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A narrative review of scar formation

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A scar is formed through a process in which the damaged skin, including the epidermis and dermis, is filled with abnormal connective tissue because of an imbalance in the response during the wound-healing process. This review investigates the process of normal wound healing, the molecular and biochemical changes during the process of scar formation, and various factors involved in the formation of scars. Scar formation is influenced by both internal and external factors which are associated with individual characteristics. It is important to have a clear understanding about these factors as they can be possible targets in the development of various scar prevention or treatment options. Also, some of them, especially some of the external factors, are preventable.

Key words: Scar; Hypertrophic scar; Keloid; Wound healing

INTRODUCTION

Wound healing process refers to normal process which occurs after the skin has been cut or damaged. A scar is formed through an imbalanced response during the wound healing process, in which the damaged skin, including the epidermis and dermis, is filled with abnormal connective tissue. Hypertrophic scars and keloids are one of the most common types of scar. Both are thick and raised scar, but hypertrophic scars are contained within the site of injury whereas keloids spread beyond the borders of the initial injury. To understand the formation process of scars, it is necessary to first comprehend the normal pathway of wound healing [1].

The wound healing process generally consists of three phases. The first phase is the inflammatory phase, which typically lasts for about 1-3 days. During this stage, the formation of a blood clot (fibrin) occurs with proliferation of various inflammatory cells such as interleukins. The second phase is the proliferative phase that takes place from day 4 to day 21. During this period, granulation tissue formation and re-epithelialization occur. Several growth factors including platelet-derived growth factor (PDGF) and transforming growth factor (TGF)-β are involved in this phase. The final phase is the remodeling phase, which can last for several months to up to 2 years. This stage is characterized by maturation of the scar with type 3 loose collagen replaced by type 1 collagen, resulting in a stronger collagen layer [2,3].

When the wound healing process occurs normally, it will result in the stabilization of normal fibrous tissue and re-epithelialization without forming scars. However, if there is an abnormal response during the healing process, it can lead to the formation of scars accompanied by abnormal structural changes in the fibrous tissue. In other words, excessive synthesis of collagen and other

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fibrous components caused by disturbances and imbalance in the metabolism of extracellular matrix (ECM) can lead to scar formation rather than their destruction [4]. These processes are summarized in Table 1.

MOLECULAR AND BIOCHEMICAL CHANGES DURING THE PROCESS OF SCAR FORMATION

There are molecular and biochemical differences between normal wound healing in skin and scars. The normal mechanism of wound healing in the skin involves aggregation of platelets and influx of plasma protein fibrinogen from surrounding blood vessels to form a fibrin clot (fibrin clot for hemostasis) and stop bleeding during early stages of wound. Platelet-secreted growth factors such as epidermal growth factor (EGF), insulin-like growth factor-I (IGF-I), PDGF, and TGF-β then induce fibroblast proliferation (Table 2). Additionally, factors such as fibroblastic growth factor (FGF) and vascular endothelial growth factor (VEGF) are secreted to promote neovascularization [5,6].

In this complex process of wound healing, TGF-β plays a crucial role. TGF-β exists in three isoforms: TGF-β1, TGF-β2, and TGF-β3. They share approximately 70%-80% structural similarity. To exert effects on cells, secreted TGF-β homodimer must first binds to TGF-β receptors present on the cell membrane. Following binding, various proteins in the cytoplasm are phosphorylated. Some of these proteins enter the nucleus where they regulate gene expression. The most well-known pathway involved in this process is the SMAD (Sma and Mad related family) pathway.

However, in contrast to the normal wound healing process, abnormal fibroblast expression is observed in scars, which is associated with inflammatory mediators that can stimulate fibroblasts such as VEGF and plasminogen activator inhibitor (PAI)-1. Supporting this, there is evidence that VEGF levels in keloid plasma are abnormally high. Zhang et al. [7] have shown that the average enzyme-linked immunosorbent assay (ELISA)-measured VEGF level is 112.0 pg/ml in keloid patients and 56.48 pg/ml in healthy control plasma.

Furthermore, an abnormal increase in TGF-β signaling involved in inflammatory response of the skin contributes to normal tissue healing. It is considered a major cause of scar formation. Compared to normal skin tissue, scar tissue has relatively high levels of TGF-β1 and TGF-β2 (TGF-β isoforms that promote collagen proliferation). Additionally, it has been reported that expression levels of TGF-β receptors do not decrease but remain sustained during later stages of the wound healing process. A comparative study between animal models of wound healing with and without scars as well as fetal wound healing has revealed that scar-free wound sites in the fetal stage exhibit high levels of TGF-β3 (an isoform that suppresses scar formation) but low levels of TGF-β1 and TGF-β2. Based on these findings, recent clinical trials have been conducted with recombinant TGF-β3 protein, aiming to inhibit scar formation [8,9].

SCAR FORMATION FACTORS

The formation of scars is influenced by both internal factors (such as size, depth, location, and healing duration) related to wound itself and external factors (such as genetics, age, and hormones) associated with individual characteristics (Fig. 1).

Table 1. Normal process of wound healing involves a complex pathway, while the formation of a cutaneous scar involves distinct mechanisms

Inflammatory phase (day 1-3)	Hemostasis clotting pathway: fibrin hemostatic plug Inflammatory cells: neutrophils
Proliferative phase (day 4-21)	Granulation tissue PDGF and TGF-β → fibroblasts to proliferate collagen Re-epithelialization
Remodeling phase (3 wk-2 yr)	The type III collagen (loose) → type I collagen (dense) Parallel bundles & basket-weave of collagen in normal dermis
The end of result	Replacement normal appearing skin Parallel-oriented collagen fibers and normal elasticity
Cutaneous scar formation	Disturbances of the wound-healing phases Depends on the depth of injury (deeper cutaneous injury) By abnormal architecture of collagen (up or down)

PDGF, platelet-derived growth factor; TGF-β, transforming growth factor-β.

Table 2. Key biochemical molecules play crucial roles in the process of wound healing

Molecule	Function
TGF-β1 and TGF-β2	Key in the proliferative phase of wound healing; promote signaling via SMAD
TGF-β3	Receptor antagonist; reduces scarring
PDGF	Secreted by macrophages during the proliferative phase of wound healing and induces fibroblasts to produce type III collagen overexpressed in hypertrophic scars and keloids

TGF, transforming growth factor; PDGF, platelet-derived growth factor.

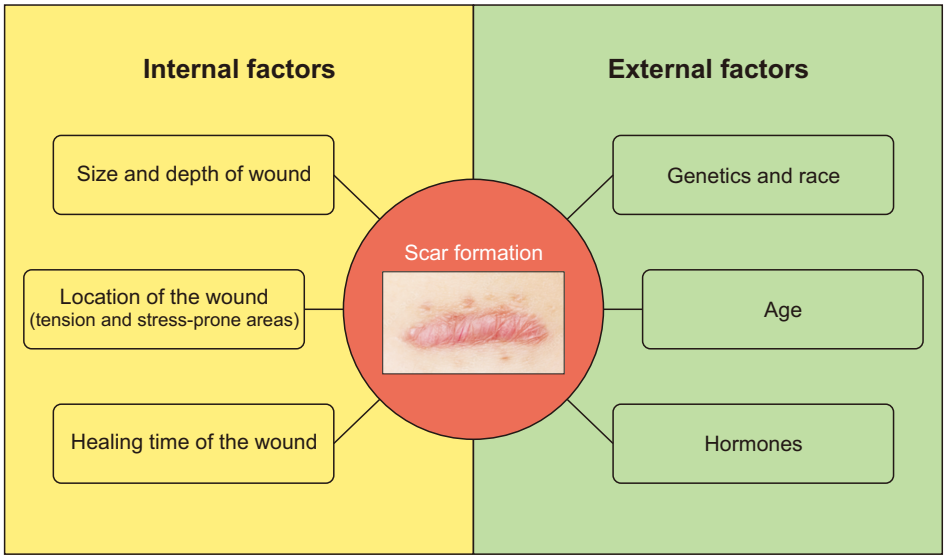

Fig. 1. Various factors are involved in scar formation.

Internal factors

Size and depth of wound

The most significant factors contributing to scar formation are the size and depth of the wound. Larger wounds are more likely to result in scars compared to smaller ones. This is because larger wounds take longer time to heal. They are subjected to increased stress from movement, increasing the likelihood of scar formation. Additionally, if the wound is confined to the epidermis, it generally heals well without scarring. However, when the injury extends beyond the epidermis into the dermis and subcutaneous layers and causes excessive stimulation, it can damage inner walls of blood vessels and trigger secretion of various inflammatory factors, which in turn can lead to collagen remodeling in the dermal layer and facilitate scar formation [10].

Location of the wound (tension and stress-prone areas)

The tension in the wound area significantly affects the amount and characteristics of scar tissue more than any other factors (Table 3). When the wound area is subjected to tension by bending or stretching the body, it can result in delayed wound healing and scar formation. This is because the interaction between local tissue tension and tension generation is crucial. Beyond a certain threshold of tension, fibroblasts can secrete more collagen possibly due to hypoxia. For example, pO_2 is significantly lower in hypertrophic scars caused by burns than in normal epidermis. Therefore, scar formation is more commonly observed in areas where wounds occur in regions with high tension and excessive tension generation, such as the chest or joints, compared to areas with lower tension.

Table 3. Areas with high tension are prone to scar formation

High tension area	Anterior chest, shoulders, neck, pre-sternum, knees, ankles, earlobes, upper arms, and cheeks
Low tension area	Eyelids, genitalia, soles, and palms

Conversely, simply reducing tension in the wound area can lead to improvements in chemical and histological aspects of hypertrophic scar tissue within 14 days [11].

Healing time of the wound

The speed of wound healing is influenced by genetic factors. Faster healing is generally associated with a lower likelihood of scar formation. On the other hand, individuals with conditions such as diabetes or chronic debilitating diseases tend to have slower wound healing, which increases the risk of scar formation. This can be attributed to a compromised healing environment in the wound site, which is more susceptible to infections [12].

External factors

Genetics and race

The occurrence of scars is closely related to genetics. If there is a family history of keloids, there is a higher likelihood of their occurrence. Thus, caution is required during surgery or scar management. The relationship between race and scar formation is also well-known. There are variations in chromosome 7p11 and 2q23 in families with a history of keloids in African and Japanese populations. Additionally, Brown has reported the presence of *HLA-DRB1*15*, *HLA-DQA1*0104*, *DQB1*0501*,

and *DQB1*0503* genes in keloid-prone families of Caucasian descent. There are also reports indicating that keloids are observed in approximately 24% of patients with genetic disorders such as Rubinstein–Taybi syndrome. Furthermore, individuals of Caucasian descent who generally have relatively loose skin tissue tend to develop fewer scars. As a result, keloids are approximately 15 times more common in individuals of African descent compared to Caucasians, while Asians have an intermediate prevalence rate between African and Caucasian populations. Among Asians, those with darker skin (skin types IV-VI) tend to have a higher incidence of scarring compared to individuals with lighter skin tones [13,14].

Age

Generally, scars are more common in younger individuals, typically between ages of 11 and 30 years, than in older adults. This is because as skin ages, collagen formation decreases (resulting in an altered collagen type I:III ratio due to increased type III collagen) and subcutaneous fat diminishes, causing skin to become thinner.

On the other hand, scar formation is very rare in newborns. The relative rarity of scar formation in newborns can be explained by various biochemical changes that occur during wound healing. Firstly, levels of TGF-β family members, specifically TGF-β1 and β2, which are associated with proliferation of fibroblasts, are relatively low in newborns compared to those in adults. Conversely, TGF-β3, which is involved in the inhibition of synthesis of fibroblasts, is relatively high in newborns. This results in less scarring in newborns because excessive action of TGF-β1 and β2 is reduced. Furthermore, the relative ratio of collagen types in the skin differs between newborns and adults. In newborns, the proportion of Type III collagen, which forms thin and loose fibrils, is higher than Type I collagen. Additionally, levels of matrix metalloproteinases (MMPs) involved in collagen degradation are higher in newborns, leading to less scar formation. Increased expression of hyaluronic acid-stimulating activity (HASA) in the ECM layer can also help prevent hardening of fibroblasts, contributing to the inhibition of scar formation (Table 4).

Table 4. Biochemical compositions of the extracellular matrix in terms of fibroblasts that differ between newborns and adults

Higher ratios of TGF-β3 to TGF-β1 and TGF-β2
Higher ratio of type III (loose collagen) to type I collagen (1:1) compared to adult skin (1:4)
Higher ratio of MMP to TIMP (favoring remodeling and less accumulation of collagen)
HASA (found in fetal skin and absent in adult): speeding wound healing and decreased inflammation

TGF, transforming growth factor; MMP, matrix metalloproteinase; TIMP, tissue inhibitors of metalloproteinase; HASA, hyaluronic acid-stimulating activity.

Hormones

One specific type of scar, known as striae distensae or stretch marks, commonly occurs during sudden growth spurts, weight gain, pregnancy, and prolonged use of corticosteroid medications. Apart from mechanical factors that stretch the skin, stretch marks can also be attributed to physiological or iatrogenic (caused by medical treatment such as prolonged use of corticosteroids) reasons. It is believed that an increase in adrenal corticosteroids within the body can lead to breakdown of dermal collagen fibers, resulting in formation of stretch marks.

Furthermore, it is speculated that the occurrence of scars during pregnancy is related to vascular dilation caused by estrogen. In such cases, improvement in scars has been observed after childbirth. The involvement of estrogen in keloid formation is also supported by therapeutic effects of tamoxifen on scars. Tamoxifen competitively binds to estrogen receptors and inhibits estrogen-induced growth. Based on this evidence, it has been reported that administering oral tamoxifen (10 mg, twice daily for two months) to surgical patients after surgery can reduce the incidence of hypertrophic scars from 92% to 52%. Additionally, in patients with keloids, weekly intradermal injections of tamoxifen (20 mmol/L, 0.01 ml/cm^2) for eight weeks have been shown to improve keloid symptoms [15,16].

SCAR PREVENTION IN LIFE CYCLE

Smoking and alcohol

In smokers, cellular inflammatory response during wound healing is delayed. Smoking also promotes blood clot formation through increased platelet aggregation. As a result, it delays wound healing and increases the risk of scarring. Numerous studies have shown that smoking affects all stages of wound healing. Smoking generates excessive levels of reactive oxygen species, increases blood clot formation, inhibits fibroblast migration, and decreases collagen deposition. Therefore, smoking cessation is recommended at least two weeks before surgery. Additionally, alcohol causes dehydration of the skin, leading to impaired remodeling of the ECM and hindered wound healing [17,18]. Moreover, alcohol's vasodilatory effects can sustain the induction of inflammatory cells [19].

Nutrition

Maintaining a balanced diet is important, with particular attention to protein intake. Protein plays a crucial role in forming the framework of newly synthesized skin. Thus, adequate protein consumption is essential. According to recent reports, konjac glucomannan found in *Amorphophallus konjac* can reduce erythema and induration of scars by suppressing neuroinflammation. Additionally, polyphenols in green tea can inhibit fibrosis by blocking cytokine signaling. Omega-3 fatty acids found in fish oil can modify lipid metabolism and reduce fibrosis. However, there have been reports that aglycones in Solanaceae vegetables can not only induce scar inflammation, but also exacerbate induration of scars. Furthermore, spicy foods have been reported to sustain the induction of inflammatory cells through their vasodilatory effects, similar to alcohol. Therefore, caution should be exercised when consuming such foods [20,21].

Endocrine and metabolic disorders

Diabetes and other chronic endocrine disorders can slow down wound healing. In particular, diabetes hinders wound healing because higher blood sugar levels interfere with the healing process. It is important to make efforts to normalize blood sugar levels to promote proper wound healing. Additionally, individuals with conditions such as hypertension and Castleman disease might also experience worsened scar formation. Thus, proper management is necessary [22].

Proper wound care and sun protection

Properly managing the wound site is crucial for preventing infection and promoting scar-free wound healing. Infections can delay wound healing and contribute to scarring. Sun exposure can also delay wound healing due to increased oxidative stress. Therefore, it is important to cover the wound site with clothing or a hat whenever possible. For areas that are difficult to cover physically, applying sunscreen is essential to protect against ultraviolet radiation [23].

Real-life activities

Various lifestyle factors can exacerbate wound and scar inflammation caused by surgery, including intense stretching activities that strain the wound. Therefore, athletes and manual laborers should avoid putting excessive strain on their wounds. Additionally, hot baths can worsen inflammation caused by surgery and exacerbate pain and hypertrophic scars. Thus, caution should be exercised in this regard.

Stress

A person's psychological stress can potentially be a risk factor for scarring. In fact, it has been known that keloids can be triggered or exacerbated by psychological factors. The evidence that stress worsens scarring lies in the fact that the neuroimmune-endocrine system, which is involved in response to stress, can modulate inflammatory metabolism and increase neuroinflammation and neuropeptides such as substance P and calcitonin gene-related peptide. Therefore, proper stress management is important for decreasing the occurrence of scar and preventing scar formation.

CONCLUSION

As mentioned above scar formation is influenced by various internal and external factors. Therefore, it is important to have a clear understanding about these factors because each of these factors can be targets in the development of various scar prevention or treatment options. More importantly, some of these factors are preventable which we can educate the patients to prevent scar formation.

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Conceptualization: KHY, HSH, SYC. Data curation: WSK, YJC. Formal analysis: HSH, KHY. Visualization: WSK, YJC. Writing–original draft: HSH, KHY. Writing– review & editing: all authors.

CONFLICT OF INTEREST

Kwang Ho Yoo is the Editor-in-Chief and Hye Sung Han is an editorial board member of the journal, but they were not involved in the review process of this manuscript. Otherwise, there is no conflict of interest to declare.

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DATA AVAILABILITY

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