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Application of Hydrogel Microneedles in the Prevention of Hypertrophic Scars

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Abstract. The scar hyperplasia period lasts several years, and the subsequent atrophy period can make it difficult for patients to recognize. The pain and functional damage caused during this process are equivalent to secondary damage to the patient's physical and mental health. However, the previous scar repair methods have some shortcomings. Surgical resection cannot guarantee that the scar will not recur, and the use of dressings makes it difficult for drugs to penetrate the skin, resulting in low drug absorption. However, the previous scar repair methods have some shortcomings. Surgical resection cannot guarantee that the scar will not recur, and the use of dressings makes it difficult for drugs to penetrate the skin, resulting in low drug absorption. Therefore, microneedles have been considered a new scar repair method due to their painlessness, convenience, and other advantages. Among all the materials, hydrogel is considered one of the most suitable materials for preparing microneedles, due to its fantastic biocompatibility and biodegradability. This article will introduce scar formation, scar repair drug gallic acid, and hydrogels by classification and examples. After discussion, we found that synthetic hydrogels and natural hydrogels have advantages and disadvantages, to combine their benefits, we need to develop composite hydrogels, however, this is a lot of energy and money, we hope that more and easier to prepare, with better performance of composite hydrogels can be developed in the future.

Keywords: hypertrophic scar, wound healing, hydrogel microneedle.

1. Introduction

Accounting for more than 10% of the body's total weight, the skin is the body's largest organ and the part of the body that interacts most intimately with the environment [1]. It maintains internal balance by preventing water loss, regulating body temperature, and warding off pathogenic microorganisms and toxic substances [1,2]. At the same time, it is a very fragile tissue. Human skin is highly susceptible to extensive bruising in accidents, resulting in unsightly and hard-to-heal wounds, especially resulting in hypertrophic scars. Hypertrophic scars (HTS) arise from dermal injuries such as trauma and burns that penetrate the deeper layers of the dermis. These scars are characterized by redness, elevation, itching,

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and pain. When hypertrophic scars affect the mobile areas of the skin, they can lead to cosmetic disfigurement or contracture [3].

Available treatments for hypertrophic scars include compression therapy, gel sheets, scar massage, corticosteroid injections, corticosteroid tapes and creams, and laser therapy. Compression therapy helps to reduce the thickness of scars but may be uncomfortable when used for long periods. Gel sheets need to be used strictly and consistently to be effective. Scar massages have mixed results and sometimes worsen scars. Corticosteroid injections are effective but can be painful and have side effects, while corticosteroid tapes and creams are less painful but require consistent use. Laser therapy can reduce redness and itching but has a high recurrence rate. In addition, surgery may lead to recurrence if not combined with tension release techniques [4].

Microneedles (MNs) are a new method of drug delivery consisting of a series of microneedles, usually less than 1 millimeter in length, that penetrate the outermost stratum corneum of the skin without reaching the deeper tissues that are more sensitive to pain. It can be made from different types of hydrogels that consist of various advantages. According to the latest research, microneedles have a great advantage in healing hypertrophic scars. Microneedling is a minimally invasive treatment in which therapeutic drugs are injected directly into the skin. Microneedles effectively penetrate the stratum corneum without causing significant pain or discomfort, thus improving patient compliance. Tiny needles create micro-channels in the skin that allow for precise delivery of medications to regulate scar formation and improve skin texture [5].

2. The process of wound healing

After the skin injury, the sub-endothelium, collagen, and tissue factor exposed will activate platelet aggregation [6]. After the hemostasis and inflammatory phase, the cytokines such as Transforming Growth Factor-β(TGF) family, and the Transient Receptor Potential (TRP) C3 will be used to make the wound encompasses fibroblasts, keratinocytes, and endothelial cells. Extracellular matrix (ECM), including proteoglycans, hyaluronic acid, collagen, and elastin forms a granulation tissue to replace the original formation of clot[6-8]. In this phase, the TRPC3 and TGF-β promote the expression of the fibroblast and fibronectin gene and lead to the increase of the fibroblast and fibronectin and wound contraction [7,8].

3. The formation of hypertrophic scars

Two main passways are reasonable for the formation of hypertrophic scar: the TGF-β passway and the TRPC3 passway [7-9].

3.1. The TRPC3 passway in the formation of hypertrophic scar

The TRPC3 channel is a potential mechanical force transducer that plays an important role in the pathogenesis of hypertrophic scarring. In the setting of repetitive mechanical stretching of cutaneous wounds, TRPC3 expression is increased and leads to the increase of the calcium ion, which results in increased calcium influx and the activation of NFkB. The NFkB will combine with the gene of fibronectin on the kB binding site and increase the expression of the gene. This in turn causes enhanced production of fibronectin [7]. As the mechanical stretch increases, the TRPC3 channel is over-activated and results in the over-expression of the fibronectin, which was reasonable for the wound contraction, the overexpression of fibronectin may cause the lock of the joints and form a hypertrophic scar [9].

3.2. The TGF-β pass way in the formation of hypertrophic scar

Dysregulation of the TGF-β/Smad signaling is a major factor in the framework of scarring and fibrosis, leading to aberrant collagen synthesis and deposition, a higher proportion of collagen I/III, and the formation of abnormally cross-linked collagen fiber bundles. TGF-β plays a pivotal role in producing the myofibroblast phenotype that is responsible for the massive collagen deposition and contraction of wounds [10]. Hence when the TGF-β is over-activated, the Smad-dependent passway will be over-activated by the expression of the Smad2, and Smad7 proteins, and this leads to the over-expression of the gene of the fibroblast, and the fibroblast will produce the protein including collagen. Which leads to the formation of the hypertrophic scar (fig. 1) [10].

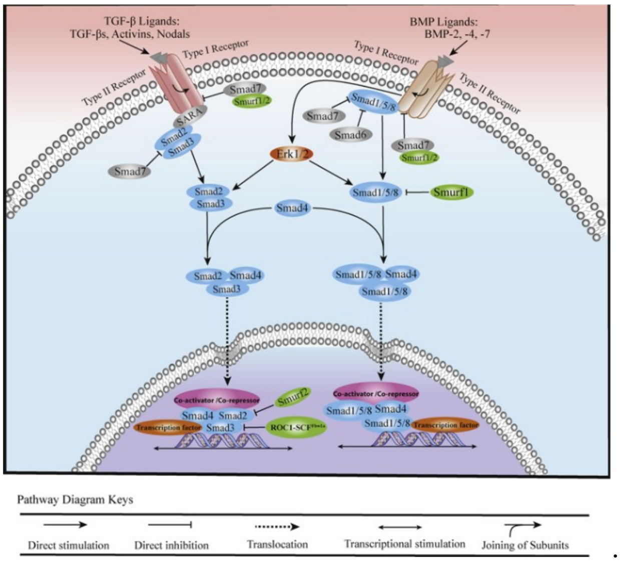

Figure 1. TGF-β-induced Smad-dependent pathway [10].

4. The prevention of hypertrophic scars

Since the TRPC3 and the TGF-β are very important channels in wound healing, at the same time, they are also mainly reasonable channels for the formation of hypertrophic scar [6]. The prevention of the hypertrophic scar based on the TRPC3 and TGF-β channels needs to be controlled, the medicine can't muse the two channels, instead, the forming of the scar can be prevented by preventing the over-activated of the two channels.

Gallic Acid (GA) is a natural phenolic compound that is widely distributed in various medicinal plants with diverse biological and pharmacological activities, including antioxidant, anti-inflammatory, antibacterial, anticancer, and anti-fibrotic properties. Recent studies have shown that GA could be used as a therapeutic agent for keloids and hypertrophic scars. GA reduced the proliferation, migration, and invasion of fibroblasts and induced apoptosis by inhibiting the TGF-β/Smad signaling pathway (fig. 2) [11]. In this way, the GA can successfully control how much the TRPC3 and TGF-β channels are activated and prevent the over-expression of the gene of the fibroblast and fibronectin leads to the prevention of the formation of the hypertrophic scar.

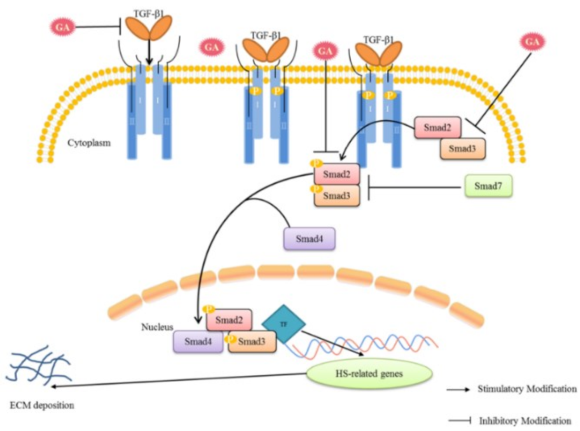

Figure 2. The HS potential inhibitory mechanism of GA via TGF-β/Smad signaling pathway(I, type I receptors; I, type receptors; GA, gallic acid; TF, the DNA transcription factor.) [11].

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5. Hydrogel

Hydrogel is a kind of hydrophilic polymer that can fix a large amount of water or biological liquid in its 3D structure through physical or chemical crosslinking. However, due to its good biocompatibility, biodegradability, and water absorption and retention, the hydrogel is now widely used in the medical and pharmaceutical industry as a relatively new material. In addition, as previously mentioned, gallic acid is a kind of organic acid containing a benzene ring structure with phenol and carboxylic acid and phenol properties [12]. Reports are showing that the hydrogel microneedle made by GA can produce the best effect of the medicine, the GA works wonderfully well with the hydrogel microneedles. GA is a small molecule with good hydrophilicity. It has high activity. These properties enable it to be loaded and released by hydrogel microneedles.

GA is a highly active hydrophilic small molecule, and these properties of hydrogel make it considered a suitable carrier for carrying GA drugs. In addition, hydrogels have the characteristics of flexibility and adjustable mechanical properties and have physical properties similar to biological tissues. The properties of hydrogel can be easily adjusted to satisfy different application scenarios of HMNs. Combining the above advantages, hydrogel becomes the preferred material for preparing microneedles (MNs) [13].

Hydrogel is an excellent drug carrier. Through the microchannels created by needle tips on the skin, the drugs can be released with the dissolution of HMNs to the affected part. Also, the use of microneedles will not cause pain, due to the tiny size of MNs [13]. Because of the features of hydrogel, the application of HMNs can be flexible and versatile, which makes HMNs expected to be widely used in the medical field.

Hydrogels can be roughly divided into three types, natural hydrogels, synthetic hydrogels, and composite hydrogels, among which natural hydrogels include polypeptide hydrogels and polysaccharide hydrogels. Because composite hydrogel can often combine the advantages of synthetic hydrogel and natural hydrogel, composite hydrogel is often used in the production of microneedles to achieve better results.

5.1. Natural Hydrogel

Natural hydrogels come from nature, so they have better biocompatibility, sustainability, and biodegradability and seldom cause an immune response. They are environmentally friendly and widely used in the pharmaceutical industry also because of the relatively lower cost due to wide sources. The most widely explored natural hydrogel includes hyaluronic acid (HA), dextran, chitosan (CS), Gelatin collagen, and so on.

Taking HA as an example, HA is widely used in treatment due to its biodegradability, diversity, biocompatibility, and excellent non-immunogenic properties since it is often extracted from biological tissues [14]. Medium molecular weight HA and low molecular weight HA are commonly used to prepare HMN because their viscosity allows them to more completely fill the mold [14]. As a result, the microneedle can satisfy the requirement of mechanical strength and a completely neat needle shape. The experimental results indicate that the degradation residues of HA are very safe. The degradation of HA and the derivation of HA are both completely harmless to humans [14]. HA hydrogel microneedles contain a large number of carboxyl groups, which can provide an acidic, oxygen-free, and anhydrous environment for drugs and protect acidic GA from degradation [14]. Also, HA microneedle patches have good penetration ability and heat transfer efficacy, contributing to the drug control release system [15].

Although natural hydrogel has a lot of advantages, most of them have several common problems. The first one is the lack of mechanical strength, which makes them more difficult to utilize for the manufacture of MNP. Too weak mechanical strength not only causes difficulty in de-molding but also may cause the hydrogel microneedle to bend or break before penetrating the skin. This shortcoming often requires more complex methods to overcome. In addition, natural hydrogel has poor stability, which is also a problem in the production of natural hydrogel microneedles.

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5.2. Synthetic hydrogel

Synthetic hydrogels are a kind of synthetic hydrophilic polymers, which can form three-dimensional networks and collect large amounts of water or biological liquids without dissolving. Synthetic hydrogels often used to prepare microneedles include polyacrylate, polyvinyl alcohol, polyacrylamide, polycaprolactone, etc.

Using poly (vinyl alcohol) (PVA) as an example. In the research, PVA is used to prepare microneedle tips. Due to the Hofmeister effect, the mechanical strength of PVA hydrogel is ion responsive, so sulfate ion can increase the hardness of the obtained microneedle tip to ensure skin penetration [16]. Also, the needle tips are softened by nitrate ions after tip–substrate detachment to adapt to the surrounding tissue and release drugs that are carried by the MNP [16]. Solubility is a significant factor in biodegradable MNP, which determines the properties of PVA since PVA highly depends on saponification [17]. So another research proves that it's necessary to use both low-saponification PVA and high-saponification PVA together to prevent low solubility lead by too high salinification [18]. The microneedle tips made by PVA show high-level penetration during the penetration experiment with porcine skin in this research, nearly 100%, which also shows the strong mechanical strength of PVA as a synthetic hydrogel.

Synthetic polymer hydrogels have controllable structures and excellent mechanical properties. However, compared with natural hydrogels, their biocompatibility and solubility are relatively poor. However, the hydrogel microneedles release the drug-loaded through the dissolution of the needle tip, and as a high-safety treatment, it does not meet the expectations of the immune response. These synthetic hydrogels are not perfect materials for making hydrogel microneedles.

5.3. Composite hydrogel

Composite hydrogels have been developed and used more widely to make up for the shortcomings of natural hydrogels and synthetic hydrogels and combine their advantages.

Composite hydrogel is a special three-dimensional network structure material, which is formed by chemical crosslinking of hydrophilic polymer chains and contains two or more different types of components. These components can be different polymers, nanoparticles, functional additives (such as drugs, and bioactive molecules), or other fillers.

For example, due to the uneven structure, poor dehydration, and mechanical properties of traditional sodium alginate hydrogels, drug delivery efficiency is reduced and mechanical robustness is insufficient. Therefore, a new type of sodium alginate composite hydrogel with a double crosslinking system was proposed in an experiment, which achieved the best surface morphology and mechanical properties, and also had good biocompatibility and dissolution characteristics, meeting the conditions for microneedle preparation, showing great potential [19].

In another research, the drug release rate of a hydrogel microneedle patch made of PVA combined with different components was compared, including 2% dimethyl sulfoxide (DMSO), 5% carboxymethyl cellulose (CMC), 5% fructose, and 5% sucrose. Through testing, it was found that compared with sugar-free microneedles, sugar effectively strengthened the microneedle structure, although it made the structure brittle and led to lower drug release. The CMC-based microneedle patch showed the highest caffeine release ($86.62 \pm 4.69\%$) and swelling rate ($283.85 \pm 3.21\%$). Therefore, CMC-based formulations have become the best choice for PVA microneedle patches [20].

In another paper, an ISF-based hydrogel microneedle patch of polyvinyl alcohol (PVA) and chitosan (CS) for POCT was developed. The phase change characteristics of PVA/CS hydrogel make the microneedles hard when dry, which is conducive to easy penetration into the skin [16].

These examples above all reflect the functional progress of hydrogel microneedles after adding a certain amount of special components, making the microneedles more in line with expectations. The addition of these components makes up for the shortcomings of the specific hydrogel itself. After the test, the best proportion is adjusted to achieve the ideal effect, which is the advantage and significance of the composite hydrogel.

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6. Conclusion

The factors affecting the formation of the scar are complex and critically rely on the TRPC3 and the TGF-β channels, the GA makes it possible to control the channels and prevent the formation of the scar, and the hydrogel microneedles made by the GA make the control-release system successfully take effect on the human body but now the existing kind of hydrogels still have problems like the insufficient mechanical strength and stability and the biocompatibility. We hope that in future research people can create the hydrogel that can overcome disabilities and prevent the formation of hypertrophic scars.

Author Contributions

Xiansong Li, Zixi Liao, and Haochuan Ding contributed equally to this work and should be considered co-first authors.

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