6 Tissue Repair and Over-regeneration: Prevention and Treatment of Scars During Tissue Repair and Regeneration

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6.1 Genomics and Genetics of Scar Formation

Wound healing is an extremely complex process, including the remodeling of parenchymal cells and surrounding cell matrix, angiogenesis and neurogenesis, immune system reconstruction, and other processes [1]. If the healing process is abnormal, the tissue around the wound continues to proliferate, causing excessive repair and regeneration of the tissue, eventually leading to the formation of abnormal scars [2].

In recent years, researches on scars are not limited to histology, biochemistry, cell biology, and other fields, using more advanced techniques to make more in-depth exploration of scar genomics and genetics from the molecular gene level. However, no specific cause of scar formation has been found so far. The production of scars is not caused by a single gene or a single factor, but by the interaction of multiple gene pathways and the combined effects of environmental factors. The research on the genomics and genetics of scar formation is of great significance for the prevention and treatment of scars.

Pathological scars mainly refer to hypertrophic scars and keloids. The pathogenesis and the treatment of these two are different.

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6.1.1 Hypertrophic Scars

Hypertrophic scars are usually secondary to burns, trauma, and surgery. The prolongation of proliferative phase during healing leads to the continuous expression of collagen, elastin, α-smooth muscle actin (α-SMA), and fibronectin, forming non-functional tissues that protrude from the surface of the wound, which has a great negative impact on the local appearance and function of the patients.

High-risk factors for hypertrophic scar formation include severe burns, women, young age, dark skin, location (neck or upper limb), multiple operations, delayed healing, etc., especially after burns, and the incidence is as high as 30–72% [2, 3].

The study of genetic factors in the pathogenesis of hypertrophic scars is in its infancy, and the current research has not found specific genetic loci that lead to the onset of hypertrophic scars. DNA genotyping suggests that genetic variation may be related to the severity of hypertrophic scars [3].

Abnormal miRNA expression promotes pathological processes such as fibrosis, inflammation, cell proliferation, and ECM metabolism in hypertrophic scars. Mu et al. applied miRNA microarray technology to analyze miRNAs in hypertrophic scars, and found that compared with normal skin, 21 miRNAs showed significant differential expression, and MiR-143-3p inhibited the formation of hypertrophic scars. According to Zhou Renpeng et al., 24 miRNAs showed significant differential expression, including miR-21 and miR-200b, which are closely related to the TGF-β pathway and fibrosis process. In addition, miR-181c, miR-10a, and miR-199a-5p have all been shown altered expression levels in hypertrophic scars [4–6].

Abnormalities in mRNA expression profiles are also associated with the onset of hypertrophic scars. Differential genes are mainly involved in cell cycle, cell proliferation, immune response, and cell adhesion, and are mainly involved in focal adhesion formation, TGF-β signaling pathway, cell cycle signaling pathway, p53 signaling pathway,

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and tumor-associated signaling pathway, which further illustrates that hypertrophic scars are regulated by multiple pathways. These differentially expressed mRNAs and their involved signaling pathways may become new targets for gene intervention therapy of hypertrophic scars with potential clinical significance.

6.1.2 Keloids

Keloid is a benign dermal proliferative tumor, which is a pathological reaction secondary to abnormal repair of skin lesions. It is characterized by excessive ECM deposition, mainly excessive proliferation of fibroblasts and accumulation of collagen, showing a tumor-like growth pattern [7]. The high-risk factors of keloids include ethnic factors, the site of injury, tissue tension around the wound, infection, hormone levels, and the presence of foreign bodies.

Keloids have obvious genetic susceptibility, which is mainly manifested in the family hereditary, and the high incidence of specific races. Data have shown that people with dark skin are more susceptible to keloids. The incidence of African-American, Hispanic, and Asian-born people is as high as 15–20%, which is much higher than that of Caucasians, while albino patients have on incidence [7, 8].

Keloid is a disease caused by multi-gene involvement and mutation of many genes, and its genetic pattern and pathogenic genes are not clear [9]. In cases of familial hereditary keloids, single or multiple genetic loci are mutated, but these susceptibility loci are heterogeneous, racially specific and lack universality. Some scientists have found that 15q21.2–22.3, 2q23, 7p11, and other loci are associated with the occurrence of keloid in different families. In a study of two keloid families, Marneros et al. found that the genetic susceptibility locus of African-American black pedigrees is located in the 7p11 region, and the susceptibility locus of Japanese pedigrees is located in the 2q23 region. Liu Xiaojun et al. excluded the effects of chromosome 7p11 and 2q23 regions on the disease in the study of family genetic patients of Chinese Han population, demonstrating the heterogeneity and race susceptibility of susceptibility loci [10, 11].

Bian Xi et al. compared differentially expressed genes between keloid and normal skin, performed bioinformatics analysis of keloid-related genes, and screened 94 keloid-related genes (71 upregulated, 23 downregulated). Among them, key genes such as TGF-β1, FN1, COL1A1, MMP9, VEGFA, TP53, IL-6, and MMP2 may play important roles in TGF-β1 signal transduction, cell proliferation and apoptosis, tumor formation, and other related pathways, leading to the occurrence and development of keloids [12, 13].

6.2 Scar Formation Mechanism: Dermis "Template Defect" Theory

The wound healing process is completed by cells, cytokines, extracellular matrix, etc. Therefore, previous researches on the mechanism of scar formation have started from cells, cytokines, and extracellular matrix. With the deepening of research and the further expansion of the research scope, it is gradually realized that in the process of wound healing, cells, cytokines, and extracellular matrix play the role of "participants" or "executors." Their changes and the interactions are the follow-up "chain" or "waterfall" effects on scar formation, which is an "intermediate process" of repair, rather than the initiating factors leading to excessive hyperplasia of scar. So what are the initiating factors that affect scar formation? Some clinical and experimental phenomena have given us great inspiration.

Clinical practice found that:

(a) There is a great difference in outcomes after natural healing of burn wounds of different degrees. Shallow burn wounds do not leave or only leave slight scars after healing, and deep burn wounds often form obvious scars after healing [14].
(b) The healing results of autologous skin grafts with different thicknesses are also different. The degree of scar hypertrophy after deep wound skin grafting is inversely proportional to the thickness of the skin graft. Full-thickness skin grafts leave no scar.
(c) In frostbite wounds, although the blood vessels and cellular components in the skin tissue have lost their activity, if the dermal tissues other than blood vessels and cells are retained, there will be almost no hypertrophic scar after healing. These phenomena suggest that hyperplasia of scars may be related to the degree of dermal tissue loss. The use of skin substitutes (such as Integra, DermagraftTC, AlloDerm) can alleviate the excessive formation of scars to a certain extent [15, 16]. Further studies have found that such dermal analogs mimicking the structure of dermal tissue can support the infiltration of host FB, the formation of new blood vessels, and epithelialization [17]. Some researchers have referred to this role of dermal analogs as "template-like action," further suggesting that the reconstruction of the structure and function of the skin tissue at the injury site requires the involvement of certain layers and/or components of the dermal tissue in order to be completed smoothly. Such skin layers or components may mimic certain properties of the dermal tissue that are necessary for the outcome of cell function in wound healing and serve as a "template" to guide the trend of cell function. Defects in dermal tissue result in the absence of a "template" leading to excessive scar formation. So how does dermal

tissue play a "template" role? What mechanisms affect the changes in cells, cytokines, and extracellular matrix to produce a series of effects? Is it through the structure or components of the dermal tissue? Therefore, the study of its mechanism is helpful to understand the biological mechanisms of scar formation, for which we have conducted a series of studies.

6.2.1 The Effect of Skin Dermis Defect and Its Defect Degree on Scar Formation

In order to understand the relationship between the degree of skin dermis defect and scar formation, we observed the degree of scar hyperplasia under different degrees of skin dermal tissue defects and the formation of scars after autologous skin replantation with different thicknesses of tissue defects in the same degree.

In this study, 45 donor sites of 24 burn patients' limbs were selected as the study wounds, which were divided into the split-thickness skin donor sites (group A) and the intermediate split-thickness skin donor sites (group B). According to whether or not to transplant autologous skin with a certain thickness, group A is divided into the following subgroups, respectively, group A1 (without autograft) and group A2 (split-thickness autograft) and group B into group B1 (without autograft), group B2 (split-thickness autograft) and group B3 (intermediate split-thickness autograft). Skin graft specimens are retained, and the thickness of the dermis is measured by microscopic imaging system and image analysis system after tissue sectioning. The degree of scar hypertrophy in the above donor sites was scored in Vancouver Score 6 months after surgery. The results showed that the thickness of defective dermal tissue in group A was 0.146–0.163 mm, and in group B was 0.456–0.656 mm (Table 6.1) [18]. After healing, the Vancouver Score increased with the degree of dermal tissue defect, and there was a positive correlation between the two ($r = 0.597$, $P < 0.01$). After autologous skin grafting, the scar score was reduced correspondingly and the thickness of the grafted skin was negatively correlated ($r = -0.569$, $P < 0.01$) (Table 6.2) [19]. It can be seen that the degree of scar hyperplasia increases with the degree of dermal tissue defect, and the degree of scar hyperplasia relieved by skin graft replantation is directly proportional to the thickness of the replanted dermal tissue. For the first time, it is demonstrated theoretically that the degree of dermal tissue defect during wound healing process is closely related to the degree of scar hypertrophy.

The above experimental results suggest that the degree of scar hyperplasia increases with the degree of dermal tissue defect, the replantation of dermal tissue can alleviate scar hyperplasia, and the degree of scar hyperplasia reduction is related to the thickness of replanted dermal tissue. This led to another level of thinking, that is, why does the degree of dermal tissue defect affect the formation of scars? What is the effect of different degrees of dermal tissue defect on wound healing process?

Table 6.1 Measurement of dermal tissue thickness of wound defects and thickness of replanted dermal tissue in each group (mm, $\bar{x} \pm s$)

Group	Number of wounds	Thickness of defect dermis	Thickness of replanted dermis
A1	9	0.146 ± 0.022	0
A2	9	0.163 ± 0.035	0.138 ± 0.084
B1	9	0.456 ± 0.150*	0
B2	9	0.656 ± 0.277*	0.152 ± 0.071
B3	9	0.603 ± 0.122*	0.558 ± 0.095#

Note: Compared with group A, *$P < 0.05$; comparison of the thickness of replanted dermal tissue between group B3 and groups A2, B2, *$P < 0.05$

Table 6.2 Comparison of wounds Vancouver scores 6 months after skin replantation with different thicknesses ($\bar{x} \pm s$)

Group	Number of wounds	Vancouver score of scar
A1	9	0.182 ± 0.050
A2	9	0.111 ± 0.033
B1	9	3.714 ± 0.498*
B2	9	1.050 ± 0.057#
B3	9	0.636 ± 0.055△

Note: Compared with each group, #compared with group A2,*$P < 0.05$; △ compared with groups B2, A2, *P < 0.05

6.2.2 The Effect of Skin Dermis Defect Degree on Wound Healing Process

In order to study the effects of different degrees of skin tissue defects on wound healing process, we carried out clinical experiments within the scope of ethics, and further verified and improved the results of clinical experiments through animal experiments.

In clinical trials, 94 cases of deep burn wounds after escharectomy were selected. The experimental group was acellular dermal matrix + autologous split-thickness skin graft, and the control group was autologous split-thickness skin graft. The wound healing process was dynamically observed from histomorphology and cell biology. In the animal experiment, 120 male Sprague-Dawley rats were used to create a 2.5 cm × 2.5 cm full-thickness skin tissue defect in the middle of the back. They were divided into four groups: natural healing group (control group), split-thickness skin graft group, full-thickness skin graft group, and composite graft group (acellular dermal matrix + autologous split-thickness skin graft). The changes in wound histomorphology, tissue biomechanical compliance, and repair of cell function were observed dynamically for 20 weeks.

Clinical trials confirmed that the granulation tissue was less in the composite graft group, fibroblasts (FB) and blood vessels could grow through the collagen gap of the acellular dermal matrix, and the structure after tissue repair (12 months after surgery) was closer to the structure of normal dermal tissue than that after simple split-thickness skin graft. Compared with the composite graft group, there was a large amount of new collagen deposition in the wound of the split-thickness skin graft group, and the ratio of FB differentiation into myofibroblast (MFB) was high and lasted for a long time, which was manifested by the sustained high expression of α-smooth muscle actin (α-SMA) in FB; high expression of endothelial cell marker CD34 suggested that vascular endothelial cells were active in function, proliferated vigorously, and had obvious capillary proliferation; TGF-β1 and its receptor TGF-βRI, II and its downstream signal transduction protein Smad3 were highly expressed, while the level of apoptosis was significantly lower than that of the composite graft group (Tables 6.3, 6.4, 6.5, 6.6, and 6.7). It can be seen that the reduction of tissue defect by composite transplantation not only decreased the proliferation, secretion, and synthesis functions of the repairing cells but also promoted the upregulation of apoptosis level. Its effect on repairing cell function is beneficial to reduce scar formation [20–24].

In view of the ethical limitations of clinical trials, we have further refined relevant research through animal experiments.

The histological observation in animal experiments showed that in the early stage of wound healing, FB morphology in the new wounds of the control group and each experimental group was spindle-shaped with obvious polarity, the long axis of the cells and the new collagen were arranged parallel to the skin surface, and the collagen fibers were thin and densely arranged; the collagen in the dermal tissue part of the graft (including the autologous dermis and the acellular dermal matrix) was thick, loose, and woven, the proliferating FB was arranged along the interstitial space of the collagen, and the cells were star-shaped with no obvious polarity. In the late stage of wound healing, compared with the control group, the new collagen in the wounds of each experimental group gradually became thick, loose, and woven, and the arrangement structure of the new collagen was close to that of normal skin tissue, the number of FB decreased significantly, and the cell morphology tend to be star-shaped from the bipolar shape in the early stage of wound healing. The proximity of collagen arrangement and cell morphology changes to normal skin tissue was most obvious in the full-thickness skin graft group, while the effect of autologous thin skin graft alone is poor, and the effect of composite graft group was close to that of full-thickness skin graft group. The above results indicate that the replantation of the dermal tissue accelerates the process of tissue remodeling in the state of natural healing.

In the first week after surgery, the collagen in the new granulation tissue of wound is thin and arranged parallel to the skin surface. In the 20th week after surgery, the procollagen gradually becomes thicker and arranged in a woven pattern, which tend to be characteristic of collagen arrangement in normal skin tissue. Among them, the full-thickness

Table 6.3 Image analysis data of positive expression of mRNA in type III collagen and type III procollagen in each group ($\bar{x} \pm s$, $n = 9$)

	Postoperative time (weeks)			
Test index group	1	2	3	4
Type III collagen composite transplantation group	65.89 ± 5.25	58.27 ± 8.36	52.02 ± 4.85	51.83 ± 5.49
Thick skin group	66.35 ± 3.24	68.23 ± 5.60*	68.28 ± 4.49*	65.64 ± 6.92*
Composite transplantation group	13.63 ± 3.40	17.34 ± 4.89	14.16 ± 3.32	5.29 ± 1.07
Thick blade skin transplantation group	24.40 ± 3.02	24.74 ± 1.87*	22.54 ± 1.65*	19.71 ± 4.16*

Note: Compared with composite graft group, *$P < 0.05$

Table 6.4 Comparison of CD34 expression in wound tissue of each group

	Postoperative time (weeks)			
Group	1	2	3	4
Composite transplantation group	4.0 ± 0.7	4.3 ± 0.9*	3.5 ± 0.5*	3.1 ± 1.13*
Thick blade skin transplantation group	5.3 ± 2.0	5.4 ± 0.8	4.9 ± 1.72	5.6 ± 2.3

Note: Compared with split-thickness skin graft group, *$P < 0.05$

Table 6.5 Comparison of p53 expression in wound tissue of each group ($\bar{x} \pm s$, $n = 9$)

	Postoperative time (weeks)			
Group	1	2	3	4
Composite transplantation group	19.87 ± 3.67	30.57 ± 10.90*	27.08 ± 7.12*	22.85 ± 5.19*
Thick blade skin transplantation group	16.04 ± 3.67	18.60 ± 2.74	19.30 ± 3.02	18.16 ± 1.51

Note: Compared with split-thickness skin graft group, *$P < 0.05$

Table 6.6 Comparison of positive expression rates of TGF-β1, TβRI, II, and Smad3 proteins in each group ($\bar{x} \pm s$, $n = 10$)

Test index group	Group	Time after transplantation (weeks)			
		1	2	3	4
TGF-β1	Composite transplantation group	13.08 ± 4.65	12.36 ± 1.51	11.18 ± 1.88	9.03 ± 1.89
	Thick skin group	19.24 ± 4.59*	14.91 ± 4.17*	13.66 ± 1.58*	11.46 ± 2.37*
TβRI	Composite transplantation group	6.87 ± 2.60	4.30 ± 2.19	2.92 ± 1.21	2.22 ± 0.68
	Thick skin group	10.62 ± 3.95*	6.21 ± 2.09*	4.22 ± 0.86*	3.51 ± 0.74*
TβRII	Composite transplantation group	4.34 ± 1.95	3.51 ± 0.88	2.76 ± 1.04	2.32 ± 0.49
	Thick skin group	6.81 ± 1.20*	5.23 ± 0.86*	3.99 ± 0.58*	2.93 ± 0.64*
Smad3	Composite transplantation group	14.59 ± 4.22	11.36 ± 4.06	10.12 ± 2.02	6.32 ± 1.56
	Thick skin group	23.38 ± 4.00*	16.54 ± 1.99*	13.39 ± 2.03*	9.60 ± 3.07*

Note: Compared with composite graft group, *$P < 0.05$

Table 6.7 Comparison of apoptosis rate in wound tissues of each group ($\bar{x} \pm s$, $n = 9$)

Group	Postoperative time (weeks)			
	1	2	3	4
Composite transplantation group	15.90 ± 6.88	15.40 ± 2.61	23.54 ± 2.48*	34.02 ± 7.20*
Thick blade skin transplantation group	10.98 ± 2.34	13.36 ± 2.52	19.12 ± 3.44	4.61 ± 2.29

Note: Compared with split-thickness skin graft group, *$P < 0.05$

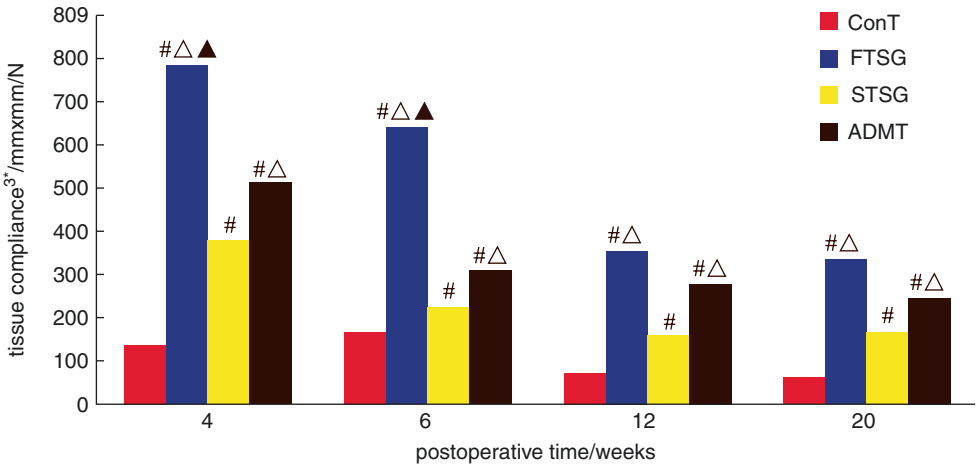

Fig. 6.1 Comparison of biomechanical compliance of wound tissue in each group

Note: Comparison of biomechanical compliance of wound tissue in each group during wound healing

ConT is the natural healing group; FTSG is the full-thickness skin graft group; STSG is the autologous split-thickness skin graft group; and ADMT is the composite graft group

#Compared with the control group, $P < 0.05$; △ FTSG, ADMT compared with STSG, $P < 0.05$; ▲FTSG compared with ADMT, $P < 0.05$

skin graft group is the most obvious, while the effect of autologous split-thickness skin graft alone is worse, and the effect of composite graft group is close to that of full-thickness skin graft group.

Comparison of tissue mechanics compliance and FB function found: in naturally healed full-thickness skin tissue defect wounds, the mechanical compliance of wound skin tissue is poor, the proportion of FB to MFB differentiation is high and lasts for a long time, and cytokines and extracellular matrix components promoting scar formation such as TGF-β1, FN, and integrin α2β1 are highly expressed. If the tissue defect is compensated by dermal tissue replantation, the mechanical compliance of the wound skin tissue is significantly improved, and the functional status of FB including cell differentiation, expression of various extracellular matrix, and expression of matrix and the expression of cytokines promoting scar formation are significantly downregulated. Moreover, this effect is closely related to the thickness of the replanted dermal tissue. Full-thickness skin graft has the best effect and is superior to split-thickness skin graft. If the acellular dermal matrix is applied simultaneously with the transplantation of split-thickness skin (i.e., composite graft), the effect of simple split-thickness skin graft can be significantly improved (Fig. 6.1, Tables 6.8, 6.9, 6.10, 6.11,

Table 6.8 Comparison of α-SMA-positive expression rates in wound tissue of each group ($\bar{x} \pm s$, $n = 6$)

Group	Postoperative time (weeks)				
	1	2	4	6	12
Natural healing group	28.02 ± 2.73	33.53 ± 1.62	26.99 ± 2.90	8.60 ± 0.74	4.85 ± 0.58
Full-thickness skin transplantation group	8.32 ± 1.44#,*	15.71 ± 1.82#,*,▲	6.29 ± 0.77#,*	5.39 ± 0.44#,*	1.71 ± 0.32#,*,▲
Thick blade skin transplantation group	20.42 ± 2.20#	22.91 ± 2.22#	12.18 ± 2.79#	6.87 ± 0.41#	2.50 ± 0.26#
Composite transplantation group	10.28 ± 3.99#,*	21.78 ± 1.66#	7.53 ± 0.98#,*	5.70 ± 0.46#,*	2.20 ± 0.28#

Note: Other groups compared with the control group, #$P < 0.01$; comparison of FTSG, ADMT and STSG, *$P < 0.01$; comparison of FTSG and ADMT, ▲$P < 0.01$

Table 6.9 Comparison of FN-positive expression rates in wound tissue of each group ($\bar{x} \pm s$, $n = 6$)

Group	Postoperative time (weeks)				
	1	2	4	6	12
Natural healing group	33.23 ± 0.88#	33.00 ± 2.38#	36.76 ± 2.88#	31.43 ± 2.06#	17.93 ± 1.66#
Full-thickness skin transplantation group	19.48 ± 2.00*,▲	20.86 ± 1.34*,▲	18.65 ± 2.24*,▲	18.03 ± 0.77*,▲	5.86 ± 0.66*,▲
Thick blade skin transplantation group	25.66 ± 1.71	29.18 ± 1.28	26.59 ± 2.61	24.55 ± 1.72	8.59 ± 1.09
Composite transplantation group	22.06 ± 1.43	23.70 ± 1.41▲	21.94 ± 2.24▲	19.27 ± 1.28▲	6.10 ± 0.41

Note: Other groups compared with the control group, #$P < 0.01$; comparison of FTSG, ADMT, and STSG, *$P < 0.01$; comparison of FTSG and ADMT, ▲$P < 0.01$

Table 6.10 Comparison of integrin α2-positive expression rates in wound tissue of each group ($\bar{x} \pm s$, $n = 6$)

Group	Postoperative time (weeks)				
	1	2	4	6	12
Natural healing group	22.15 ± 2.04	26.96 ± 3.18	16.69 ± 3.26	7.94 ± 1.26	4.89 ± 0.69
Full-thickness skin transplantation group	14.40 ± 1.62#,*,▲	16.78 ± 3.08#,*,▲	7.76 ± 1.06#,*	5.11 ± 0.43#,*	3.49 ± 0.99
Thick blade skin transplantation group	19.45 ± 1.22#	23.12 ± 1.51#	11.72 ± 1.56#	6.48 ± 0.56#	4.35 ± 0.63
Composite transplantation group	17.26 ± 1.38#,*	19.97 ± 2.04#,*	8.18 ± 1.07#,*	5.69 ± 0.66#	3.95 ± 0.68

Note: Other groups compared with the control group, #$P < 0.01$; comparison of FTSG, ADMT, and STSG, *$P < 0.01$; comparison of FTSG and ADMT, ▲$P < 0.01$

Table 6.11 Comparison of integrin β1-positive expression rates in wound tissue of each group ($\bar{x} \pm s$, $n = 6$)

Group	Postoperative time (weeks)				
	1	2	4	6	12
Natural healing group	25.25 ± 1.13#	34.35 ± 2.96#	40.68 ± 3.23#	10.56 ± 1.08#	8.12 ± 1.35#
Full-thickness skin transplantation group	17.61 ± 1.59*,▲	18.71 ± 1.07*,▲	13.16 ± 1.44*,▲	5.89 ± 0.44*,▲	4.31 ± 0.36*,▲
Thick blade skin transplantation group	20.57 ± 2.17	26.51 ± 2.61	20.28 ± 1.94	9.04 ± 0.98	6.46 ± 0.36
Composite transplantation group	21.72 ± 1.17	21.64 ± 1.46*	17.96 ± 1.15*	7.05 ± 0.79*	5.20 ± 0.98

Note: Other groups compared with the control group, #$P < 0.01$; comparison of FTSG, ADMT, and STSG, *$P < 0.01$; comparison of FTSG and ADMT, ▲$P < 0.01$

and 6.12). The results suggest that tissue compliance and functional status of FB are closely related to the degree of dermal tissue defect. The smaller the defect, the better the tissue compliance and the regulation of FB function, thus promoting the process of tissue repair to reduce scar formation [25, 26].

The mechanical compliance of wound tissue healed naturally is poor. Skin transplantation can improve the mechanical compliance of wound tissue, among which, the full-thickness skin graft group has the best effect, while the split-thickness skin graft group has the worst effect, and the effect of the composite graft group is between the full-thickness skin graft group and the split-thickness skin graft group.

The results of animal experiments are basically consistent with the trend of clinical experiments, indicating that the degree of skin dermis defect can regulate multiple aspects in wound healing process and is a key factor affecting scar formation.

Then, why does the defect of dermal tissue affect the mechanical compliance of skin tissue and the function of FB? What mechanism does dermal tissue play its regulation during wound healing? Is it through the structure or composition of dermal tissue? For this, we have carried out further research.

Table 6.12 Comparison of TGF-β1-positive expression rates in wound tissue of each group ($\bar{x} \pm s$, $n = 6$)

Group	Postoperative time (weeks)				
	1	2	4	6	12
Natural healing group	24.09 ± 0.96#	36.83 ± 2.63#	28.24 ± 1.62#	24.23 ± 2.43#	23.29 ± 2.11#
Full-thickness skin transplantation group	18.27 ± 1.18	15.79 ± 0.80*	16.74 ± 1.13*,▲	13.22 ± 1.89*,▲	10.67 ± 0.93*,▲
Thick blade skin transplantation group	18.88 ± 2.13	19.12 ± 1.93	22.66 ± 1.33	19.72 ± 1.44	16.79 ± 0.85
Composite transplantation group	18.31 ± 1.62	16.41 ± 1.88*	18.66 ± 0.79*	14.94 ± 1.11*	14.39 ± 0.99*

Note: Other groups compared with the control group, #$P < 0.01$; comparison of FTSG, ADMT, and STSG, *$P < 0.01$; comparison of FTSG and ADMT, ▲$P < 0.01$

6.2.3 The Role of Three-Dimensional Structure and Composition of Dermal Tissue in Regulating Biological Behavior of FB

The dermal tissue consists of two parts: the tissue structure and the composition. In vitro studies have shown that various extracellular matrix components can have different effects (inhibition or promotion) on cell function, and the relevant results are often obtained without involving their three-dimensional structure. Tissue structure can also have an important impact on cell function. So is the effect of dermal tissue on the wound healing process achieved through its structure or its composition? What is the relationship between the structure and composition of the tissue? For this reason, we have carried out further research.

6.2.3.1 The "Permissive Effect" of the Dermal Tissue Structure on the Composition

We studied the effects of three-dimensional structures and three-dimensional structures of different materials on FB. The decalcified cancellous collagen and the biological sponge (porous material) were implanted into the subcutaneous of SD rats, and the samples were taken at the first week and the second week, respectively. The histological observation revealed that the collagen arrangement of the fibrous wrapping part (i.e., the part without the three-dimensional scaffolds) outside the decalcified cancellous collagen and the biological sponge was single and uniformly parallel, and the FB morphology was spindle-shaped with obvious polarity, which was similar to the FB morphology and collagen arrangement in the granulation tissue of the wound. While the morphology of FB migrating into the pores of decalcified cancellous collagen and biological sponge (i.e., the part with three-dimensional scaffolds) was diverse, and the collagen was arranged along the scaffold in a multidirectional manner, which was similar to the cell morphology and collagen arrangement of the autologous dermal part or acellular dermal matrix part of the wound graft. It is worth noting that:

(a) FB showed distinct cell morphology in different parts of the same wound (with three-dimensional structure part and no three-dimensional structure part).

(b) There were no significant differences in the effects on cell morphology and collagen arrangement between two different materials, decalcified cancellous collagen and biological sponge. Does this suggest that the three-dimensional structure of the tissue may play a dominant role in the effect of repairing cell function, and that the effect of dermal tissue on the wound healing process is mainly through its physiological structure? In order to further clarify the relationship between structure and composition, we carried out in-depth studies.

We used an in vitro culture model to study the relationship between structure and composition. The in vitro culture system of adherent cells is basically divided into two-dimensional culture and three-dimensional culture. Inoculation of cells directly on the culture dish or coating the culture dish with a certain extracellular matrix component and then inoculating the cells on it all belong to two-dimensional culture. Traditional three-dimensional culture coats the suspension of collagen and cells on the culture dish. If the collagen gel adheres to the culture dish base, it forms an anchoring matrix; if the collagen gel is separated from the culture dish base, it is a floating matrix. The anchoring matrix is in a high tension state due to adhesion to the culture dish base, similar to the two-dimensional culture, and the situation is similar to the hypertrophic scar. And the floating matrix has low tension, similar to normal skin, and is relatively close to the physiological state. A new three-dimensional culture model is currently established, which utilizes repeated passages of cells in situ and accumulates extracellular matrix secreted by cells during growth. This three-dimensional culture model has been proven to be more in line with the physiological situation in terms of composition, structure, and mechanical properties, and can more mimic the physiological state, known as the new three-dimensional matrix. On this basis, the new three-dimensional matrix is compressed by external pressure, which is called the new three-dimensional culture compressed matrix; or the new three-dimensional matrix is dissolved by enzymatic digestion and coated on the Petri dish, which is called the new three-dimensional culture dissolved matrix. The latter two methods aim to destroy their three-dimensional structure and essentially belong to two-dimensional culture.

The experiments were grouped as follows: FN, LN, collagen-coated culture matrix and new three-dimensional culture matrix, new three-dimensional culture compression matrix, and new three-dimensional culture dissolution matrix were used to observe the effects of different substrates on MFB induction. The results showed that FN, LN, collagen-coated culture matrix, and new three-dimensional culture dissolution matrix could induce MFB, especially the FN-coated culture matrix; the new three-dimensional culture compression matrix with structural damage can also induce the production of MFB compared with the new three-dimensional culture dissolution matrix, but the new three-dimensional matrix is difficult to induce MFB.

Why can different matrix components induce MFB under two-dimensional culture conditions? Why does the dissolved matrix or the compressed matrix with damaged three-dimensional structure can induce MFB, whereas the more physiological three-dimensional matrix does not induce MFB? Studies have shown that the mechanical properties of the two-dimensional culture system are similar to those of tissues in the early stage of wound healing, and can make the cell function in the culture system more active. The new three-dimensional matrix has been proven to be more physiological in terms of composition, structure, and mechanical properties. It can be seen that although the components of the extracellular matrix may have an effect on the function of FB, the effect is conditional and closely related to the structure of the extracellular matrix and its corresponding mechanical properties. Under non-physiological conditions, extracellular matrix components can promote the development of FB function toward over proliferation; when the structural and mechanical properties of the extracellular matrix return to the physiological state, the abnormal effects of the extracellular matrix components on cell function will disappear. Therefore, the three-dimensional structure of the extracellular matrix plays a "permissive role" in regulating cell function and affecting the outcome of tissue repair.

6.2.3.2 Tissue Structure Is the "Template" that Guides the Trend of Cell Function

We observed that the morphology and collagen arrangement of FB in the larger pore size of decalcified cancellous collagen were closer to the granulation tissue wound, while those of FB in the smaller pore size were closer to the autologous dermis. This phenomenon suggests that the size of tissue spatial structure may have an effect on the function of the cells, and we have studied this phenomenon.

In the experiment, collagen membranes with three-dimensional spatial structure and pore sizes of 200 μm, 500 μm, and 1000 μm were implanted subcutaneously in SD rats, and the samples were taken for three consecutive weeks to observe the effect on FB function. It was found that the cell proliferation level of the 500 μm collagen membranes reached its peak at the second week, which was higher than that of the 200 μm and 1000 μm, and began to decline rapidly at the third week, which was lower than the latter two materials. The apoptotic level was opposite: The apoptotic level of 500 μm collagen membrane was lower than that of the 200 μm and 1000 μm collagen membranes in the first 2 weeks, and higher than the latter two materials in the third week.

The results suggest that there is a degree of regulation of cell function by tissue spatial structure. The appropriate three-dimensional structure can promote the completion of the cell cycle as soon as possible, and the inappropriate tissue structure is not conducive to the recovery of cell function.

This result was further confirmed in vitro experiments. The new three-dimensional matrix cannot induce MFB, and the cell morphology recovered quickly. Five hours after cell inoculation, the FB morphology was short fusiform and spread, basically normal FB morphology, indicating that the physiological cycle of cells on the physiological matrix was shortened. The cell adherent rate on the new three-dimensional matrix was about six times that of the two-dimensional culture (Fig. 6.2), and there was no significant difference in cell adherent rate between different two-dimensional culture matrices.

The above results indicate that the structure of the extracellular matrix is a "template" to guide the functional trend of cells, and the closer its structure is to the physiological state, the more favorable it is for the recovery of cell biological behavior [27–30].

6.2.3.3 The Integrity and Continuity of the Tissue Structure Is the Key for Dermal Tissue to Play a "Template Role"

In vivo experiment, we observed that the acellular dermal matrix was filled with more granulation tissue in the void portion caused by dermatome in the composite graft, and the function of FB in this part was also active. Does this suggest

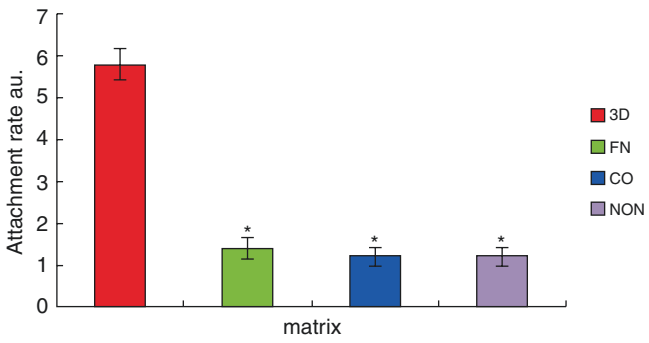

Fig. 6.2 Comparison of FB adherent rate on different matrices in 10 min
Note: Compared with the 3D group, $^{*}P < 0.01$

that the tissue integrity or continuity has a great impact on tissue repair? To verify this hypothesis, we designed experiments in which collagen membranes cut into pieces and structurally intact collagen membranes (with three-dimensional structure) were implanted subcutaneously into the back of SD rats, respectively, and sampled 1–3 weeks after the operation. Histological observation of sections showed that the granulation tissue with incomplete collagen membrane structure proliferated obviously, while the granulation tissue with intact structure was less. It can be seen that the integrity or continuity of the tissue structure is also crucial to the full play of its "template role."

In summary, the defect of the dermal tissue and its degree are the fundamental causes of scar hypertrophy. The mechanism is that the degree of dermal tissue defect affects the wound healing process. The three-dimensional structure of dermal tissue has a "template" guiding effect on the function of repairing cells, which can not only induce the growth of repairing cells but also improve the mechanical state of wound skin tissue, regulate the biological behavior of repairing cells, and promote tissue remodeling. The structure of the dermal tissue has a "permissive" effect on the composition. Under the non-physiological conditions, the extracellular matrix components can have an abnormal effect on the function of the repairing cells. Once the structural and mechanical properties of the extracellular matrix return to the physiological state, the abnormal effect of the extracellular matrix components on cell function will disappear. The appropriate three-dimensional structure can promote the completion of the cell physiological cycle, and the closer the structure is to the physiological state, the more favorable to the recovery of cell biological behavior. The integrity and continuity of the dermal tissue is the necessary prerequisite for tissue structure to fully play the role of "template." The damage of integrity and continuity of dermal tissue caused by trauma, which leads to the loss of "template effect" of dermis, may be one of the important mechanisms affecting the function of repairing cells and leading to scar formation. Therefore, the "template defect theory" of scar formation is proposed.

6.2.4 The Microscopic Discussion of "Template Defect Theory"

6.2.4.1 The Influence of the "Bridge Piers" Like Structure of the Dermal Template Unit on FB

What is a suitable three-dimensional structure? What characteristics should a suitable three-dimensional structure have? To understand the role of the dermal template, it is necessary to be explored at the microscopic level.

We conclude that the template-like function of the dermis, as a functional manifestation of the dermal tissue structure, must have its basic composition. It has the necessary information of the dermal template, including the basic structure and composition of the dermal template. We call this basic composition the "dermal template unit." The dermal tissue can regulate normal biological behavior and phenotype of the cells through dermal template unit at the microscopic level.

So, how can we understand the regulation of dermal template unit on cells at the microscopic level? Firstly, fibroblasts in dermal tissue have adhesion characteristics. Secondly, the adhesive components are widely distributed in the extracellular matrix of the dermal tissue, and the cells can only function by forming adhesion points (focal adhesion) in combination with the adhesive components. Therefore, these adhesion components, which form focal adhesion with adherent cells, are arranged in the extracellular matrix like "bridge piers" to guide cell proliferation, migration, and expansion. In the local wound, the appropriate arrangement of "bridge piers" can effectively guide the cells to play normal functions, participate in the wound repair process, and maintain the original mechanical properties of the wound.

In this study, type I collagen was selected as the cell adhesion point material. A "bridge piers" like structure array consisting of type I collagen was fabricated on a planar matrix using micro printing technology. Meanwhile, molecular self-assembly technology was applied to cover cell non-adhesive material poly-lysine-grafted polyethylene glycol (PLL-g-PEG) molecules around the "bridge piers" to ensure that cells only adhere to the "bridge piers" (Fig. 6.3). This allows us to explore the regulatory effect of micropier grid used for cell culture (MPGCC) on cell function by adjusting the size and spacing of the piers within the micro scale of cells. After culturing with different parameters of MPGCC, FB morphology showed diversity, α-SMA expression increased, cell viability decreased, and hydroxyproline level increased, suggesting that MPGCC with cell adhesion characteristics can regulate cell biological behavior. However, the impact of the "bridge piers" like array design on cell biological behavior is far from the expected [31]. Therefore, how to understand the rational layout of cell adhesion points in the dermal matrix, that is, how to set the arrangement and effective spacing between the "bridge pier" and the "bridge pier," in order to achieve the desired purpose of tissue repair by regulating cell function, is worth our deep exploration.

6.2.4.2 Mathematical Derivation of the Spatial Relationship of the "Bridge Piers" Structure Array of the Dermal Template Unit in the Three-Dimensional Structure

In order to clarify the relationship between the "bridge piers" like structure and the dermal template and the template unit, and to explore the rational layout of the "bridge piers" like structure in depth, we synthesized the previous research

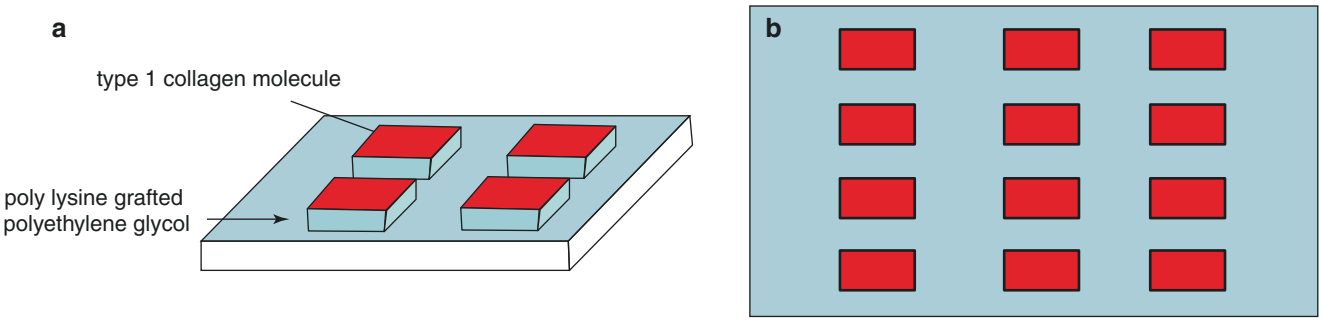

Fig. 6.3 Schematic diagram of "bridge piers" like structure array for cell adhesion

Note: **a**—stereogram; **b**—plan. Red is slightly convex, coated with cell adhesion material; blue is base, coated with non-adhesive material

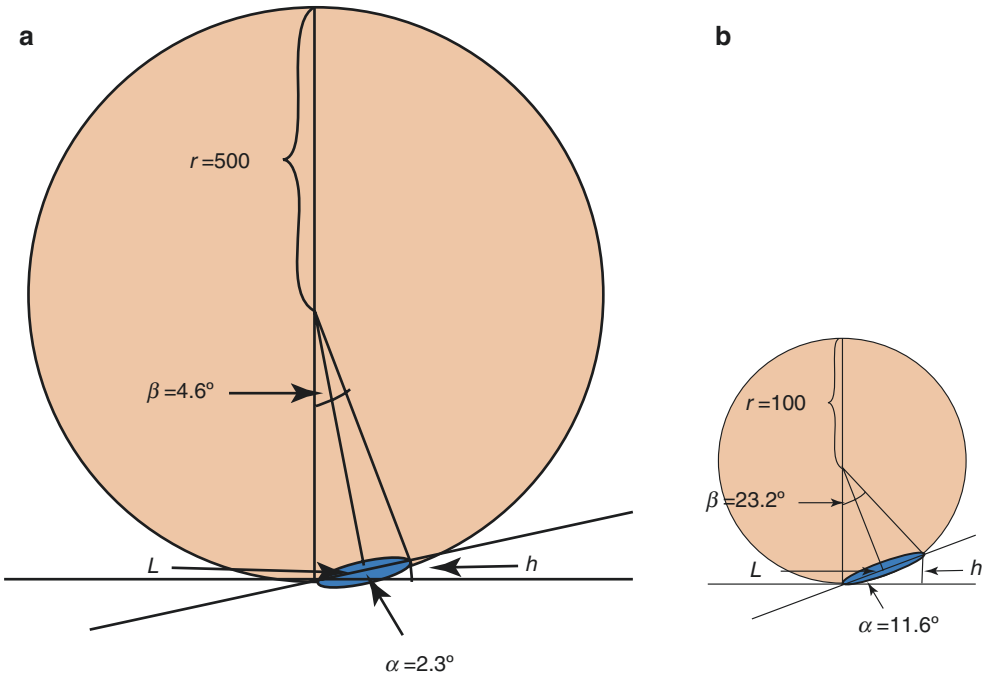

Fig. 6.4 Mathematical schematic of cell adhesion in different pore sizes
Note: h represents the height difference between the two ends of cells' long axis after cell adhesion. L represents the long axis of the cell. r represents the pore size. α represents the adhesion angle, and β represents the arc angle occupied by cells after adherence to the pore. $\angle \beta = 360°/(2\pi r/L)$, $\sin\alpha = h/L$, $\sin(\beta/2) = (L/2)/r$, $\sin\alpha = \sin(\beta/2)$, therefore, $h/L = (L/2)/r$, $h = L^2/2r$

results and used mathematical methods such as trigonometric function and plane geometry for analysis and verification.

Previous studies have suggested that the geometry in three-dimensional structures of tissues can alter the biological function of cells. The change of geometric shape in three-dimensional structure can be summarized as a combination of various curvatures. So, how to find the intrinsic relationship related to cell regulation in such a complex and variable curvature combination? We select circles with a single curvature for analysis. Assuming that the diameters of the circles are 100 μm and 1000 μm, and assuming that the length of the adherent cells is the same (40 μm), a mathematical derivation is used to illustrate the effect of curvature on cells. It is found (Fig. 6.4) that different curvatures have different deviation angles ($\angle\gamma$).

The larger the curvature, the smaller the aperture and the larger the deviation angle. Since dermal fibroblasts have the properties of contact adhesion with the material surface, the proliferation, migration, and extension of the cells are inseparable from the presence of adhesion points on the material surface. Therefore, the adhesion points on the material surface play a key role in the influence of curvature on the bending of the cell. When the cells adhere to the curved surface, the two ends of the cells' long diameter have different heights (h) from the cross-sectional observation. The smaller the aperture, the larger the deviation angle, the larger the height difference between the two ends of the cells' long diameter, and the greater the bending degree of cell adhesion on the curved surface. Ingber's study also suggests that the bending of the cell body will cause the cytoskeleton to bend, which in turn causes changes in cell function. It indicates that curved surfaces with different deviation angles can cause different degrees of cell body bending, which may be one of the reasons for the difference of cell function [32].

6.2.4.3 Study on the Effect of Spatial Angle Arrangement of "Bridge Piers" Like Structure of Dermal Template Unit on Fibroblasts

Studies have shown that the movement of adherent cells in the extracellular matrix is fan-shaped, and this special shape is related to the distribution of focal adhesion on the cells. According to our view that the cells are regulated by the angle formed by the adhesion points, this sector shape seems to be simulated with different triangles. In order to verify this hypothesis, this study used CAD to design a "bridge piers" like structure array with different angles to observe their effects on cell biological behavior.

The horizontal and vertical lines are arranged on a 2 × 2 cm plane, and the spacing between the horizontal lines and vertical lines is 40 μm, forming a square grid with a side length of 40 μm. In each square, make a circle with a diameter of 40 μm. A vertical line from the center of the circle intersects with the circle as the first line, intersects with the circle through the center of the circle, and forms a θ angle with the first line as the second line, forming a sector area. Take the three vertices of the sector area as the center to make a circle with a diameter of 5 μm as the pier. The "bridge piers" like structure arrays with different angles are prepared by changing the angles of θ (20°, 40°, 60°, and 80°). The array consists of isosceles triangles with different apex angles. Define the two same sides (pier spacing) of the isosceles triangle as L and the apex angle as θ.

Then, the area of the triangle (S) = (bottom × height)/2 = $[L \times (L \times \sin\theta)]/2 = (L^2 \times \sin\theta)/2$.

That is to say, the area formed by the triangular "bridge-piers" like array is related to the angle change. The larger the angle is, the larger the area is. Fibroblast function test showed that with the increase of the regulation angle, the cell proliferation increased, the expression of α-SMA was downregulated, and the level of hydroxyproline secreted by the cells decreased, showing a trend of benign cell growth. It can be seen that the triangular structures with different angles composed of three cell adhesion points can regulate the cell functions differently.

Donald's research found that with the increasing of cell adhesion area, the extent of cytoskeleton stretching increased, and the cells could expand effectively, which was beneficial to cell survival. In this study, by changing the angle, the triangle area in the array increases with the angle, and the line between the three vertices of the triangle determines the area of the triangle. Therefore, through the variation of the spatial position of the three apexes with adhesion, the degree of stretch of the cells exerts an influence. Mathematical analysis found that this effect was related to the cell effect caused by the increase of adhesion area.

By adjusting the different triangular structures formed by cell adhesion points and their relationship with the degree of cell stretching, this study further demonstrates the view that cell biological behavior is regulated by the environmental structure. It is speculated that the triangle formed by the three cell adhesion points may be the basic framework for cells to manifest their functions in the matrix environment or the basic unit of the dermal template—"dermal template unit."

This study not only further enriches and supports the "dermal template defect" theory of scar formation mechanism but also provides a research platform for further studying the relationship between extracellular matrix material, three-dimensional structure, and cell biological behavior at the microscopic level by establishing a cell culture system of "bridge piers" array.

6.3 Scar Prevention

The formation of scars not only affects the appearance but also the severe scar deformity affects the function of the body [33]. The prevention and treatment of scars caused by different reasons are also different.

6.3.1 The Prevention of Therapeutic Scars

The therapeutic scars mainly refer to scars caused by iatrogenic injuries such as surgery, injection, and laser treatment.

(a) Prevention during operation: Superb suture technique is the key to scar prevention. Appropriate choice of operation timing and mode, aseptic technique during operation, elimination of invalid cavity, no foreign body residue, adequate reduction of wounds, and layered suture are all crucial [34]. The knot should be buried under the skin in subcutaneous suture, and the skin edge should be slightly everted [35] using the noninvasive suture needle thread and the knot strength to prevent the formation of "centipede-like scar" in the future [36].

(b) Prevention after operation: firstly, prevent wound infection. Antibiotic treatment is used prophylactically for contaminated or susceptible wounds [37]. After wound healing, early application of drugs and appropriate pressure therapy, at least 3–6 months [38]. Recent studies have confirmed that regular and quantitative injection of botulinum toxin type A around wounds can effectively inhibit the formation of postoperative scars [39].

6.3.2 The Prevention of Non-therapeutic Scars

Non-therapeutic scars mainly refer to scars caused by trauma and burns. These injuries are often severe and have different degrees of pollution. Therefore, the prevention of such scars focuses on prevention and control of infection, reduction of inflammatory reaction in wound healing, promotion of wound healing, and early closure of wounds.

(a) For large wounds that are difficult to heal with autologous skin, the transfer of adjacent flaps or autologous skin grafting can be considered to promote wound healing [40].
(b) Intervention in wound healing process. Physiotherapy can be used in the healing process, such as hyperbaric oxygen therapy, wax therapy, infrared therapy, and He-Ne laser treatment after the injury, to promote the early healing of wounds [41].
(c) Intervention after wound healing. The wound is healed, continuous compression therapy is applied for half a year. Early application of anti-scar hyperplasia drugs to prevent scar hyperplasia [42].

The prevention of scars is very complicated. A single method is sometimes difficult to work, and comprehensive intervention in a variety of methods can achieve better results.

6.4 Keloid Treatment

6.4.1 Surgical Resection

Surgical treatment is the main method for mature scars or keloids, which has the characteristics of direct operation and the most significant effect of reducing scar area in the near future. In view of the high recurrence rate after surgery, no single surgical treatment is used, but the combination of radiotherapy, drug injection therapy, and surgery is advocated. It should be emphasized that it is impossible to remove the scar completely by any surgical method, but to minimize or correct the damage caused by the scar; and after the healing of the surgical knife edge, it is faced with the occurrence of new scars, and the evaluation of the therapeutic effect needs to be observed for more than 1 year [43].

6.4.2 Physical Therapy

Commonly used are compression therapy, cryotherapy, laser therapy, radiation therapy, silicone gel sheeting, and adhesive tape therapy.

6.4.2.1 Compression Therapy

Commonly used compression methods include binding elastic bandages, wearing stretch fabrics, wearing pressure earrings (for keloids on the earlobe), and wearing compression clothing. The effect of compression therapy on keloids is slow, the treatment time is long, and some body parts are inconvenient to operate.

6.4.2.2 Cryotherapy

Cryotherapy uses cryogens such as liquid nitrogen to destroy cells and micro vessels in scars at low temperatures, resulting in hypoxic necrosis and exfoliation of tissues, so as to eliminate scars. The main adverse reactions are blister formation, delayed wound healing, depigmentation, or pigmentation.

6.4.2.3 Laser Therapy

Laser therapy is currently the most promising and constantly updated treatment model for keloids. However, the main problems are insufficient penetration, insufficient treatment depth, unsatisfactory efficacy, and inevitable recurrence, which need further improvement [44].

6.4.2.4 Radiation Therapy

Radiation therapy can be used as a single treatment or an adjuvant treatment after surgery. Side effects of radiation therapy include erythema, skin atrophy, ulceration, telangiectasia, pigmentation, and delayed wound healing. For younger people, potentially carcinogenic sites (breast and thyroid) and large area, multi-site lesions should be prohibited [45].

6.4.2.5 Silicone Gel Sheeting

The application of silicone gel sheeting is easy to use, no pain and fewer side effects, which has been gradually promoted. It can avoid spinal growth and development deformity caused by chest bandage compression therapy in children, and is suitable for patients who cannot tolerate other methods.

6.4.2.6 Adhesive Tape Therapy

Adhesive tape is used to prevent and treat keloids. It is characterized by low sensitization, suitable viscosity, multi-microporous, and some elasticity.

6.4.3 Drug Treatment

These drugs mainly include steroid hormones, retinoic acid, antitumor drugs, cytokine-related treatments, drugs regulating collagen metabolism, antihistamines, and traditional Chinese medicine, as well as calcium antagonists and tacrolimus (FK506), bleomycin and newly emerged drugs botulinum toxin type A (BTX-A), and other drugs [46].

6.4.3.1 Apoptosis-Related Drug Therapy

(a) Steroid hormones: Corticosteroids for the treatment of keloids are mostly topical, and can be used alone or in combination with other methods. Postoperative steroid hormone therapy has become one of the most popular treatments for keloids. Common adverse reactions of corticosteroid therapy include skin atrophy, pigmentation or depigmentation, necrosis, ulceration, Cushing's syndrome, and physiological dysfunction, which can be reversed in a small part after withdrawal.

(b) Retinoic acid: Retinoic acid is a vitamin A-related drug that interferes with the synthesis of DNA in fibroblasts, inhibits proliferation, prevents collagen synthesis, and thus inhibits the growth of keloids [47].

(c) Fluorouracil: 5-Fluorouracil is a tumor chemotherapy drug, which can inhibit the proliferation of fibroblasts and the ability to synthesize collagen, and at the same time degrade the total amount of collagen, thereby achieving the purpose of treating keloids.

6.4.3.2 Cytokine-Related Therapy

Anti-positive growth factors and negative growth factors such as interferon-γ can inhibit the secretion of recombinant basic fibroblast growth factor by fibroblasts, thereby inhibiting collagen synthesis, reducing wound inflammation, and inhibiting scar hypertrophy [48].

6.4.3.3 Traditional Chinese Medicine Treatment

Traditional Chinese medicine believes that keloid is qi and blood stagnant in the meridians, is a sputum disease, is a meridian sputum, sinister poison and body turbidity, blood stasis caused by the disease. Traditional Chinese medicine has provided new ideas for the treatment of keloids with its advantages of syndrome differentiation and treatment, natural, non-toxicity, and various kinds [49].

Although there are many treatments for scars at present, there is a lack of recognized and universally effective standard methods. At present, it is generally advocated that a variety of methods should be used in combination at home and abroad, such as surgery, drugs, radiotherapy, cryotherapy, laser, and other therapies should be combined with two, three, or even four to achieve better results [50]. In general, surgical treatment is the main treatment for various mature scars, while compression therapy, radiation therapy, and drug injection therapy have a poor effect on mature scars, which are often used as auxiliary measures for surgical treatment. For keloids, surgery and drug injection therapy or surgery and radiation therapy should be used in combination, or drug injection therapy or radiation therapy alone can be used, but surgery should not be used alone. The research on the treatment of keloids has progressed rapidly and has now reached the level of gene and cell molecular biology. The recent development of gene therapy, stem cell therapy, and bioengineering technology will undoubtedly bring new hope for keloid treatment [51].

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