

## Serum and Tissue Marker in Keloids and Hyper Trophic Scars : A Comprehensive Review

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### Abstract

**Background:** The irregularities in the healing process may result in hypertrophic scars and keloids, despite the fact that the goal of wound healing is to restore skin integrity with minimum scarring. Patients' quality of life is negatively impacted by these scars, which are defined by abnormal fibroblast activity and excessive collagen synthesis. The purpose of this extensive study is to investigate prolargin's function in keloids and hypertrophic scars, with a particular emphasis on its relationships with variables that contribute to scar formation and its possible use as a biomarker and therapeutic target. **Conclusions:** Essential for the formation of hypertrophic scars and keloids, prolargin has a substantial effect on collagen synthesis and fibroblast activity. It seems to be an important regulator of scarring based on its interactions with the immune system and the extracellular matrix. There are encouraging treatment options for reducing pathological scarring that include prolargin, due to its ability to inhibit pathways in the complement system and improve skin layer adhesion. To find out how prolargin contributes to scar development and how to treat them effectively, more research is required.

**Key words :** Relevant Terms: Hypertrophic Scars, Keloids, Prolargin, Tissue Expression, and Serum Level.

### 1. Introduction

Wound In most cases, the process of healing is highly organised and aims to leave behind hardly perceptible scars. Scars like keloids and hypertrophic scars may form when this delicate equilibrium is upset. Excessive collagen production during healing causes hypertrophic scars and keloids to have elevated, rigid tissue. In contrast to hypertrophic scars, which shrink back into the original wound area with time, keloids grow outside the original wound area and often don't shrink on their own, making therapy difficult [1].

Itching and soreness are the most common symptoms of these atypical scars, but they may also restrict a person's mobility and make them self-conscious about their appearance. People of darker complexion, especially those of African, Asian, and Hispanic descent, seem to be more prone to developing keloids, suggesting a hereditary component to the condition. Hypertrophic scars, on the other hand, may be more common among darker-skinned people in places where the skin is more likely to stretch, but they do not have such a strong hereditary tendency [2].

Hypertrophic scars affect both sexes equally; the incidence rates after burns vary from 33% to 91% and after surgical treatments from 39% to 68%. At the same time, the PRELP gene's encoded protein prolargin is becoming more important in maintaining skin homeostasis. It enhances epidermal-dermal

cohesiveness in the dermis and inhibits pathways of the complement system, which may impact joint disorders. It is present in a variety of tissues. In settings when collagen is depleted, increased prolargin levels or its addition decrease fibrotic activity in fibroblasts, demonstrating its function in regulating fibrotic signals and improving dermo-epidermal adherence [3].

Hence, the purpose of this extensive study is to investigate prolargin's function in keloids and hypertrophic scars, paying special attention to its connections with variables that contribute to scar formation and its possible use as a biomarker and therapeutic target.

### 2. Keloids and hypertrophic scars

Wound Haemostasis, inflammation, proliferation, re-epithelialization, and remodelling are the five phases that make up the complex healing process. The first step of hemostasis is the rapid production of clots, which halt the bleeding. The second step is an inflammatory phase, during which the location is visited by immune cells. New tissues and blood arteries are formed during the proliferation stage, which causes the wound to constrict. After that, the wound is covered by keratinocytes during re-epithelialization. Lastly, the scar tissue is refined by collagen restructuring during remodelling, resulting in the minimalization of the scar [4].

Hypertrophic scars and keloids, characterised by excessive fibrosis and

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collagen deposition, may result from disruptions in this highly controlled process. The patient's quality of life might be negatively affected by these, which can lead to substantial functional and cosmetic problems,

such as itching, discomfort, and movement limits. For effective management of these disorders, it is essential to have a clear understanding of the different kinds of scars and their features Table (1) [5].

**Table (1)** Various scar kinds [6].

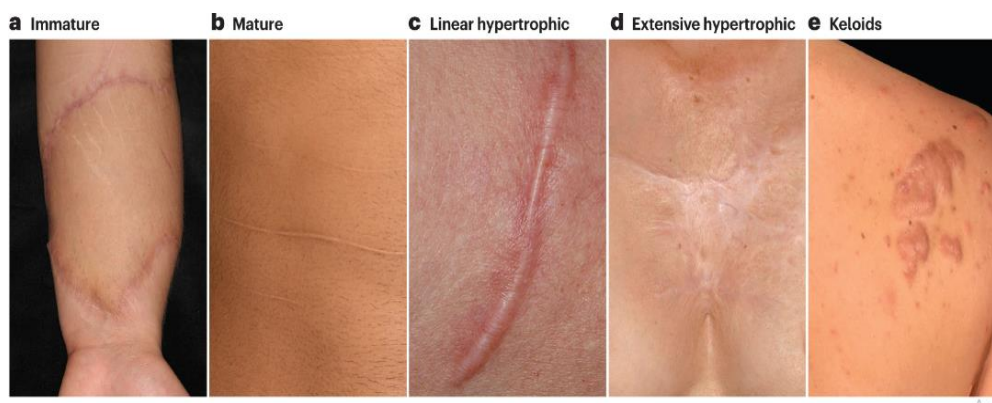
Scar Type	Description
Mature scar	Flat, light-colored scar
Immature scar	Slightly elevated, red scar. Recovers in time and becomes similar in color to surrounding skin
Pitted (atrophic or ice pick)	Pitted, with a sunken appearance. Associated with acne and chickenpox
Scar contractures	Shrunk and tight appearance. Usually caused by skin burns
Linear hypertrophic scar	Elevated, red, and sometimes pruritic scar, associated with surgery or trauma. Scar is confined to the border of the surgical incision or trauma, occurs weeks after cutaneous insult, and can grow in size for 3 to 6 mo before maturing progressively to an elevated, rope-like appearance
Widespread hypertrophic scar	Elevated, widespread, and sometimes pruritic, usually associated with burns. Scar is confined to the borders of the burn injury
Minor keloid	Elevated (< 0.5 cm), small/focal scar. It invades surrounding tissue and can grow and spread for years and can occur up to 1y after cutaneous insult. Does not regress on its own, and surgical excision is often followed by recurrence. Common sites: anterior chest and earlobes
Major keloid	Elevated (>0.5 cm), large, and sometimes pruritic and/or painful scar. It invades surrounding tissue and can grow and spread for years.

### ❖ Clinical and histopathologic features

Hypertrophic Wounds don't show up until 4 to 8 weeks post-injury, then they expand rapidly for 6 months before gradually flattening out over years with no noticeable change. Particularly in the midchest, keloids may develop years after little traumas or even in the absence of harm and often do not go away on their own. They may be lustrous with a surface ranging from pink to purple and have

uneven borders; they are firm and somewhat sensitive. Although keloids and other kinds of scars might itch, keloids can also be painful and sensitive [7].

Keloids tend to appear on the chest and earlobes, whereas hypertrophic scars tend to appear in parts of the body that experience significant levels of stress, such as the shoulders. Unlike hypertrophic scars, which never re-form following excision Fig (1) [8], keloids often re-appear after removal.



**Hypertrophic scar (HS) and keloid appearance in clinical practise Fig (1). Immature scars (a), linear hypertrophic scars (c), large hypertrophic scars (d), and keloids (e) are all types of scars that may form [9].**

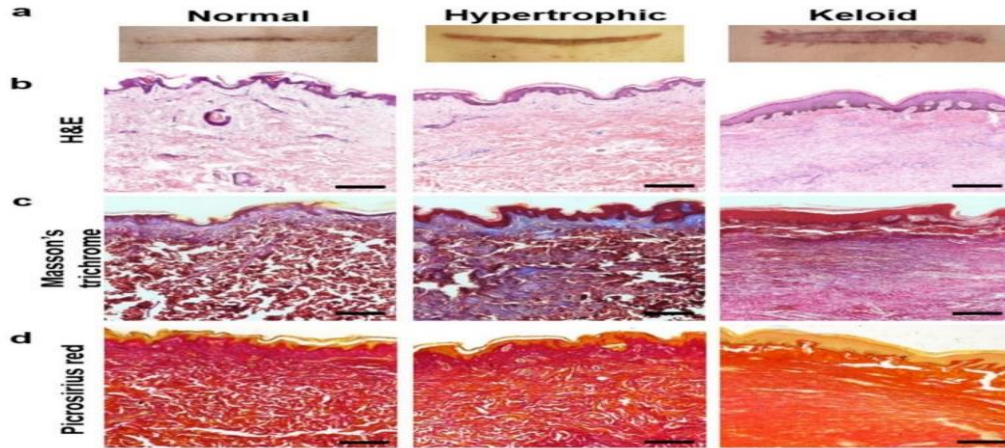
Initially, Although histological examinations showed distinctions, there was no way to tell hypertrophic scars and keloids

apart. In both cases, the dermis is thick and vascularized, full of inflammatory cells and collagen, while the epidermis is normal. One

of the main factors in their creation is injury to the dermis, which is abundant in fibroblasts and loosened collagen fibres [6].

Hypertrophic scars differ from keloids in that their collagen fibres are ordered and parallel rather than thick and hyalinized and

tightly packed. Levels of dermatan sulphate proteoglycans are primarily raised in hypertrophic scars Fig (2) [10], while chondroitin sulphate and dermatan sulphate are more abundant in keloids.



Hypertrophic scars and keloid scars were examined histologically using a normal skin sample Fig (2). (a) Examples of scar tissues from patients shown in gross photos. (b) Nuclei (purple) and extracellular matrix (ECM) stained by hematoxylin and eosin (H&E) in scar tissues (ECM, pink). scar tissues stained with Masson's trichrome (blue) and cytoplasm (red) for collagen deposition (pink). (d) Scar tissues stained with Picrosirius red to show collagen deposition (red) and cytoplasm (orange). According to reference 11, the scale bar measures 200 µm.

Hypertrophic Histological analysis of scars reveals a decline in cellular and protein expression with time, moving from an abundance of cells in the early stages to a sparser distribution in later scars. Keloid histology, on the other hand, does not alter with age and always displays less cellular changes [6].

Genetic and epidemiological characteristics

Common occurrence in siblings and twins and higher rates of keloid development in certain groups provide strong evidence that genetic factors contribute to the aetiology of keloid formation. Keloids affect about 15% to 20% of individuals of African, Hispanic, or Asian origin, but white people experience them at a far lower rate. It seems that people

with albinism do not experience keloid development, suggesting that melanocytes may have a role in this process [12].

An autosomal dominant mode of inheritance manifests itself in the propensity to develop keloids. Several human leukocyte antigen (HLA) alleles, including HLA-DRB1\*15, HLA-DQA1\*0104, DQ-B1\*0501, and DQB1\*0503, and locations on chromosomes 2q23 and 7p11, are known to be related with keloids [13].

Factors and molecular mechanisms

Proliferation, inflammation, ECM formation, and other variables are the four main categories that interact at various stages of wound healing when discussing the pathophysiology of hypertrophic scars and keloids Fig (3).

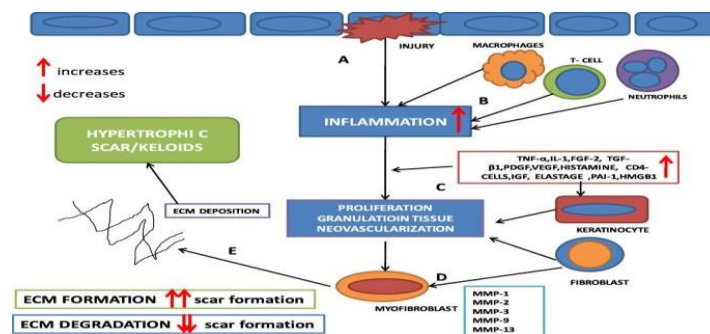


Fig. (3) Scar formation mechanism [14].

### I. Proliferation

Keloid Abnormal scarring and excessive collagen synthesis are caused by fibroblasts, which exhibit stronger proliferation and apoptosis resistance than hypertrophic scars. Keloids have distinct genetic alterations and enhanced expression of the antiapoptotic protein Bcl-2, which distinguishes them from both kinds of scars in terms of apoptotic gene expression and response to apoptosis. The fact that they are formed implies that a delicate equilibrium between growth and apoptotic processes is involved [15].

#### Inflammation

The unbalanced immune response plays a role in the development of hypertrophic scars and keloids. Specifically, a TH2-mediated response, which is responsible for producing cytokines such as IL-4, IL-5, and IL-13, promotes fibrosis and keloid formation. The influence of immunological dynamics on scar pathology is shown by the significant role that persistent immune cell infiltration in the dermis plays in excessive scarring, as is particularly the case in keloids [6].

The overexpression of transforming growth factor  $\beta$  (TGF- $\beta$ ), which stimulates the formation of collagen in scars, is crucial to this progression. An anti-inflammatory cytokine called IL-10 may be able to modulate inflammatory and fibrotic responses, which might lead to a reduction in abnormal scarring [15].

#### Matrix outside of cells

All tissues and organs have some noncellular component called extracellular matrix. This matrix helps cells communicate with each other and provides structural and biochemical support to the tissue. Protein glycosides (PGs) like chondroitin sulphate, heparan sulphate, and keratan sulphate and fibrous proteins (FN) like collagen, elastin, laminin, and fibronectin (FN) are the two main macromolecule components of the extracellular matrix (ECM). The ECM has a role in abnormal wound healing and in distinguishing keloids from hypertrophic scarring, which is not unexpected [16].

#### Fibronectin

Cells that make up scar tissue, called fibroblasts, are engaged in the remodelling process because they produce matrix proteins. One important glycoprotein component of the extracellular matrix (ECM) is fibronectin (FN), which is produced by fibroblasts. FN binds to integrins, which are receptor proteins that bridge cell membranes, and to other components such as fibrin and collagen. As a wound heals, the expression of FN is carefully controlled. The availability of FN is enhanced

during the early stage of wound healing, when collagen fibre expression is minimal; however, this tendency is reversed throughout the maturation and remodelling phase of wound healing [17].

#### Integrin

The integrin proteins mediate the communication between fibroblasts and other cells inside the extracellular matrix (ECM). When skin is injured, integrin proteins assist the collagen ligand attach to matrix metalloproteinases (MMPs), which re-epithelialize the lesion and contribute to scar formation. One  $\alpha$  and one  $\beta$  subunit make up an integrin. In mammals, there are 18  $\alpha$  subunits and 8  $\beta$  subunits. Diverse integrin proteins, characterised by their unique signalling capabilities, are produced by different combinations of these subunits. It is plausible that cellular tension and cell signalling are variably regulated by various integrins, and that various integrins attract distinct signalling molecules [18].

#### • Matrix metalloproteinases

Matrix Enzymes known as matrix metalloproteinases (MMPs) and serine proteinases such as tissue plasminogen activator and urokinase plasminogen activator are essential for regulating the amount of extracellular matrix (ECM) protein that cells may produce. Collagen types I, II, and III are targeted by MMP-1, MMP-8, and MMP-13, respectively. In abnormal scar conditions like keloids and hypertrophic scars, MMP-13 levels are higher and MMP-1 and MMP-8 levels are lower. This suggests that there is a disruption in the processes of ECM degradation and scar formation, as these factors, including TGF- $\beta$ , affect their activity and expression [19].

#### Endothelin 1 and elastin

These ECM components enable tissues to withstand stresses that are either tensile or stretching. Elastic fibres primarily consist of microfibrils that are rich in fibrillin and elastin. Hypertrophic scars and keloids have a considerably different distribution of elastin and fibrillin 1 compared to normal scars. There is no substantial difference in fibrillin 1 expression between hypertrophic scars and keloids in either the superficial or deep dermis, while both scar forms have decreased expression compared to normal skin [20].

#### Collagen

In the interstitial extracellular matrix (ECM), the most abundant fibrous protein is collagen, which is released by fibroblasts. Collagen, in conjunction with elastin, regulates cell motility, adhesion, and development, and provides tensile strength. Hypertrophic scars and keloids, which are characterised by

excessive scarring, are believed to be caused by collagen types I and III, which are assumed to be deposited during scar development. Although hypertrophic scars and keloids both have elevated collagen expression levels when compared to normal skin, keloids have a far higher ratio of type I to type III collagen [21].

#### Connexin

Cells are able to communicate and exchange signalling molecules, such as proteins and ions, via gap junctions, which are structured clusters of protein channels in the cell membranes. The connexin proteins are the fundamental building blocks of gap junctions. Dysregulation of connexin expression has been linked to cancer, and connexin proteins are crucial for fibroblasts' ability to communicate with other cell types. To a lesser extent, keloid and hypertrophic tissues inhibit gap junctional intercellular communication and connexin-43 expression [22].

#### • Decorin

Decorin binds to several components of the extracellular matrix (ECM), including collagen and FN, and plays a significant role in controlling the ECM's construction and structure. It is a tiny PG found in the dermis. Hypertrophic scars and keloids are characterised by a decrease in decorin expression. The fact that recombinant human decorin inhibits TGF- $\beta$ 1 synthesis and causes keloid fibroblasts to experience growth inhibition implies that it might be used therapeutically as an antifibrotic drug. Good expression of PGs may be crucial for proper scar healing [23]. The altered physical features of hypertrophic scars and keloids are likely related to the aberrant expression of decorin and other small leucine-rich PGs.

#### Hyaluronan

After a skin injury, hyaluronan levels rise to help with tissue regeneration; however, they fall abnormally in keloids and hypertrophic scars, suggesting that hyaluronan is essential for scar formation. There is a clear difference in the way hyaluronan is regulated by TGF- $\beta$  between hypertrophic scars, where it is distributed like normal skin, and keloids, where it is located deeper, suggesting that these two types of scars have different healing processes [24].

#### Dermatopontin

Dermatopontin is a non-collagenous ECM component that binds decorin, collagens, and tiny dermatan sulphate PGs. It also modifies collagen fibrillogenesis and increases cell adhesion via integrin binding. Atypical scarring is linked to reduced dermatopontin expression. A limited amount of dermatopontin is expressed by keloid

fibroblasts. The expression of dermatopontin mRNA was raised when fibroblasts were treated with TGF- $\beta$ 1 in vitro, but it was decreased when fibroblasts were treated with IL-4, in comparison to untreated samples. The pathophysiology of hypertrophic scarring and keloid development is likely influenced by changing amounts of TGF- $\beta$  and, by extension, dermatopontin [25].

#### Periostin

By stimulating fibroblast development and activation, this ECM protein contributes to tissue remodelling. After a wound has healed, periostin levels usually rise for a few days before levelling out after a week. In vitro, TGF- $\beta$ 1 strongly induces periostin. Keloids are associated with increased periostin mRNA expression compared to hypertrophic scars, suggesting that periostin may play a role in keloid development [26].

#### Tenascin

Encapsulated in ECM glycoproteins, tenascins play an essential role in cell migration, which is necessary for both embryonic development and wound healing. In mature tissue, they are few, but in wounds, they are many. The expression of tenascin C is much greater in keloids compared to normal skin, and they also have a unique pattern of distribution [27].

#### Laminin

By interacting to several cell surface receptors and other ECM components, this basal lamina integral glycoprotein facilitates cell adhesion. When comparing keloid fibroblastic cell lines to normal fibroblasts, there is a notable increase in the expression of the laminin  $\beta$ 2 protein [28].

#### Distinct Elements

##### Cells lining the mast

In hypertrophic scars and keloids, the number of mast cells is significantly elevated. Histamine, which mediates collagen fibre production, tryptase, which accelerates type I collagen synthesis, and chymase, a protease that cleaves procollagens, assists in fibril creation, and contributes to scar formation, are among the fibrogenic mediators released when mast cells are activated [29].

##### Cyclooxygenases

Cyclooxygenase enzymes (COX-1 and COX-2) create prostaglandins, which are metabolites of arachidonic acid and have important functions in skin physiology. Different pathophysiology is shown by the marked up-regulation of COX-1 in hypertrophic scars and the strong expression of COX-2 in keloids. COX-2 expression in keloids, which is present in macrophages and lymphocytes, implies that inflammatory cells

are involved. The fact that COX-1 is stimulated by TGF- $\beta$  and COX-2 by TNF- $\alpha$  suggests that distinct cytokine milieus impact COX expression and scar formation [30].

Proteins that prevent heat shock

As molecular chaperones, heat shock proteins (HSPs) ensure proper folding of proteins and stabilise their production. They are essential for the production of ECM proteins, and HSP47 in particular helps to stabilise collagen. An irregular healing of wounds is linked to an imbalance in HSP expression. Overexpression of HSP27, HSP47, and HSP70 in keloids is indicative of their role in keloid formation; in contrast, expression of HSP60 and HSP90 does not differ in keloids from normal skin [31].

### • Calcitonin gene-related peptide and plasminogen activator inhibitors

Recently, is a tiny ECM PG found on the dermis that binds to many components, including collagen and FN, and regulates the ECM's construction and structure. Keloids and hypertrophic scars had decreased decorin expression. It has been suggested that recombinant human decorin might be used as an antifibrotic drug due to its ability to inhibit TGF- $\beta$ 1 synthesis and cause growth inhibition in keloid fibroblasts. The altered physical features of hypertrophic scars and keloids are likely related to the aberrant expression of decorin and other small leucine-rich PGs. Proper scar healing may rely on optimal expression of these PGs [23].

Hyaluronan

Hyaluronan is an important component of wound healing. Its levels go up after skin injuries to help with tissue regeneration, but they go down in hypertrophic scars and keloids, suggesting that it is vital for scar formation. Differences in the healing mechanisms may be indicated by the fact that the regulation of hyaluronan, which is influenced by TGF- $\beta$ , differs significantly between hypertrophic scars and keloids. In hypertrophic scars, hyaluronan distribution is similar to normal skin, while in keloids, it is deeper [24].

Dermatopontin

Dermatontin is a non-collagenous ECM component that enhances cell adhesion by integrin binding, modifies collagen fibrillogenesis, binds decorin and collagens, and binds tiny dermatan sulphate PGs. Abnormal scarring is linked to decreased expression of dermatopontin. Dermatopontin expression is low in keloid fibroblasts. Relative to untreated samples, dermatopontin mRNA expression was decreased after IL-4 treatment, while it was raised after exogenous

stimulation of fibroblasts in vitro with TGF- $\beta$ 1. Hence, changes in TGF- $\beta$  levels, and hence dermatopontin, are probably involved in the development of hypertrophic scarring and keloid formation [25].

Periostin

This extracellular matrix protein promotes fibroblast differentiation and activation, which is an important step in tissue remodelling. In most cases, periostin levels rise in the days after a wound heals, reach a maximum after 7 days, and then gradually decline. In vitro, periostin is strongly stimulated by TGF- $\beta$ 1. An further component in keloid development is periostin, whose mRNA expression is greater in keloids compared to hypertrophic scars [26].

Tenascin

Cell migration is aided by tenascins, which are extracellular matrix glycoproteins essential for both foetal development and wound healing. Although wounds have them in abundance, mature tissue does not. There is a clear distribution pattern of tenascin C expression in keloids, which is much greater than in normal skin [27].

Laminin

This basal lamina glycoprotein promotes cell adhesion by binding to several receptors on cell surfaces and other ECM components. In contrast to normal fibroblasts, keloid fibroblastic cell lines have a substantial increase in the production of the laminin  $\beta$ 2 protein [28].

Aside from That

Cells that line the scalp

Hypertrophic scars and keloids are characterised by an abnormally high mast cell count. Upon mast cell activation, various fibrogenic mediators are released, including histamine, which facilitates the synthesis of collagen fibres, tryptase, which promotes the production of type I collagen, and chymase, a protease that cleaves procollagens, assists in fibril synthesis, and contributes to the formation of scars [29].

Cyclooxygenases

An important part of skin physiology is the production of prostaglandins, which are metabolites of arachidonic acid by the cyclooxygenase enzymes (COX-1 and COX-2). The unique pathophysiology of hypertrophic scars and keloids is shown by the highly up-regulated levels of COX-1 and COX-2, respectively. Inflammatory cells may be involved if COX-2 expression is detected in keloids, which is present in lymphocytes and macrophages. The fact that TGF- $\beta$  induces COX-1 and TNF- $\alpha$  induces COX-2 suggests that distinct cytokine environments impact the

expression of COX and the formation of scars [30].

Proteins that are sensitive to heat

Protein folding and stability are both helped along by heat shock proteins, which function as molecular chaperones. Their involvement in ECM protein production is vital, and HSP47 in particular helps stabilise collagen. Abnormal wound healing is linked to irregular HSP expression. While HSP60 and HSP90 expression is unaltered in keloids compared to normal skin, there is a noticeable overexpression of HSP27, HSP47, and HSP70 in keloids, indicating their participation in keloid formation [31].

#### A. Adjuvant and Emerging Therapies

##### • Radiation Therapy

Radiation therapy has an uncertain mechanism of action, but it shows promise as an adjuvant treatment after keloid excision because to its low recurrence rates. It may have anti-angiogenic effects and interferes with fibroblast repopulation or modifies substances that stimulate fibroblasts. Among the options, brachytherapy provides more targeted radiation using catheter-directed sources, but external beam and other methods are also viable choices. Radiation treatment is helpful, but it may cause problems, especially for pregnant women, young patients, or those with keloids in sensitive regions, which can lead to radiation-induced cancers [39].

##### Interferon

As cytokines, interferons play an important role in many systems and have antiviral, antifibrotic, and antiproliferative actions on different kinds of cells. Evidence suggests that interferons may modulate TGF- $\beta$ 1 to disrupt collagen production and fibroblast proliferation. Collagenase levels are increased while matrix metalloproteinases, which block collagenase, are inhibited by interferon alpha-2b. Generalized flu-like symptoms are the most often reported adverse effect. Injection site irritation and moderate discomfort are two additional adverse effects [40].

##### 5-Fluorouracil

The fluorinated pyrimidine 5-fluorouracil (5-FU) inhibits thymidylate synthase, which stops the production and activity of ribonucleic acid, and so acts as an antimetabolic agent (RNA). While 5-FU is most often used to treat cancer, it may also be helpful in the treatment of keloids and hypertrophic scars. Both in laboratory settings and in living organisms, it has been shown to hinder the growth of fibroblasts and the production of Type I collagen generated by TGF- $\beta$ . Injection site discomfort, ulceration, burning, and

hyperpigmentation are common adverse effects [41].

##### Imiquimod

Imiquimod is a toll-like receptor 7 agonist and a topical immunomodulatory (TLR7). Imiquimod, when applied topically, activates toll-like receptor 7 (TLR7), which in turn triggers the local production of IL-6, IL-12, IFN-alpha, and tumour necrosis factor (TNF), all of which are proinflammatory cytokines. In keloidal tissue, which is often dysregulated, imiquimod increases expression of apoptotic genes via the generation of these proinflammatory cytokines. Hyperpigmentation, irritation, erosion, and soreness are the most often reported side responses, which may need a temporary withdrawal from the product [42].

##### Tacrolimus

In order to avoid organ rejection, the immunosuppressant tacrolimus (or FK-506) is often prescribed to transplant recipients. Dermatologists also often use it topically to treat common skin problems including atopic dermatitis. For the treatment of keloids, tacrolimus has many possible therapeutic targets. In vitro studies have shown that it inhibits the TGF- $\beta$ /Smad signalling cascade in keloidal fibroblasts by lowering the expression of TGF- $\beta$  receptors, which in turn decreases the proliferation, migration, and collagen synthesis of these cells [43].

##### Sirolimus

*Streptomyces hygroscopicus* produces the macrolide antibiotic sirolimus, which inhibits the mammalian target of rapamycin (mTOR) pathway. The mTOR pathway is a serine/threonine kinase that controls cell proliferation, migration, and survival. Tissue extracts from keloids have shown increased mTOR expression, and mTOR has been found to regulate the production of Type I collagen in dermal fibroblasts [43].

##### • Bleomycin

Bleomycin comes from the bacterium *Streptomyces verticellus* and is a cytotoxic antibiotic that has antibacterial, antiviral, and antineoplastic effects. Dermatologists use it to treat stubborn warts and keratoacanthomas; it may also be useful for keloids and hypertrophic scars. When cultivated fibroblasts are given bleomycin, collagen production is reduced in vitro. One possible explanation is a decrease in lysyl oxidase, an enzyme critical for collagen maturation. Injection site crusting and superficial ulceration, temporary hyperpigmentation, cutaneous atrophy, and discomfort are the most frequent side effects. No systemic toxicity has been recorded with modest dosages injected subcutaneously with

bleomycin, while systemic administration of this medication may produce pulmonary, renal, cutaneous, hepatic, and myelogenous damage [44].

### Doxorubicin

Because of its DNA-intercalating properties, the anthracycline antitumor antibiotic doxorubicin is also used as an antineoplastic agent. Patients undergoing this cancer therapy had delayed wound healing, which may have implications for the management of keloids and hypertrophic scars due to a decrease in collagen production. Both hydroxyproline production and fibroblast proliferation may be inhibited by doxorubicin in vitro [45].

### Factor-Beta Transforming Growth

Scarring is thought to be heavily influenced by transforming growth factor-beta and its three isoforms. One reason why scarring does not occur during foetal repair is because various TGF- $\beta$  isoforms are expressed differently. The ratio of TGF- $\beta$ 3 to TGF- $\beta$ 1 and 2 isoforms is greater in foetuses that do not develop scars, whereas it is lower in skin that generates scars. An higher ratio of TGF- $\beta$ 3 to TGF- $\beta$ 1 is seen in mouth wounds that heal more quickly and usually leave no scars compared to dermal lesions on the skin in the same adult. Consequently, it is reasonable to assume that TGF- $\beta$ 3 inhibits scarring, whereas TGF- $\beta$ 1 and 2 exacerbate it [46].

### Skin-Renewing Hormone

Platelets, macrophages, and monocytes all contribute to the production of epidermal growth factor (EGF). The EGF receptor on keratinocytes and fibroblasts is the molecular mechanism by which it exerts its effects. In addition to its role as an essential cytokine in scar-free foetal repair, EGF is up-regulated in the early stages of pregnancy. EGF shortens healing time and improves tensile strength by stimulating keratinocyte proliferation and influencing fibroblast activity [47].

### Verapamil

One example of a calcium channel blocker is verapamil, which stops calcium from entering cells by blocking L-type calcium (Ca<sup>2+</sup>) channels in cell plasma membranes. Although its main usage is as an antihypertensive, it causes a cascade of other changes due to its effect on intracellular calcium levels. In keloids, hypertrophic scars, and normal cultured fibroblasts, verapamil enhances procollagenase synthesis, which in turn causes actin filament depolymerization, cell conformational shift, cell death, and decreased fibrous tissue creation. According to [48], verapamil has the potential to suppress

cytokines including IL-6, VEGF, and TGF- $\beta$ 1, which are often increased in keloids.

### Prolargin

One subfamily of short leucine-rich repeat proteoglycans (SLRPs) includes prolargin, also known as PRELP (proline and arginine-rich end leucine-rich repeat protein). SLRPs include 10 central leucine-rich repeat domains. In the N-terminal region that comes before the disulfide-bonded domain, there is a lot of structural diversity among the core proteins of different subfamily members. This domain is abundant in aspartic acid or sulfated tyrosine residues in fibromodulin and decorin, respectively, while it bears attachment sites for one or two chondroitin sulphate chains in biglycan and asporin, respectively. On the other hand, PRELP is cationic rather than anionic owing to its abundance of arginine residues in its N-terminal domain [49].

### End Leucine Rich Repeat Protein Rich in Proline and Arginine (PRELP)

A 55-kDa core protein devoid of glycosaminoglycans (GAG) and a very distinctive, conserved, and proline-and arginine-rich N-terminal region make up prolargin, also known as PRELP. Behaving as a molecule, it secures basal membranes to the connective tissue underneath. The basement membrane, which separates the skin's epidermis and dermis, is one place where prolargin is expressed [50].

### • Prolargin as an important regulator of cell adhesion and behaviour

In contrast to its relatives, prolargin's N-terminal region is rich in positively charged amino acids and proline. Inhibiting osteoclast differentiation and binding chondrocytes have been shown for this region in the past [51].

Investigating the many potential effects of prolargin in different illness settings

Collagens, elastin, fibronectin, laminins, glycoproteins, proteoglycans (PGs), and GAGs make up the majority of the extracellular matrix (ECM), which is both a static and dynamic component of the tumour microenvironment. The unique amino-terminal area and glycosaminoglycan-binding domain of prolargin likely allow it to form strong binding relationships with perlecan and procollagen, as shown by electron microscopy. The prolargin-released neopeptide contributes to the development and worsening of osteoarthritis (OA). Prolargin has a role in the process of osteoblasts forming new bone by influencing the  $\beta$ -catenin/connexin43 pathway. Prolargin has the potential to bind to respiratory tract pathogens in human congenital immunity mechanisms, preventing



them from adhering to lung epithelial cells [52].

#### Conclusions:

The formation of hypertrophic scars and keloids is dependent on fibroblast activity and collagen synthesis, both of which are greatly affected by prolargin. Its roles in regulating scarring are supported by its interactions with the extracellular matrix and immune system components. Therapeutic options for minimising pathological scarring are offered by prolargin, which has the ability to disrupt pathways in the complement system and improve the adhesion of skin layers. To develop effective therapies for scars, more research into the function of prolargin in scar development is required.

#### References

- [1] S. Tripathi, K. Soni, P. Agrawal, V. Gour, R. Mondal, V. Soni. Hypertrophic scars and keloids: a review and current treatment modalities. *Biomedical Dermatology*;4:11. 2020
- [2] U. Betarbet, T.W. Blalock. Keloids: A Review of Etiology, Prevention, and Treatment. *J Clin Aesthet Dermatol*;13:33-43. 2020
- [3] M.P. Mony, K.A. Harmon, R. Hess, A.H. Dorafshar, S.H. Shafikhani. An Updated Review of Hypertrophic Scarring. *Cells*;12. 2023
- [4] H.N. Wilkinson, M.J. Hardman. Wound healing: cellular mechanisms and pathological outcomes. *Open Biol*;10:200223. 2020
- [5] A. Lubczyńska, A. Garnarczyk, D. Wcisło-Dziadecka. Effectiveness of various methods of manual scar therapy. *Skin Res Technol*;29:e13272. 2023
- [6] F.M. Ghazawi, R. Zargham, M.S. Gilardino, D. Sasseville, F. Jafarian. Insights into the pathophysiology of hypertrophic scars and keloids: how do they differ? *Advances in skin & wound care*;31:582-95. 2018
- [7] G.C. Limandjaja, F.B. Niessen, R.J. Scheper, S. Gibbs. Hypertrophic scars and keloids: Overview of the evidence and practical guide for differentiating between these abnormal scars. *Exp Dermatol*;30:146-61. 2021
- [8] N. Barone, T. Safran, J. Vorstenbosch, P.G. Davison, S. Cugno, A.M. Murphy. Current Advances in Hypertrophic Scar and Keloid Management. *Semin Plast Surg*;35:145-52. 2021
- [9] G.G. Gauglitz, H.C. Korting, T. Pavicic, T. Ruzicka, M.G. Jeschke. Hypertrophic scarring and keloids: pathomechanisms and current and emerging treatment strategies. *Mol Med*;17:113-25. 2011
- [10] R. Ogawa, S. Akita, S. Akaishi, N. Aramaki-Hattori, T. Dohi, T. Hayashi, et al. Diagnosis and Treatment of Keloids and Hypertrophic Scars-Japan Scar Workshop Consensus Document 2018. *Burns Trauma*;7:39. 2019
- [11] H. Kim, L.D. Anggradita, S.J. Lee, S.S. Hur, J. Bae, N.S. Hwang, et al. Ameliorating Fibrotic Phenotypes of Keloid Dermal Fibroblasts through an Epidermal Growth Factor-Mediated Extracellular Matrix Remodeling. *Int J Mol Sci*;22. 2021
- [12] A.S. Halim, A. Emami, I. Salahshourifar, T.P. Kannan. Keloid scarring: understanding the genetic basis, advances, and prospects. *Arch Plast Surg*;39:184-9. 2012
- [13] S. Amjadian, S. Moradi, P. Mohammadi. The Emerging Therapeutic Targets for Scar Management: Genetic and Epigenetic Landscapes. *Skin Pharmacol Physiol*;35:247-65. 2022
- [14] A.D. Menchaca, C.C. Style, O.O. Olutoye. A Review of Hypertrophic Scar and Keloid Treatment and Prevention in the Pediatric Population: Where Are We Now? *Adv Wound Care (New Rochelle)*;11:255-79. 2022
- [15] G.C. Limandjaja, F.B. Niessen, R.J. Scheper, S. Gibbs. The Keloid Disorder: Heterogeneity, Histopathology, Mechanisms and Models. *Front Cell Dev Biol*;8:360. 2020
- [16] M. Hu, Z. Ling, X. Ren. Extracellular matrix dynamics: tracking in biological systems and their implications. *Journal of Biological Engineering*;16:1-13. 2022
- [17] L. Moretti, J. Stalfort, T.H. Barker, D. Ababayehu. The interplay of fibroblasts, the extracellular matrix, and inflammation in scar formation. *J Biol Chem*;298:101530. 2022
- [18] L.E. Tracy, R.A. Minasian, E.J. Caterson. Extracellular Matrix and Dermal Fibroblast Function in the Healing Wound. *Adv Wound Care (New Rochelle)*;5:119-36. 2016
- [19] X. Wang, R.A. Khalil. Matrix Metalloproteinases, Vascular Remodeling, and Vascular Disease. *Adv Pharmacol*;81:241-330. 2018
- [20] K. Pfisterer, L.E. Shaw, D. Symmank, W. Weninger. The Extracellular Matrix in Skin Inflammation and Infection. *Front Cell Dev Biol*;9:682414. 2021
- [21] D. Singh, V. Rai, D.K. Agrawal. Regulation of Collagen I and Collagen III

- in Tissue Injury and Regeneration. *Cardiol Cardiovasc Med*;7:5-16. 2023
- [22] C.H. Li, M.L. Hao, Y. Sun, Z.J. Wang, J.L. Li. Ultrastructure of gap junction and Cx43 expression in gastric cancer tissues of the patients. *Arch Med Sci*;16:352-8. 2020
- [23] X. Pang, N. Dong, Z. Zheng. Small Leucine-Rich Proteoglycans in Skin Wound Healing. *Front Pharmacol*;10:1649. 2019
- [24] M. Xue, C.J. Jackson. Extracellular Matrix Reorganization During Wound Healing and Its Impact on Abnormal Scarring. *Adv Wound Care (New Rochelle)*;4:119-36. 2015
- [25] T. Kim, K. Ahmad, S. Shaikh, A.T. Jan, M.G. Seo, E.J. Lee, et al. Dermatopontin in Skeletal Muscle Extracellular Matrix Regulates Myogenesis. *Cells*;8. 2019
- [26] S.L. Yin, Z.L. Qin, X. Yang. Role of periostin in skin wound healing and pathologic scar formation. *Chin Med J (Engl)*;133:2236-8. 2020
- [27] T. Sumioka, K.-i. Matsumoto, P.S. Reinach, S. Saika. Tenascins and osteopontin in biological response in cornea. *The Ocular Surface*;29:131-49. 2023
- [28] X. Pang, X. He, Z. Qiu, H. Zhang, R. Xie, Z. Liu, et al. Targeting integrin pathways: mechanisms and advances in therapy. *Signal Transduct Target Ther*;8:1. 2023
- [29] T.A. Wilgus, S. Ud-Din, A. Bayat. A Review of the Evidence for and against a Role for Mast Cells in Cutaneous Scarring and Fibrosis. *Int J Mol Sci*;21. 2020
- [30] R.K. Sivamani. Eicosanoids and Keratinocytes in Wound Healing. *Adv Wound Care (New Rochelle)*;3:476-81. 2014
- [31] C. Hu, J. Yang, Z. Qi, H. Wu, B. Wang, F. Zou, et al. Heat shock proteins: Biological functions, pathological roles, and therapeutic opportunities. *MedComm (2020)*;3:e161. 2022
- [32] O.A. Bakry, R.M. Samaka, N. Fayez, I. Seleit. Krox20 expression in abnormal scars: An immunohistochemical study. *J Cosmet Dermatol*;21:5116-26. 2022
- [33] S. Li, J. Yang, J. Sun, M. Chen. Adipose-Derived Mesenchymal Stem Cells Alleviate Hypertrophic Scar by Inhibiting Bioactivity and Inducing Apoptosis in Hypertrophic Scar Fibroblasts. *Cells*;11. 2022
- [34] S.W. Kim. Management of keloid scars: noninvasive and invasive treatments. *Arch Plast Surg*;48:149-57. 2021
- [35] S. Tejiram, J. Zhang, T.E. Travis, B.C. Carney, A. Alkhalil, L.T. Moffatt, et al. Compression therapy affects collagen type balance in hypertrophic scar. *J Surg Res*;201:299-305. 2016
- [36] M. Morelli Coppola, R. Salzillo, F. Segreto, P. Persichetti. Triamcinolone acetonide intralesional injection for the treatment of keloid scars: patient selection and perspectives. *Clin Cosmet Investig Dermatol*;11:387-96. 2018
- [37] J.W. Lee, K.H. Seol. Adjuvant Radiotherapy after Surgical Excision in Keloids. *Medicina (Kaunas)*;57. 2021
- [38] C.P. O'Boyle, H. Shayan-Arani, M.W. Hamada. Intralesional cryotherapy for hypertrophic scars and keloids: a review. *Scars Burn Heal*;3:2059513117702162. 2017
- [39] I.G. Petrou, K. Jugun, E.M. Rüegg, T. Zilli, A. Modarressi, B. Pittet-Cuénod. Keloid treatment: what about adjuvant radiotherapy? *Clin Cosmet Investig Dermatol*;12:295-301. 2019
- [40] S.J. Bergman, M.C. Ferguson, C. Santanello. Interferons as therapeutic agents for infectious diseases. *Infect Dis Clin North Am*;25:819-34. 2011
- [41] N. Zhang, Y. Yin, S.J. Xu, W.S. Chen. 5-Fluorouracil: mechanisms of resistance and reversal strategies. *Molecules*;13:1551-69. 2008
- [42] A. Angelopoulou, N. Alexandris, E. Konstantinou, K. Mesiakaris, C. Zanidis, K. Farsalinos, et al. Imiquimod - A toll like receptor 7 agonist - Is an ideal option for management of COVID 19. *Environ Res*;188:109858. 2020
- [43] C. Jaloux, B. Bertrand, N. Degardin, D. Casanova, N. Kerfant, C. Philandrianos. [Keloid scars (part II): Treatment and prevention]. *Ann Chir Plast Esthet*;62:87-96. 2017
- [44] N.D. Huu, S.N. Huu, X.L. Thi, T.N. Van, P.P.T. Minh, T.T. Minh, et al. Successful Treatment of Intralesional Bleomycin in Keloids of Vietnamese Population. *Open Access Maced J Med Sci*;7:298-9. 2019
- [45] R. Mattioli, A. Ilari, B. Colotti, L. Mosca, F. Fazi, G. Colotti. Doxorubicin and other anthracyclines in cancers: Activity, chemoresistance and its overcoming. *Mol Aspects Med*;93:101205. 2023
- [46] Y. Zhang, S. Wang, Y. Yang, S. Zhao, J. You, J. Wang, et al. Scarless wound healing programmed by core-shell microneedles. *Nat Commun*;14:3431. 2023

- [47] S.H. Shin, Y.G. Koh, W.G. Lee, J. Seok, K.Y. Park. The use of epidermal growth factor in dermatological practice. *Int Wound J*;20:2414-23. 2023
- [48] R. Vaiciuleviciute, D. Bironaite, I. Uzieliene, A. Mobasher, E. Bernotiene. Cardiovascular Drugs and Osteoarthritis: Effects of Targeting Ion Channels. *Cells*;10. 2021
- [49] S.W.Y. Low, T.B. Connor, I.S. Kassem, D.M. Costakos, S.S. Chaurasia. Small Leucine-Rich Proteoglycans (SLRPs) in the Retina. *Int J Mol Sci*;22. 2021
- [50] X. Lin. Towards improved vascular grafts: exploration of coatings of recombinant perlecan domains for control of vascular cells: UNSW Sydney; 2018.
- [51] E. Jimi, T. Katagiri. Critical Roles of NF- $\kappa$ B Signaling Molecules in Bone Metabolism Revealed by Genetic Mutations in Osteopetrosis. *Int J Mol Sci*;23. 2022
- [52] K. Dzobo, C. Dandara. The Extracellular Matrix: Its Composition, Function, Remodeling, and Role in Tumorigenesis. *Biomimetics (Basel)*;8. 2023