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Skin Normal and Abnormal Scarring and Tissue Repair

Lucero Carmen Leon Rocha MD

Hospital General de Zona 2A Francisco del Paso y Troncoso, IMSS

ABSTRACT

The skin's primary response to any type of aggression is scarring, a physiological process that aims to restore the skin's integrity. The body's defensive mechanisms against tissue injury include the recovery, regeneration, and healing of tissues with the goal of returning the tissue to its regular anatomical and functional state. The main processes that control the amount and functioning of cell populations in normal tissues are cell proliferation, differentiation, and death. Based on their capacity for cell division, tissues are categorised into three groups, each of which has unique cell characteristics. In order to maintain tissue homeostasis and stop the organ from collapsing as a result of cell loss or absence, guide cells or stem cells are essential. Polypeptide growth factors are an example of a chemical mediator that is crucial in regulating cell differentiation and development.

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BACKGROUND

Skin is a flexible organ. In addition to its defensive and metabolic functions, it also serves aesthetic and social purposes (1, 2). Every form of skin aggression results in "scarring," a remodeling phenomenon whose goal is to accomplish the best possible restoration of the skin's integrity. (3,4)

Recovery, regeneration, and tissue healing are physiological processes that occur in an injured tissue. In response, the tissue activates a number of defense mechanisms to neutralize or contain the aggressor, and once the aggressor has been neutralized, the preparation of functional cells for cell division starts. The major goal of these physiological processes is to restore the tissue to its normal anatomical and functional condition without any side effects or functional loss. The utility of the organ or tissue assaulted may occasionally be threatened by some form of modification brought on by significant morphological and functional losses caused by this physiological process. (5-7)

PHYSIOLOGICAL SCARING

Cell proliferation, differentiation, and death are examples of mechanisms that regulate the number and functionality of cell populations in all tissues of the organism that are in normal physiological states. These mechanisms react to a variety of hormonal physiological stimuli to either inhibit or stimulate their action. (8-11)

The link between cell growth and cell death determines how many cells make up a specific tissue in all multicellular animals. A deviation from any of these mechanisms will result in serious issues. For instance, disorders involving cell accumulation may result in diseases like hyperplasia, cancer, and autoimmune diseases, while disorders involving cell loss may result in symptoms like atrophy, degenerative diseases, AIDS, and other conditions. (12, 13)

Tissues are divided into three types based on how capable they are of proliferating.

1. Continuous or labile: Because of the population's short lifespan, replication for this sort of cell will always be happening. Epithelial and hematopoietic cells are included in this category of cells. (14)
2. Stable or dormant: These populations have a low ability for replication in healthy tissues, but they can multiply in response to tissue damage. Fibroblasts, smooth muscle fibers, and endothelial cells are included in this category. (14)
3. Permanent or without division: These cells have a terminal differentiation, thus since they lack the ability to reproduce, they do not proliferate during postnatal life. Recent research, however, suggests that adult brain neurons, skeletal striated muscle cells, and cardiac muscle cells may all be susceptible to regeneration by stem cells. (14)

GUIDE CELLS

Guide cells, also known as totipotent cells or "stem cells," differ from mature cells in two key ways: first, by their enormous capacity for self-replication and the formation of new guide cells, and second, by their capacity to develop into differentiated and specialized cells for various types of

histological tissues, including muscle, neuronal, cardiac, and other cells, under physiological, pathological, or laboratory-induced conditions. (15-17)

These cells are present at all stages of embryonic development and are dispersed throughout the body in lesser quantities in adults. Adult stem cells lose a considerable amount of their cellular flexibility, which limits the number of cells that they can develop into. On the other hand, multipotential cells will also be noticed; they serve the same purpose as totipotent cells and are more prevalent in the body than the previously stated cells, but they can differentiate into just a small number of cells. Modern medicine has made it feasible to create undifferentiated cells from adult cells with specific functions; this procedure is known as reprogramming. (18-20)

In order to maintain tissue homeostasis and prevent the organ from collapsing due to the absence or loss of cells in its structure, guide cells, as previously noted, have as their primary purpose the generation of mature and specialized cells of the organ in which they exist (15–18).

Because mature cells do not divide but instead just shift from the basal region of the tissue to the most superficial to later desquam, the epithelium is a tissue where cells are constantly lysing and renewing. In order to maintain the tissue's normal functionality and appearance, the stem cells in this tissue will need to continuously make new epithelial cells. (21)

Hepatocytes and biliary epithelium can be formed from the guide cells present in Hering channels in the liver. Hepatocytes, unlike epithelial tissue, have the capacity to divide, and because of this, the liver's guide cells only work when this system is disrupted, keeping the damaged organ functioning and structural and preventing collapse. (22)

Within the head. As was previously noted, neurons are cells that fall under the category of "permanent cells," and as such, lack the ability to divide. In this situation, replacing damaged neurons and integrating them into neural circuits is the role of neuronal stem cells. (23, 24)

In muscle tissue, myocytes are cells that belong to the group of permanent cells and therefore do not replicate. Muscle cell regeneration is mediated by satellite cells, which are a form of multipotential stem cell in muscle. (25, 26)

Chemical mediators control cell differentiation and growth (27, 28), with polypeptide growth factors playing a key role since they promote cell migration and tissue remodeling. Epidermal growth factor (EGF) and transforming growth factor alpha (TGF-a), which are mitogens for epithelial cells, hepatocytes, and fibroblasts and are released by cells involved in inflammation, are among the principal growth factors. (29)

2. Hepatocyte growth factor (HGF), which encourages embryonic development and has mitotic effects on epithelial and hepatocyte cells. Pro-HGF is produced by fibroblasts and endothelial cells in a healthy organism, and serine protease will activate it in the event of damage. (30)

3. Development of the vascular endothelium (VEGF), which plays a major role in angiogenesis during an adult organism's lesion and in vasculogenesis during the embryonic stage. Moreover, it will encourage angiogenesis in tumors, scarring, and persistent inflammations. (31)

4. Platelet-derived growth factor (PDGF), which is essential for angiogenesis and is generated by platelets, endothelial cells, macrophages, and smooth muscle, promotes the movement and proliferation of fibroblasts, monocytes, and smooth muscle cells. (32)

Mediators are categorized into four different sorts of signals since they might originate from nearby or far-off cells (33):

1Autocrine signaling refers to the mediator's action on the secreting cell. This kind of secretion is important for the immune response's cytokine production and compensatory epithelial hyperplasia. (33)

2. Paracrine signaling: Mediators only affect cells that are nearby. This system plays a crucial role in both the normal healing process and the recruitment of inflammatory cells. (33)

3. Synaptic signaling: Via nerve tissue, which might be muscle or other neurons, neurotransmitters are released into target cells. (33)

4. Endocrine signaling: The mediator moves large distances via the circulation to reach its target cell. (33)

TISSUE REPAIR AND SCAR FORMATION

New tissues are created to replace damaged ones during the process of tissue healing, which starts during the stage of active inflammation but is unable to complete due to the presence of unfavorable factors. As long as the tissue's connective tissue or the tissue itself can create cells to replace those lost during damage and inflammation, the tissue can be healed. In order to replace the cells in tissues that are unable to regenerate during scarring, the tissue will have a lymphoproliferative response, whilst extracellular matrix is continuously deposited throughout healing (ECM). If the lesion is left untreated and the inflammation persists, tissue damage and healing will take place at the same time, leading to aberrant ECM deposition and ultimately fibrosis. (34, 35)

As was previously mentioned, the scar results from the deposition of ECM in damaged tissue, which is unable to regenerate on its own. In response to chronic inflammation, parenchymal connective tissue cells will then proliferate and migrate, almost simultaneously forming new blood vessels, and remodel the deposition of tissue by contracting it. (36)

The four stages of scar development are identified in this manner (37, 38):

Phase of inflammation: When an injury occurs, the blood vessels in the affected region break and produced blood components leak out. Vasodilation takes place concurrently, enabling the entry of phagocytic cells to clear injured cells, while proteins including fibronectin, fibrinogen, and growth factors are released, promoting the development and activity of fibroblasts. (37, 38)

Phase of elimination or lysis: During this stage, phagocytic cells remove any cells that have lost function as a result of tissue injury. The use of corticosteroids, immunosuppressants, and antibiotics postpones this period. (37, 38)

Fibroblasts replace destroyed tissue by synthesizing and depositing ECM components, which subsequently develop into a scar made up of fibroblasts and collagen. (37, 38)

Reorganizing unstructured collagen fibers and fewer blood vessels are created during tissue remodeling, which lasts for a protracted period of 6 to 12 months. This process reduces the size of the scar and contracts the wound to increase severity. (37, 38)

Scarring can take one of two forms:

First intention healing. The healing process is quick and extremely successful in tissues with little cell death and little damage to the basement membrane, leading to tissue restoration in 1 to 2 months on average. (39)

Second intention healing takes place in lesions with more severe tissue and structural loss. The inflammatory reaction is more intense, and myofibroblasts contract as they attempt to unite the borders of the incision, giving it a rounded edge. (40)

PATHOLOGICAL SCARRING

Many variables that impact wound healing might result in sequelae and functional loss. Infections are one of the most significant factors since they are the main reason why inflammation lasts longer, potentially worsening local tissue harm. Additional factors may include a rise in local pressure or torsion, which could result in a wound dehiscence; on the other hand, poor blood flow and the presence of foreign substances would prevent healing. These components will produce significant amounts of exudate, which will then be broken down by leukocyte proteolytic enzymes and reabsorbed, allowing the tissue to regain its normal structure in the absence of cell necrosis. (41-43)

The following are the most typical kinds of aberrant scarring (44–46):

scars with hypertrophy: These are elevated, crimson, and lumpy scars. They develop when large amounts of scar tissue form in the vicinity of the incision but do not spread past the site of the initial damage. With time or medical interventions like compression therapy or corticosteroid injections, they might become better. (44-46)

Keloids: Unlike hypertrophic scars, keloids are scars that extend beyond the site of the initial lesion. They are elevated, bumpy, and frequently protrude over the boundaries of the initial incision. Compression treatment, corticosteroid injections, or surgery are all options for treating keloids. (44-46)

Atrophic scars: These thin, sunken scars can appear where acne, chickenpox, or smallpox have injured the skin. Compared to hypertrophic or keloid scars, they are frequently smaller. (44-46)

Scars that are hyper- or hypopigmented (darker or lighter) in comparison to the surrounding skin tone. While hypopigmented scars may be more challenging to cure, hyperpigmented scars can be treated with depigmenting creams or laser therapy. (44-46)

Scars that can produce contractures, or skin that stretches and tightens as a result of the growth of scar tissue, are known as contractile scars. They may be brought on by surgery, severe injuries, or burns. Movement can be hampered by contractile scars, which may need to be treated with surgery or physical therapy. (44-46)

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