia virus (related to smallpox) [23]

Necrotic tissue due to infection is most often seen on the extremities, particularly the hands and feet, as well as the genitals. [24]

3.6. Disease Factors

Necrosis has been linked to a number of autoimmune illnesses, the most prevalent of which is systemic lupus erythematosus. Since long-term use of corticosteroids damages bones, it is believed that those who use them to treat their SLE are most at risk. [25]

Necrosis can be brought on by a variety of various illnesses that harm blood vessels and prevent blood from reaching bones and tissues, such as: [26]

- Alcoholic
- Sickle cell disease
- Decompression disease (also called diver's disease)
- Chronic kidney failure
- Cushing's disease, in which the body makes too much of the hormone cortisol
- Gautier disease, a genetic disorder that causes the buildup of fat cells in certain organs

3.7. Toxins

Necrosis is caused by chemical agents, including venom, poisons, and several recreational drugs. Kidney necrosis can result from exposure to arsenic, a metal present in rat poison, and contaminated groundwater. [27] Kidney necrosis is also associated with cocaine, which contains levamisole, which is a white substance. [28]

If not treated immediately, venom injections from brown recluse spider bites may result in necrosis. Necrosis is caused by the bites and stings of many other animals, such as spiders, snakes, scorpions, and jellyfish. [29]

4. Risk factors

As people age, they become more susceptible to issues such as accidents and vascular diseases, which can cause necrosis. Your age is therefore one of the main risk factors for necrosis.[30]

Additionally, alcohol abuse increases the risk of necrotic tissue formation. Alcohol is cytotoxic and therefore damaging to cells. Excessive alcohol consumption can cause liver necrosis and damage to the liver cells. [31]

An open wound, such as an abscess or a surgical incision, increases the risk of infection and necrosis. Insect bites and traumatic injuries are other risk factors for necrosis.

An increased risk of necrosis is associated with long-term corticosteroid use, such as prednisolone. One common side effect of lupus, an autoimmune disease, is necrosis. Individuals who use corticosteroids to manage lupus symptoms are particularly vulnerable. [32]

Other conditions that increase the risk of necrosis include

- Diabetes mellitus
- Vascular disease
- Chronic renal (kidney) failure
- HIV

5. Symptoms

The location of necrotic tissue in the body determines the symptoms of necrosis. For instance, the following are signs of renal necrosis: [33]

Pain in the back or flanks; dark, hazy, or bloody urine

Frequent or painful urination; heavy or frequent nighttime urination

Symptoms of necrosis originating from a wound may include: [34]

- Pain that seems more severe than it should
- Fever (greater than 100.4 degrees) or chills
- Rapid heartbeat (more than 100 beats per minute)
- Numbness or pain extending past the wound
- Rapidly spreading redness from the wound
- Pain and warmth near the wound
- Skin blisters
- A crackling sensation under the skin
- Grayish, smelly liquid draining from the wound
- Difficulty thinking clearly
- Sweating
- If you notice symptoms of necrosis, it is important to seek treatment immediately.

6. Treatment

When there is total obstruction of blood flow, it is frequently painful enough to prompt someone to seek medical attention immediately. Surgery to repair damaged tissues or restore blood flow, debridement, amputation, hyperbaric oxygen therapy, supportive care, advanced therapies, antibiotics to prevent or treat infection, or treatment of burns or other issues that cause the initial damage are some possible forms of treatment. [35]

6.1. Amputation

Surgical debridement or removal of necrotic tissue prevents the spread of infection. Amputation of a limb may also be a part of the treatment. [36]

6.2. Medication

- Allopathic Approach

Modern medicine focuses on removing or repairing dead tissues to prevent infection and promote healing. Common treatments include

- Debridement: Surgical or nonsurgical removal of dead tissue. Types include:
  - Enzymatic debridement: Using topical agents like collagenase to dissolve necrotic tissues.
  - Autolytic debridement: Moist dressings (e.g., hydrocolloid or hydrogels) promote the body's natural enzymes to break down dead tissue. [37]
- Antibiotics: For infections associated with tissue necrosis. [38]
- Hyperbaric Oxygen Therapy (HBOT): Enhances oxygen supply to the affected area to promote healing. [39]
- Skin Grafts or Reconstructive Surgery**:** For significant tissue loss.
- Wound Dressings: Specialized dressings like silver-impregnated dressings for infection control
- Bromelain is used as an enzymatic debriding agent to remove dead tissue in necrotic wound. Its enzymatic activity helps break down protein in necrotic tissue, facilitating wound cleaning and promoting healthy tissue regeneration. [40]

- Homeopathic Approach

Homeopathy emphasizes stimulating the body’s natural healing processes. Remedies may vary based on symptoms and the individual's constitution. Commonly used remedies include:

- Arnica montana: For bruised tissues or to improve circulation in healing areas. [41]
- Calendula: Applied as a cream or taken orally for wound healing and reducing infection risks. [42]
- Silicea: For expelling necrotic material and promoting tissue regeneration.
- Carbo vegetabilis: For cases of tissue damage with poor circulation or oxygen deprivation.
  Homeopathic remedies are usually used alongside traditional wound care techniques.

- Ayurvedic Approach

Ayurveda focuses on detoxification, rejuvenation, and improving circulation to support tissue repair. Treatments include

- Herbal Formulations
  - Manjistha (Rubia cordifolia): Known for blood purification and tissue healing.
  - Neem (Azadirachta indica)**:** Antiseptic properties to prevent infections. [43]
  - Turmeric (Haridra): Anti-inflammatory and wound-healing properties. [44]
- External Therapies
  - Jatyadi Taila: An herbal oil for wound healing and promoting tissue regeneration. [45]
  - Kshara Sutra: A treatment for infected tissues, often in anal fistulas or other small wounds.
- Panchakarma Therapy: Detox procedures like Virechana (purgation) to cleanse the body and support tissue repair. [46]

Diet and Lifestyle: Emphasis on eating nutrient-dense, easily digestible foods to support healing.

Table 1 Comparison of focus

Aspect	**Allopathy**	**Homeopathy**	**Ayurveda**
Primary Goal	Remove necrotic tissue and prevent infection	Stimulate natural healing	Detoxification and tissue rejuvenation
Treatment Nature	Surgical, pharmacological	Noninvasive, remedy-based	Herbal, holistic, detox-focused
Infection Control	Antibiotics, sterilized dressings	Remedies like Calendula	Antiseptic herbs like Neem
Tissue Repair	Surgery, skin grafts	Remedies to promote circulation	Herbal oils and formulations

7. Conclusion

skin tissue engineering aims to develop effective skin substitutes for wound healing, with approaches ranging from allopathic to homeopathic and Ayurvedic treatments. While allopathic medicine focuses on removing necrotic tissue and preventing infections through surgical methods, antibiotics, and advanced therapies, homeopathy promotes natural healing with remedies like Arnica and Calendula. Ayurveda emphasizes holistic healing using herbal formulations, detoxification, and rejuvenation. Integrative therapies offer promising outcomes for complex tissue damage.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclsoed.

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