African Journal of
Biochemistry and Molecular Biology Research

ISSN : 3434-6120

Index: Harvard, Boston, Sydney University, Dimensions, Lens, ResearchGet Scilit, Semantic, Google Scholar, Base etc

https://doi.org/10.58578/AJBMBR.v1i1.3704

Biochemical Basis of Collagen Defect: Keloids

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Article Info:

Submitted:	Revised:	Accepted:	Published:
Jun 28, 2024	Jul 13, 2024	Jul 26, 2024	Jul 31, 2024

Abstract

Obscure in their genesis, keloids are benign fibro-proliferative disorders. They take place as a result of disturbances in the typical wound healing process in vulnerable people. Transforming Growth Factor beta (TGF-ß) family members have been linked to the pathogenesis of this illness, despite the fact that many other factors have been hypothesized to contribute to its aetiopathogenesis. Finding the right therapeutical notion requires understanding the differences between hypertrophic scars, keloids, and typical scars. Even though keloids are rather common in the general population, the mechanisms that cause keloid formation are still poorly understood. The fact that there are numerous treatment modalities reflects the reality that no single treatment has consistently demonstrated to be highly successful. New pathophysiological theories for keloid formation are revealed by improvements in our understanding of the wound healing process. This review distinguishes between keloids and hypertrophic scars, provides an overview of physiological wound healing, examines current theories for keloid formation, and describes the etiology of scar formation. This knowledge could aid in unraveling the complicated keloid etiology and aid in the creation of a successful treatment approach.

Keywords: Keloids; TGF-ß; Fibroplasia; Extracellular matrix; Tissue inhibitor of metalloproteinase; Plasminogen activator inhibitor

Introduction

The most enormous organ in the human body is the skin. Since it is always in contact with the environment, it may adjust to extrinsic stresses and strains to shield the body's delicate systems from outside influences. After a skin wound, repair mechanisms start immediately and consistently, which can be summed up as the typical healing response that leads to scar formation. When the delicate balance of reparative processes is upset, wound healing can be severely hampered, leading to two pathological extremes: chronic wounds (such as ulcers during head and neck radiotherapy) or excess scar formation, which can range from hypertrophic scars to keloids. Despite numerous analyses highlighting the parallels and discrepancies of scar formation have been published over the past three decades, the precise nomenclature used in these reviews has initially received little attention. The publications by Alster and Williams (Alster and Williams, 1995) and McGrouther (McGrouther, 1994) provide excellent examples of the consequent interchangeability of the words or a dubious advantage of additional distinction. This generalization had resulted in a lack of knowledge on the pathophysiology of various scar forms. The phrases "hypertrophic scar" and "keloid" are still frequently used synonymously, which might result in inaccurate clinical diagnosis and erroneous therapeutical regimens. These structures appear to be unique from one another, nevertheless, based on a number of clinical, pathological, and biochemical variations (Slemp and Kirschner 2006). After skin damage, repair processes must start right away and consistently. This is known as the typical healing response, which causes scarring. The patient who observes the resulting scar from a surgical procedure frequently judges the skill of the physician. In facial plastic surgery, managing scar tissue is crucial (Mustoe *et al.,* 2002). Patients who are not happy with the results request the facial plastic surgeon in the hopes of obtaining a flawless outcome with no residual scar tissue. The facial plastic surgeon faces a twofold challenge: in addition to minimizing the patient's unrealistic expectations, a very challenging tissue needs to be accurately identified and treated using the most promising therapeutic approach. One of the most annoying issues with wound healing is keloidal scarring. Keloids are scars that seldom regress over time and penetrate nearby healthy tissue, according to clinical definitions. They typically don't happen at the extremes of age but rather in people with darker skin who have a familial inclination (Al-Attar, *et al.,* 2006).

Improvements in our knowledge of the similarities and distinctions between keloids and hypertrophic scars may aid in the creation of effective preventative or treatment methods.

According to Rapini *et al.* (2007), a keloid is a type of scar that develops and is primarily made up of either type III (early) or type I (late) collagen, depending on its development. It is also known as a keloid disease and keloidal scar. It happens when collagen type 1 gradually replaces granulation tissue (collagen type 3 overgrowth) at the site of a healed skin injury. The color of keloids can range from red to dark brown, but they are typically firm, rubbery lesions or glossy, fibrous nodules. Although keloid scars are benign and not contagious, they can occasionally cause intense itching, pain, and texture changes (Ogawa, 2010). In extreme circumstances, it may impair skin's ability to move. People of sub-Saharan African heritage in the US experience keloid scarring 15 times more frequently than those of European descent. These elevated scars can appear on both men and women worldwide of African, Asian, or Hispanic origin. However, certain people are more likely to develop a keloid when they scar, including those who have a family history of keloids and those who are between the ages of 10 and 30.

Collagen Defects

Most collagen-related illnesses are caused by nutrient deficiencies or genetic flaws that interfere with collagen biosynthesis, assembly, post-translational modification, secretion, or other activities necessary for proper collagen formation. Twelve of the more than twenty different forms of collagen have each been found to contain 1,000 different mutations. At the tissue level, these mutations can cause a variety of disorders.

Osteogenesis imperfecta – Weak bones and uneven connective tissue are symptoms of this dominant autosomal condition, which is brought on by a mutation in type 1 collagen. Milder instances have lower levels of collagen type 1 whereas severe cases include structural flaws in collagen.

Chondrodysplasias – More study is being done to confirm the theory that a mutation in type 2 collagen is the cause of the skeletal condition.

Ehlers-Danlos Syndrome – There are ten main varieties of this illness, which causes connective tissue abnormalities. Some varieties have the potential to be fatal, causing arteries to burst. Every syndrome has a unique mutation that causes it, such as the mutation in collagen type 3 that causes this disorder's type 4 syndrome.

Alport syndrome – It is a genetic condition that is often X-linked dominant but can also be autosomal dominant or autosomal recessive. Patients may experience issues with their kidneys, eyes, or hearing during their teenage years.

Osteoporosis – Growth hormone injections are being studied as a potential treatment to reverse any collagen loss because it is not inherited genetically, brought on by aging, and linked to lower levels of collagen in the skin and bones.

Knobloch syndrome- Patients with the disorder, which is brought on by a mutation in the collagen XVIII gene and manifests as protrusion of brain tissue and retinal degeneration, are more likely to get it themselves because there is a familial component to the condition.

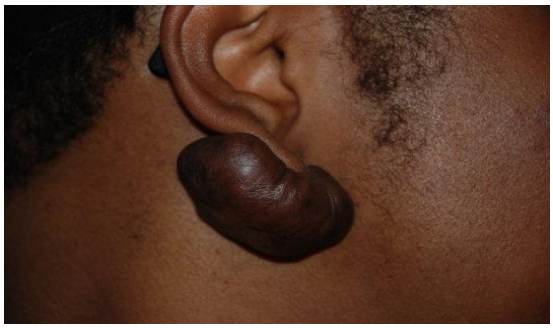
Fibroplasia

This is how fibrous tissue is created as a wound heals. The majority of keloid research focuses on analyzing protein components and signaling pathways that may contribute to the creation of keloid lesions. Every stage of the response cascade has a significant number of cytokines and growth factors associated with it. Numerous cytokines could potentially play a part in the etiology of keloid lesions, based on the diversity. A greater number of growth factors and their receptors are present in keloid fibroblasts. Additionally, keloid fibroblasts also react more quickly to signals induced by growth factors (Slemp *et al.,* 2006). Therefore, growth factors have a significant impact on how matrix production in keloids is disrupted. The growth factors TGF-ß and PDGF are crucial for the physiological healing of wounds. According to Al-Attar *et al.* (2006), both factors exhibit noticeably aberrant activity in keloid fibroblasts. PDGF and TGF-ß both increase ECM formation whereas PDGF also promotes cell migration and proliferation. Other cytokines must also be noted in addition to these two crucial growth factors. Basic fibroblast growth factor (FGF) stimulates angiogenesis, tumor necrosis factor (TGF-) and interleukin-1 enhance inflammation, cell migration, and proliferation. One of the most well researched growth factors, TGF-ß, appears to be the key player in the pathophysiology of excessive scarring, such as that seen in keloids (Border *et al.*, 1994). The production of TGF-ß by neo-vascular endothelial cells is the first step in the onset of a fibrotic reaction in scar tissue. They cause nearby fibroblasts to express more type I and type VI collagen as well as higher levels of TGF-ß (Peltonen *et al.,* 1991). In comparison to normal fibroblasts, keloid fibroblasts are more responsive to TGF-ß activation and respond to a lower factor concentration (Bock *et al.,* 2002). Shah and colleagues used TGF-ß to illustrate its significance. TGF-ß neutralizing antibodies were applied, and the quality of wound healing improved along with the creation of scar tissue (Shah *et al.,* 1995). TGF-ß encourages the growth of fibroblasts and the

production of ECM substances including elastin, fibronectin, and collagen types I and III. TGF-ß indirectly stimulates matrix development by inducing PDGF. In the final stages of wound healing, PDGF has been demonstrated to accelerate the creation of granulation tissue and to stimulate the production of collagen (Niessen *et al.*, 1999). In comparison to normal skin fibroblasts, keloid fibroblasts also have a greater reactivity to PDGF (Haisa *et al.,* 1994). The growth factors TGF-ß and PDGF were therefore found to have markedly aberrant activity in keloidal tissue (Al-Attar *et al.*, 2006). Keloid fibroblasts exhibit higher transcription of the relevant receptors in addition to enhanced cytokine production (Butler *et al.,* 2008). Different TGF-ß isoforms are expressed during keloid development and during the natural healing of skin wounds. TGF-ß3 appears to prevent fibrotic reactions, whereas TGF-ß1 and -ß2 are known to exhibit profibrotic features (Bock *et al.,* 2005). A multitude of different cells produce TGF-ß. Thrombocytes have the highest concentrations.

Keloids

Keloids are aberrant elevated scars that are only found in humans and are caused by an overabundance of collagen being deposited in the dermis and subcutaneous tissues as a result of trauma or surgical injuries. Clinical keloids are described as dermal fibro-proliferative tumors that seldom regress over time and spread beyond the boundaries of initial wounds (Bayat *et al.*, 2003).



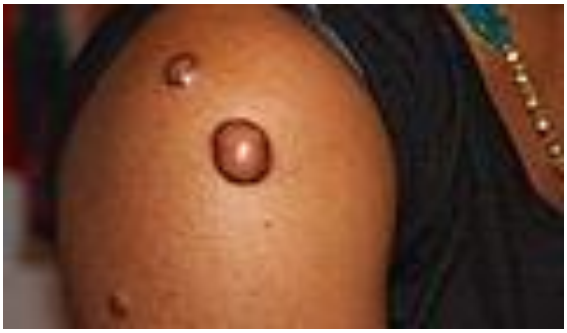


Figure 1. a. Earlobe keloid **b. Keloid nodules**

Components of Keloids

The analysis of keloid tissue using electron microscopy revealed that the extracellular matrix of connective tissue made up the majority of the keloid. Biochemical evaluations of

keloid specimens provided the following quantitative results: Significantly greater water content. Desmosine and uronic acid tests revealed that the amounts of elastin and glycosaminoglycans were significantly higher in keloids (a minor fraction).Based on the hydroxyproline assay, the relative collagen concentrations showed that this protein made up the majority of the keloid (around 60% of the dry weight of the tissue).When collagen composition was compared to genetically distinct collagen types, it was discovered that type I collagen concentration was much higher in keloid tissues while type III collagen concentration was lower (Gauglitz *et al.,* 2011).

Histopathology

According to Gauglitz *et al.* (2011), keloid histology is characterized by a thicker epidermal layer than normal skin, extensive vasculature, a thicker dermis, and a greater number of inflammatory cells than normal or undamaged skin. In healthy skin, collagen fibers are loose and dispersed at random (Chung *et al*., 2001); however, collagen fibers are thicker and more numerous in keloid tissue (Lavker *et al.,* 1998). Additionally, the ECM frequently exhibits an excess of proteoglycan deposition in keloids. According to Butler *et al.* (2008), the reticular dermis is characterized by the deposition of substantial volumes of fibrous bands. Despite the exact mechanism causing KS to develop has not yet been identified, it has been suggested that KS develops as a result of a number of deregulations occurring simultaneously during the normal healing process (Davidson *et al.,* 2009). The normal healing of scars may be hampered by factors like environmental variables, ethnic variations, anatomical sites, skin tension, hormonal factors, genetic predisposition, and prolonged healing phases, among other causes (Brown *et al.,* 2009). The variation shown among the many anatomical regions is one of the unique characteristics of KS (Clark, *et al*., 2009). On the areas with higher skin tension, KS are more likely to appear and grow more aggressively and repeatedly (Suarez, *et al.,* 2013). According to Alenghat *et al.* (2002), keloids are thought to be the result of an inability to control and stop the wound healing process, which is fueled by excessive fibroblast activation and supported by the strain created by natural body movements on the skin. According to Wong *et al.* (2011), skin tension during the keloid development and progression promotes abnormal cell signaling transduction.

Signs and symptoms of Kelloids

A keloid is a thick, fibrous tissue development that protrudes past the lines of the initial lesion. A hypertrophic scar, on the other hand, is normally limited to the borders of the original wound and tends to flatten over time. Keloids are commonly itchy, uncomfortable, elevated, firm, and do not typically spontaneously regress. Lee et al. discovered that 86% and 46%, respectively, of patients who had 28 keloid patients had concomitant pruritus and pain.13 Keloids are typically erythematous and telangiectatic in Caucasian patients, although they are frequently hyperpigmented in those with darker skin tones. The chest, shoulders, upper back, posterior neck, and earlobes are the areas where keloids most frequently develop.19 Ramakrishnan et al. discovered that 34% (336 of 1000) of the keloids in the study population occurred in the parasternal area in a retrospective analysis of 1000 keloid patients during an 8-year period. The deltoids (17%), upper limbs (13%), lower limbs (10%), and ears (9%) were additional frequent locations. Although the cause of this site-specificity is unknown, it is widely acknowledged that keloids frequently develop in regions of high skin tension and mechanical stress. Two exceptions to this notion, including keloids on the earlobe, point to other causes. We postulate that keloids develop in areas of low tension as a result of trapped dermal components proliferating in susceptible people following injury.

Scar classification

By considering the dynamic equilibrium during the creation of the scar and the tissue regeneration, abnormal scars can be categorized. The following scar type spectrum is also produced by additional elements, including the type of injury, its severity, depth, anatomical location, tensional stress, infection, environmental factors, genetic predisposition, sex, and hormone levels (Bayat *et al.*, 2003).

Widespread scars or stretched scars: Blemishes that develop following surgery when the original thin lines that make up the scar progressively extend and widen. Three to four weeks following surgery, stretched scars frequently appear. These scars are typically found on the shoulders and knees and are flat, pale, and delicate. Stretch marks are viewed as a variant of common scars in which the dermis is fractured but the epidermal layer is unaffected (Bayat *et al.,* 2003).

Atrophic scars: Flattened, depressed scars surrounded by healthy skin. Acne or smallpox can cause atrophic scars, which are depicted as small, circular forms with inverted centers (TSAO, *et al.,* 2002).

Scar contractures: Each area of the body that experiences contraction, such as joints or skin crevasses, develops scar contracture. When the wounds are still young, one can see these scars. Scar contractures frequently turn into hypertrophic scars over time. Scar contractures are typically the result of burn injuries and can be severely debilitating for the patients (Bayat *et al*., 2003).

Raised dermal scars: A variety of reasons, including weak scarring mechanisms, can result in raised scars. These scars are noticeable, thick, and occasionally unpleasant and irritating. Keloid scars and hypertrophic scars are two types of raised scars that develop within the borders of the wound (Bayat *et al.,* 2003).

Hypertrophic scars: Raised, erythematous, pruritic, and fibrous scars that are still contained within the original lesion's borders and may spontaneously disappear. Dermal layer destruction is a common feature of these kinds of scars (Berman *et al*., 1988).

Keloid scars

Keloid scars (KS) are elevated, fibrous scars that extend past the edges of the original lesion. They are characterized by unchecked collagen synthesis and deposition. These scars encroach on the nearby healthy skin and do not naturally disappear over time (Marneros *et al.,* 2004). The term "cheloid," which comes from the Greek words "Chele" (crab's claw) and "oid" (like), was first used to characterize keloids as a cutaneous illness in 1802 by Alibert, who described them as crab claw-like lesions (Seifert, *et al.,* 2009). The patient's quality of life degrades with time as a result of KS. According to Wong *et al.* (2011), keloids can disable or alter normal movement by affecting aspects including the biomechanical qualities of the location. In keloid patients, aesthetic changes are also common; the skin's natural suppleness is altered, leaving patients with sparse, glassy skin that lacks hair follicles (Bayat *et al.,* 2005). The patients' lifestyle can also be compromised by psychological and social effects, which frequently include depression, anxiety, post-traumatic stress disorder, sleep disturbance, disability, loss of self-esteem, and stigmatization (Butler *et al.,* 2008).

Keloid Development

The failure of the body to maintain the balance between the healing phases and being able to terminate the process is one of several variables that have been put forth to explain the development of keloid scars (Seifert, *et al.*, 2009). While some studies argue that a greater granulation stage is the primary cause of keloid formation, others contend that an aberrant modulation of the inflammatory phase is to blame. However, until now, there hasn't been any solid proof that adequately explains the illness (Shih *et al.*, 2009).

A large variety of compounds, including growth factors, cytokines, and ECM components, are released during the inflammatory stage of wound healing. According to some research, these factors encourage cellular proliferation and excessive ECM deposition, which results in a lack of control during the inflammatory stage and ultimately leads to the development of KS (Seifert *et al.*, 2009). After conducting a thorough literature analysis, Shih *et al.* 2009 provided a list of molecules that exhibit noticeably different expression patterns between healthy wound healing and KS (Shih, *et al.*, 2010). TGF-1, TGF-2, TNF-, and IL-6 were among those with increased expressions in keloids. In keloid samples, it was also discovered that growth factors such EGF, PDGF, PDGF-receptors, VEGF, CTGF, and IGF-I-receptor were up-regulated. Additionally, keloids expressed more metalloproteinases (MMP-1, 2, 3, 13 and 19), histamine, p53, PAI-1, and p53 than normal scars did. Cellular functions such ECM synthesis and deposition, cell recruitment, proliferation, and migration, re-epithelialization, and a delay in granulation tissue formation are modulated by signaling pathways involving the substances indicated above (Wolfram *et al.*, 2009).

Growth factors including VEGF, PDGF- and CTGF seem to be expressed more when granulation tissue is forming in keloids (Robles *et al.,* 2007). According to reports, the expression of these factors is tightly correlated with the expression of the TGF-family (Abdou, 2011). These elements work together to control, among other things, the production of collagen I and III, neovascularization, and cell migration. When KS scars are compared to typical scars, an increase in collagen I and III concentration is usually observed (Bayat *et al.,* 2004).

In addition, it has been demonstrated that whereas the equilibrium is lost in keloids, there is a well-regulated generation and degradation of ECM components during the last stage of wound healing, allowing scar development. Reduced collagen fiber degradation is seen in keloid fibroblasts. While keloid illness appears to display low apoptotic ratios, a factor that

may contribute to produce the imbalance between the ECM synthesis and breakdown, apoptosis is also crucial during the ultimate healing stage, generating scar tissue devoid of cells and vascularity (Lu, *et al.,* 2007).

Concepts of pathogenesis

The two main causes of keloid formation are generally agreed to be genetic predisposition and skin lesions. Although clinical observations proved the aforementioned variables to be the widely acknowledged key requirements for keloids, in-depth understanding of the pathophysiological backdrop is rare, and the most crucial question is still unsolved. What is the primary stimulation that starts the chain of actions leading to the creation of keloids? The stimulus changes or remains constant. The theories that have been put up to explain the keloid phenomenon are included in the next part, along with aspects that may have an effect on the pathophysiology of keloid formation but have not yet been officially authorized.

Genetics and immunology. According to predictions, keloids affect Caucasians less frequently than Blacks, Hispanics, and Orientals (15–20%). The darker skinned appear to have a hereditary tendency to keloid formation (Robles, *et al.,* 2007). Albinos have not yet shown signs of keloid development, according to Baisch *et al.* (2006). Melanocytes might be crucial in the development of keloid lesions, although more research is needed. Although a favorable family history is not exceptional, the majority of instances are sporadic (Bayat *et al.*, 2003). To pinpoint the chromosomal position of the predisposing gene, linkage analyses were carried out. No particular gene has been connected to the growth of keloids up to this point. Researchers Marneros and colleagues looked examined keloids in families with an autosomal dominant inheritance pattern. First-ever proof of keloid susceptibility loci on chromosomes 2q23 and 7p11 was obtained by gene scans (Marneros *et al.,* 2004). A polygenic inheritance pattern is suggested by inherited tendencies. According to a study of 175 Malaysian keloid patients, darker skin tone does not, however, correspond with a higher rate of keloid formation (Al-Attar *et al.,* 2006). It is thought that the human HLA status can influence how keloid phenotypes develop. According to preliminary research, the HLA-DR5, HLADQw3, DQA1, and DQB1 types are associated with keloid formation (Lu et al., 2008). In Caucasian patients, a number of gene polymorphisms encoding for TGF-ßsubtypes ß-1, ß-2, and ß-3 as well as the TGF-ß-receptor have been examined, but

no evidence of statistically significant relationships with keloids has been found (Bayat *et al.,* 2002). According to Robles *et al.* (2007), it is likely that many genes contribute to keloid susceptibility, with various genes contributing to keloid formation in different families. A new understanding of keloid etiology was gained through the simultaneous investigation of many genes. Thus, higher levels of fibronectin and the type I collagen protein -1 chain were discovered, both of which are frequently linked to poor wound healing. The tumor suppressor gene p53 was not expressed in keloid fibroblasts, despite elevated levels of the proto-oncogenes bcl-2, c-jun, and c-fos being present in healthy skin fibroblasts (Teofoli *et al.,* 1999). When compared to normal and hypertrophic scars, keloids have the highest level of p53 (Tanaka *et al*., 2004). Keloid disease may be related to the two oncogenes ribosomal protein 18 and Stat-3, both essential proteins for cell proliferation (Satish, *et al*., 2006).

Dysregulation of apoptosis may be a significant contributing element to the development of keloid lesions (Luo *et al*., 2001). The hypertrophic and progressive nature of keloids may stem from keloid fibroblasts failing to go through physiologically scheduled cell death and continuing to create and secrete connective tissue over the time frame anticipated in normal scar formation (Sayah, *et al.,* 1999). According to Messadi *et al.* (1999), keloid fibroblast cultures exhibit a 2-fold higher percentage of apoptotic cells than normal skin fibroblast cultures. Additionally, keloid fibroblasts have dramatically lower expression of apoptosis-related genes, such as DAD-1 (defender against cell death 1) or TRADD (TNF R-1 associated death domain) (Sayah *et al.,* 1999). Apoptosis-inducing genes like ADAM12 and genes that cause extracellular matrix degradation like matrix metalloproteinase-19 were upregulated in the regressing keloid center, whereas Seifert et al discovered an upregulation of the apoptosis inhibitor AVEN at the margin of keloids (Seifert, *et al*., 2008). According to Al-Attar *et al.* (2006), some human leukocyte subtypes are linked to keloids. Another viewpoint on the pathophysiology of keloid formation is provided by an inherited aberrant immune response to skin damage. An immunological phenotype may be used to direct a genetic effect. Multiple research teams have reported immunological changes. Patients who develop keloids had higher serum concentrations of the immunoglobulins IgG, IgA, and IgM than those with healthy skin, as well as a higher prevalence of allergic diathesis (Al-Attar, *et al*., 2006). Numerous studies have discovered patterns in the concentrations of immunoglobulin G and M as well as serum complement in keloid-forming patients (Bloch *et al.,* 1984). According to clinical data (Al-Attar *et al.,* 2006), persons with keloid lesions have an innately hypersensitive cell-mediated immune system. Appleton and colleagues

discovered a large number of apoptotic cells at the dermis and keloids interface, a signature of cell-mediated immune attack, in agreement with the immune-response theory (Appleton *et al*., 1996). According to Placick *et al.* (1992), the implications range from a local immune response to an autoimmune connective tissue disease. The marker cells during the inflammatory stage of physiological wound healing include neutrophils and mast cells. It's interesting to note that higher mast cell densities are frequently found in fibrotic lesions (Diegelmann *et al.,* 2004). Interleukins and TGF-ß in particular increase mast cell chemotaxis and collagen fibroblast synthesis when cytokines are released. The pilosebaceous unit is exposed to systemic circulation as a result of skin injury, and in sensitive people, this stimulation causes T-lymphocyte identification and the proliferation of antigen-specific T-lymphocytes, which is akin to a delayed-type hypersensitivity reaction (Abbas *et al*., 1994). As the keloid growths and further pilosebaceous units on the advancing boundary are disturbed, this process proceeds (Fong *et al*., 2002). Memory cells emerge and greater secondary immune responses are triggered. The sebum hypothesis describes how keloids appear and behave. Animals lack sebaceous glands comparable to those seen on humans, hence keloids only affect humans. Since the palms and soles lack sebaceous glands, they do not develop there. When sebum production is at its peak in adolescence and early adulthood, keloids develop (Fong *et al*., 2002). A sebum vaccination can successfully desensitize the antigens from keloid recurrence following excision in patients with keloids who exhibit a positive skin reaction to intradermal sebum antigen.

Causes of Kelloids

Skin lesion: It is commonly acknowledged that skin damage or inflammation cause keloids to form. The majority of times, keloids develop during the surgical or non-surgical healing of a wound. They may also develop as a result of mild skin trauma, such as a mosquito bite or a vaccine, or inflammatory skin disorders, such as varicella infection, folliculitis, or acne vulgaris (Bock *et al*., 2006). Patients occasionally forget the trauma or inflammatory process that caused them. As the perniciousness of keloidal pathology may be their appearance after a protracted, uneventful period, the causal event may be undetected or forgotten. Mechanical strain builds up within the constricting wound site during physiological wound healing. According to Sussmann *et al.* (1996), locations of elevated stress (such as the chest, deltoid, and back) are known to be sites of keloid predisposition. Mechanical tension on a

healing wound stimulates fibroblast proliferation and increases the synthesis and deposition of collagen. In contrast to the elderly, whose skin often has low tension, keloids are more common in young people due to skin tension (Fong *et al.,* 2002). After auto-transplanting keloids to the anterior abdominal wall, a place of low wound tension, Calnan and Copenhagen found a regression of keloid tissue (Calnan *et al.,* 1967). Studies conducted in vitro and in vivo indicate that mechanical strain influences collagen architecture, orientation, and dermal remodeling in addition to promoting collagen synthesis. Collagen's physiological orientation runs counterclockwise to the direction of muscle contraction. Therefore, incisions made parallel to the lines of relaxed skin tension and perpendicular to muscle contraction will heal with little to no collagen distortion, whereas scars placed at sites of high tension (such as flexor surfaces) or non-aligned tension forces caused by poor incision line selection will almost certainly lead to the formation of pathologic scars (Slemp *et al*., 2006). Wang *et al*., 2006 evaluated the results of mechanically stressed normal and keloid fibroblasts. In keloid fibroblasts, they noticed elevated expression of TGF-ß1, -ß2, and collagen I. In addition, there was a correlation between higher focal adhesion kinase activation and an increase in the production of focal adhesion complexes (Wang *et al.,* 2006). However, there are some locations where keloid formation occurs often that are not typically thought to be in a stressed state (such as the chest or earlobe). Stretch and strain are significant factors in the ultimate appearance of the scar, however they are more likely to contribute to the development of hypertrophic scars than keloid lesions (Slemp *et al.,* 2006).

Extracellular matrix. The extracellular matrix (ECM) is crucial to both the proper physiology of skin and the responses that lead to wound healing. The fibroblast, which makes up the majority of scar tissue, is responsible for producing collagen as well as other extracellular matrix elements and remodeling-related enzymes. The sticky contact of connective tissue cells with their surrounding ECM regulates cellular gene expression. Integrin receptors create the connection between fibroblasts and the surrounding ECM (Eckes *et al*., 2000). Cytokines like TGF-ß can alter the expression of integrins. The integrins 1ß1, 2ß1, and 3ß1 are known to bind to collagen, with some members, such as laminin (1ß1) and fibronectin (3ß1), also exhibiting binding to other ECM elements. Following the addition of TGF-ß1 to cultures of keloid fibroblasts, Fujiwara *et al.* (2005) detected an increase in the synthesis of MMP-1 and -2 but no effect on TIMP-1. Further research is needed to determine how TGF-ß affects the expression of MMPs in keloid

fibroblasts, as current advances in molecular treatment offer promising potential for the control of matrix turnover.

Phases of wound healing

Clarifying the molecular variations in the pathophysiology of scar tissue formation requires an understanding of the fundamental concepts of wound healing. According to Baisch *et al.* (2006), a wound is defined as a disturbance of anatomical structure that interferes with its normal function. The restoration of anatomical continuity and function is the end outcome of healing, which is a dynamic and complex process (Lazarus *et al.,* 1994). According to Diegelmann *et al.* (2004), skin injury sets off a highly complicated chain of local and systemic events that occur in a precise order and can be divided into four phases: hemostasis, inflammation, proliferation, and remodeling. Scarring is a typical side effect of the healing process. However, when reparative processes are out of balance, wound healing can be severely hampered, leading to one of two pathological extremes: inadequate healing that results in chronic wounds (such as ulcers brought on by head and neck radiotherapy) or excessive healing that results in an excess buildup of connective tissue (such as hypertrophic scars or keloids).

As soon as the skin is wounded, the healing process starts. Blood components pour into the wound site during bleeding. Collagen that has been exposed and other components of the extracellular matrix come into touch with platelets. This interaction causes the release of critical growth factors, including platelet-derived growth factor (PDGF) and transforming growth factor ß (TGF-ß), and clotting factors start the healing process. Clotting is necessary to achieve hemostasis, which is the initial response that starts the first stage of wound healing. As a result, a fibrin clot forms at the location of the injury, acting as a temporary matrix for subsequent healing processes. The two most significant cytokines that start new steps in the healing cascade are the aforementioned growth factors. Neutrophils, macrophages, smooth muscle cells, and fibroblasts are all induced to chemotaxis by PDGF. Additionally, it promotes fibroblast and smooth muscle cell mitogenesis. TGF-ß draws macrophages and encourages the release of more cytokines from them. Additionally, it modifies the production of collagen and collagenase and improves chemotaxis in smooth muscle cells and fibroblasts (Diegelmann *et al.,* 2004). The proliferative phase, which comes after the inflammatory phase, is when this signaling's

effects can be most clearly seen, according to the overlap concept of wound healing phases. Within 24 hours of injury, neutrophils penetrate the wound site and use phagocytosis to remove foreign objects, pathogens, dysfunctional host cells, and damaged matrix components, which increases inflammation (Thurston, 2000). (Baisch, *et al.,* 2006) state that this period can extend up to 8 days. Mast cells are another hallmark cell during this stage in addition to neutrophils. They cause the classic indications of inflammation surrounding a wound site (rubor, calor, tumor, dolor, and subsequently functio laesa) by releasing enzymes, histamine, and other active amines. It's interesting to note that higher mast cell densities are frequently found in fibrotic lesions (Diegelmann *et al.,* 2004). Monocytes are stimulated to become wound macrophages 48 hours after damage. The most crucial inflammatory cells involved in the typical healing response are thought to be these cells. Their presence indicates that the inflammatory phase is about to stop and the proliferative phase is about to begin (Diegelmann *et al.,* 1981). The healing response is delayed when macrophage function is inhibited. Continued phagocytosis by macrophages along with the production of PDGF and TGF-ß help draw fibroblast and smooth muscle cells to the wound site. After the wound site has been cleaned, the proliferative phase starts with fibroblast migration and the deposition of fresh extracellular matrix, which is required to restore the wounded tissue's structure and function. The coordinated production of TGF-ß by several cell groups develops into the master control signal that controls a wide range of fibroblast functions as the proliferative phase moves along (Philipp *et al.,* 2004).

Fibroblasts are the main cells connecting to the temporary fibrin matrix after proliferation and collagen deposition during the proliferative phase (from day 8 to day 14 after skin damage) (Clark, 2001). The formation of collagen is crucial because it strengthens the wound. Collagenases and other elements break down collagen as it is produced. The level of production first outpaces the rate of decay, but eventually a homeostasis is achieved. The next phase begins when collagen production and breakdown are in balance.

Growth factors encourage fibroblasts to develop into myofibroblasts, which resemble smooth muscle cells and are in charge of contracting wounds. The borders of the wound are drawn together when the myofibroblasts contract, which reduces the size of the wound and increases tensile strength in the wound region (Lorenz *et al.,* 2008). Collagen that has been deposited helps to support the healing wound. Myofibroblasts cease to function and undergo apoptosis at the conclusion of contraction (Mercandetti *et al.,* 2008).

Fibroblasts are forced to stop migrating and multiplying as a result of the concurrent disintegration of the temporary matrix. The maturation and remodeling period starts. Depending on the original size of the wound and whether it was closed or left open, the maturation phase may span a year or longer (Hinz, 2008). Type III collagen, which predominated in the proliferation phase, is broken down and replaced by type I collagen, which is more robust, during this phase. Newly produced collagen fibers are smaller and seem more haphazardly than collagen in healthy tissue. Initial tension lines are followed by rearranging, cross-linking, and alignment of disordered collagen fibers (Lorenz *et al.,* 2008). As a result, the wound's tensile strength rises. The high degree of organization of normal dermal architecture, however, can never return to a mature scar, therefore scar tissue is always weaker than the surrounding normal tissue, with a maximum tensile strength of about 80% of normal skin (Burd, *et al.,* 2005). At the conclusion of maturation, blood vessels are eliminated by apoptosis, activity at the wound site decreases, and the scar loses its erythematous look (Lorenz, *et al.,* 2008). Growth factors and other cytokines have a major role in determining the order and intensity of each healing phase (Gillitzer *et al.,* 2001). An effective approach for examining differential gene expression in diseased scar tissue, unharmed skin, or normal scars is the application of cDNA microarray analysis. In addition to identifying novel or different molecules that are crucial to scar pathophysiology, the resulting large-scale evaluation may also pinpoint when these molecules are essential to the overlapping phases of wound healing indicated above (Cole, *et al.,* 2001). The new information acquired here may pave the way for intriguing ideas of genetic therapies that mimic or improve physiological systems to speed up wound healing under challenging skin wounding settings.

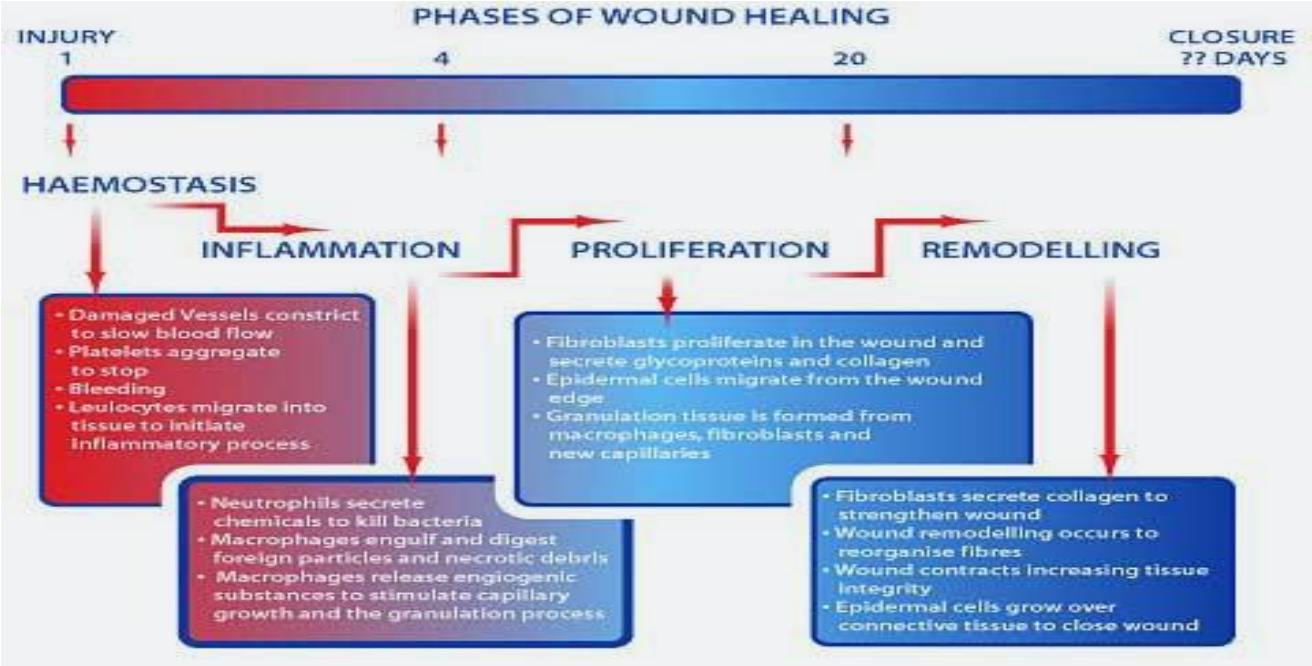


Figure 1. Sequence of events during physiological wound healing

Molecular mechanism of normal injury repair

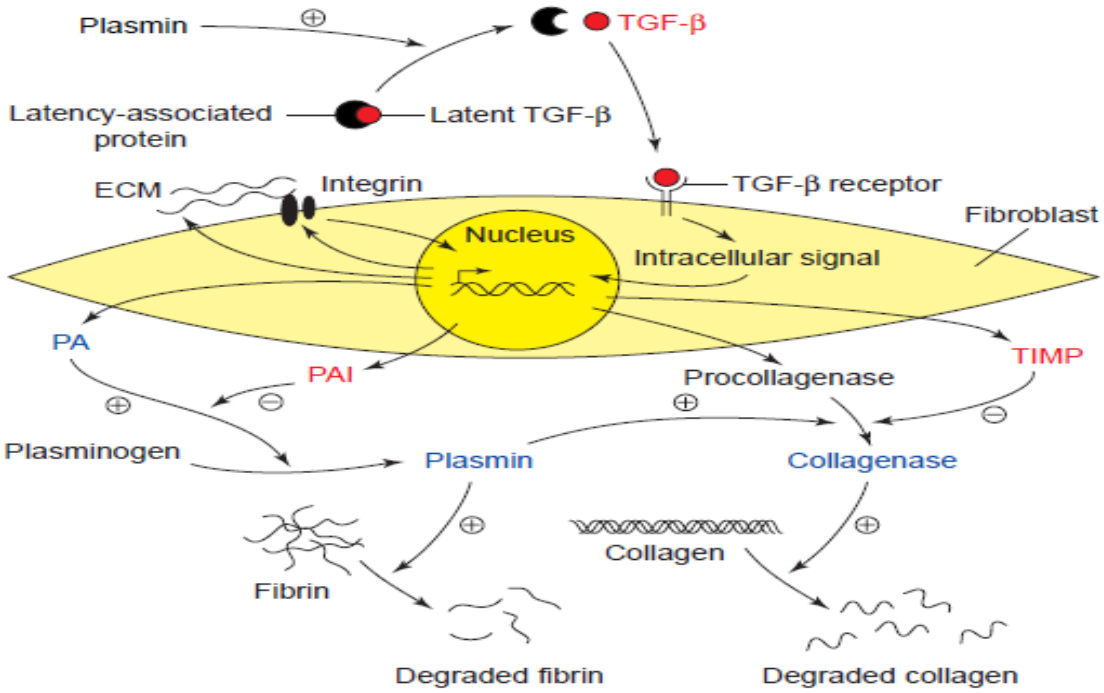


Figure 2. Cellular and molecular mechanism of normal injury repair

TIMP – Tissue inhibitor of metalloproteinase PAI – Plasminogen activator inhibitor. Collagenase and Plasmin are ECM degrading enzymes. Plasmin activation is inhibited by PAI Collagenase activity is inhibited by TIMP.

Abnormal wound healing

When equilibrium is lost during the stages of wound healing, abnormal wound healing results. The type of aberrations present and the stage the wound healing process is in will determine the anomaly that is formed on the healing outcome. It is possible to enumerate a wide variety of anomalies in wound healing, including ulcerations, fibrotic processes, chronic wounds, and elevated dermal scars.

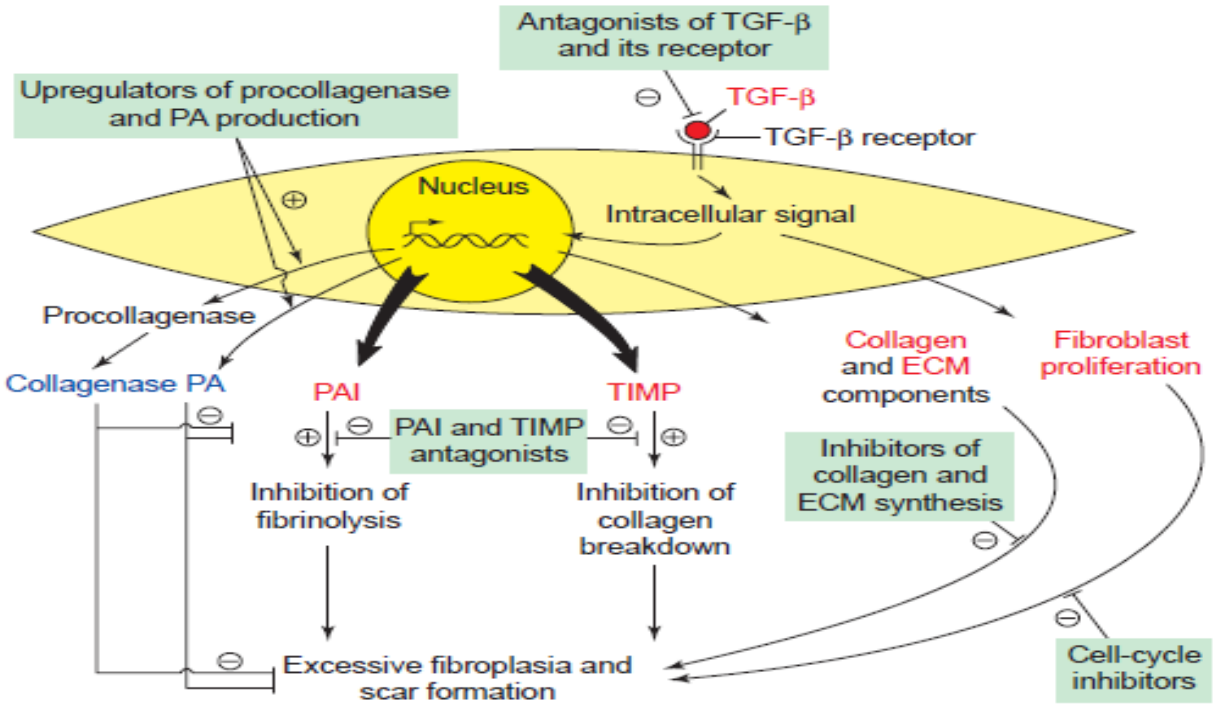


Figure 3: Pathways of excessive fibroplasia by transforming growth factor β (TGF- β)

Epidemiology of Keloid

Although keloid illness is not a race-dependent condition, it is believed that Black, Hispanic, and Asian racial groups are genetically predisposed to the condition (Chike-Obi *et al.*, 2009). The frequency of keloid in the Caucasian population in the UK is less than 1%, but that of Blacks and Hispanics ranges from 4.5 to 16% (Seifer *et al.,* 2009). According to Slemp *et al.* (2006), KS are rarely seen in people over the age of 60. Instead, they typically manifest in people between the ages of 10 and 30. Women are more likely to get keloid illness than men do, and it is more likely to do so during puberty or pregnancy (Schierle *et al.,* 1997).

Treatment of keloids

When feasible, patients with a documented propensity for keloid scarring should avoid unnecessary trauma or surgery (such as elective mole excision and ear piercing). In order to reduce areas of inflammation, any skin issues (such as infections or acne) in those who are predisposed should be treated as soon as feasible.

Pressure therapy, silicone gel sheeting, intra-lesional triamcinolone acetonide (TAC), cryosurgery (freezing), radiation, laser therapy (PDL), IFN, 5-FU, and surgical excision are among the treatments (both preventive and therapeutic) that are available (Gauglitz, *et al.,* 2011). Age determines the best course of action for treating keloid scars, thus radiation, anti-metabolites, and corticosteroids are not advised for usage in youngsters to prevent negative side effects like growth anomalies. Corticosteroids combined with 5-FU and PDL as a triple therapy for adults improve outcomes and lessen adverse effects, according to Arno *et al.* (2014).

The use of extremely cold temperatures to cure keloids is referred to as cryotherapy (or cryosurgery). This course of treatment is the least likely to recur, is simple to follow, efficient, safe, and successful. For a sizable number of keloid lesions, surgical excision is still the most typical treatment. However, there is a high recurrence rate of between 70 and 100% when utilized as a sole type of treatment. On recurrence, it has also been observed to result in the creation of a bigger lesion. Even while it isn't always effective on its own, surgical excision significantly lowers the recurrence rate when used in conjunction with other treatments. Radiation therapy, pressure therapy, and laser ablation are a few examples of these treatments. Results from pressure therapy after surgical excision have been encouraging, particularly in cases of keloids in the ear and earlobe. Many patients with

keloid scars and lesions have benefited from pressure therapy, although its precise mechanism of action is still unknown (Andrews *et al*., 2016).

It does appear that intralesional injection of a corticosteroid like Kenalog (triamcinolone acetonide) helps to lessen fibroblast activity, inflammation, and itch. Keloid lesions are unresponsive to tea tree oil, salt, or any other topical oil.

Some Herbal medicine are now available for the treatment of keloids. example Agnijith – Keloid Removal Cream (India)

This cream acts through the following ways

1. Absorbed by the affected skin
2. Causes lysis of the keloids dead tissues
3. Keloids break, and blood and puss come out (Tirgan, *et al*., 2012)

Conclusion

TGF-ß is currently thought to be one of the primary cytokines that stimulates a wide range of signaling processes, according to research evidence. Platelets, lymphocytes, macrophages, endothelial cells, and fibroblasts all release this growth factor collectively, and the divergence of the explanatory theories put forth suggests that keloid formation is not the result of a single disrupted wound healing process, but rather that a wide variety of subsequent healing mechanisms are involved. Keloid scarring is still a challenging and poorly understood topic. The intricate process of keloid scar development is slowly starting to come into focus as we get a better understanding of growth factor processes, wound matrix degradation, and immune response. Keloid disorder is genetically predisposed, yet it has been treated (ineffectively) with a variety of methods that stop TGF- from being fully expressed. Studying the TGF- expression-inhibiting properties of naturally occurring substances that are readily available in the area may stop the overproduction of collagen and offer different, less expensive methods of regulating keloids.

Recommendation

We need to keep improving our comprehension of the biological mechanisms underlying scar formation in general, and keloid formation in particular, in order to identify more efficient therapy regimens and to advance preventative efforts. It's critical to have a thorough understanding of the keloid scar formation processes in order to effectively treat

the physical and physiologically distressing disorder. Additionally, more research needs to be done to fully comprehend the keloid formation mechanisms.

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