Multifunctional Alginate Hydrogel Protects and Heals Skin Defects in Complex Clinical Situations

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ABSTRACT: Skin defects, soft tissue damage, and fractures often occur simultaneously in severe trauma. Under current medical technology, fractures can be quickly fixed by internal or external repair techniques, and early functional exercises can be performed. However, skin defects heal over a long time and can even be difficult to heal. Functional exercise may cause cutting of fresh granulation to break and impair wound healing. Functional exercise and wound healing seem to contradict each other. In this study, an alginate hydrogel was developed. With self-healing characteristics, the hydrogel tightly adhered to the wound and could self-heal breaks in the gel caused by functional exercises. These characteristics enable this hydrogel to be used in complex clinical situations to solve sports rehabilitation and skin defect repair problems. In addition, this hydrogel can slowly release strontium ions, promote angiogenesis and collagen deposition in the wound, and quickly heal the wound.

INTRODUCTION

With the development of industrialization and the construction industry and the popularization of transportation, the incidence of high-energy damage, which is usually compound damage, including soft tissue, bone tissue, and skin tissue damage simultaneously, has increased significantly in recent decades. Reconstructive surgery can quickly repair broken tendons, blood vessels, and nerves, as well as can fix fractures in one step by internal or external repair techniques. However, skin defects need to take a long time and are even difficult to heal. Functional exercises should be performed to prevent soft tissue adhesion and shortening during tendons, blood vessels, and nerves forming tissue connections within 2–4 weeks after anastomosis. Additionally, functional exercises can be performed immediately after stable repair in fractures to promote fracture healing and functional recovery. However, early functional exercise may impair the repair of skin defects. Although normal limb skin lacerations can heal within 2 weeks with good sutures, skin defects with large area heal very slowly or cannot heal. Functional exercise of bone fractures and soft tissues may break the granulation tissue that has just grown out of the skin defect or avulsion and affect the repair of skin tissue. Such dilemmas are often faced by clinical orthopedic surgeons but are difficult to resolve. Therefore, it is particularly important to develop a treatment method that allows functional exercise and rapid healing of skin defects.

Many clinical problems have been solved due to the development of biological materials. In this study, alginate, whose biosafety has been extensively verified, was employed to develop a biomaterial to solve the problem of repairing skin defects in complex clinical situations. Self-healing hydrogels pose the property that self-heal after rupture. Skin tissue is easily distorted, stretched, and deformed during the movement of the limb. Thus, the self-healing hydrogel should possess the ability that makes it adhere firmly to the skin tissue and match the distortion, stretching, and deformation of skin during functional exercise while covering and protecting the wound.

In this study, the as-prepared aldehyded alginate and polyetherimide (PEI) were utilized to fabricate a self-healing hydrogel. First, the aldol reaction between the amino group of PEI and the aldehyde group of aldehyded alginate can cross-link quickly to form a hydrogel. Second, the amino and aldehyde groups can undergo aldol reactions again after the hydrogel is broken so that the alginate hydrogel has self-healing abilities. In the end, the amino group of PEI and the carboxyl group of aldehyded alginate can form an electronic interaction with the function group of skin, and the aldehyde group of aldehyded alginate can also form an aldol reaction with the amino group of skin. Moreover, strontium ions were incorporated into the hydrogel to accelerate tissue repair.
Strontium ions have been shown to play an important role in angiogenesis of bone and skin tissues. Many engineering methods use strontium ions to promote tissue angiogenesis and accelerate tissue repair. We take advantage of the combination of oxidized alginate and strontium ions to load and slowly release strontium ions to accelerate the healing of skin tissue. Although many reported hydrogels have the characteristics of self-healing or high adhesion or have the ability to promote angiogenesis, the hydrogels we developed have multiple functional integration characteristics, which can better adapt to clinical needs.

We tested hydrogels for biological effects (Scheme 1). In vitro, we observed the effects of hydrogel soaking solution on fibroblast and endothelial cell proliferation and migration. In vitro, we used a rat skin defect model for research. The skin defect was close to the moving part of the limb, simulating the skin pulling and movement caused by functional exercise. The healing rate and angiogenesis were observed by gross observation, tissue sectioning, and immunohistochemistry. The results showed that this hydrogel has good biocompatibility, no tissue cytotoxicity, and promotes the proliferation and migration of vascular endothelial cells and fibroblasts. In vivo, the hydrogel protected the wounds and accelerated wound healing.

**RESULTS AND DISCUSSION**

**Sodium Alginate Aldehyde Preparation.** Sodium alginate aldehyde (SAA) was prepared using NaIO₄ to oxidize the chain of sodium alginate as previously described. As shown in Figure 1a, the oxidation occurred on the C2 and C3 sites of the sodium alginate repeated unit. To confirm oxidation, FTIR characterization was employed. As shown in Figure 1b, SAA presented a peak at 1735 cm⁻¹, which was assigned to the stretching vibration of aldehyde groups. Comparably, there was no detected peak at 1733 cm⁻¹ in the SA spectrum. Based on the above results, SAA was successfully synthesized.

**Strontium-Ion-Loaded SAA/PEI Hydrogel Preparation and Characterization.** The strontium-ion-loaded SAA/PEI (SAP) hydrogels were prepared through Schiff base reaction between the aldehyde and amino groups in the polymer compound (Figure 2a). An appropriate gelation time is the essential requirement for the hydrogel. First, we investigated the cross-linking ability of the divalent Sr²⁺ ions by testing the gelling time, which is critical for the injectability of the hydrogels. The results are shown in Figure 2b. The gelling process became faster with increasing Sr²⁺ concentration. Generally speaking, a gelling time between 3 and 5 min might be the most suitable time for practical applications of injectable hydrogels, and our results showed that the gelling time was more than 5 min when the Sr²⁺ concentration is less than 1 mg/mL, while the gelling time had no obvious change with increasing Sr²⁺ concentration, which indicated that all the available cross-linking sites in sodium alginate reacted with ions. Therefore, in the subsequent experiments, we used a strontium ion concentration of 1 mg/mL to prepare the SAP hydrogel. The time-dependent rheological properties of these hydrogels were assessed to evaluate the effect of Sr²⁺ introduction. As shown in Figure 2c, SAP exhibited a higher storage modulus (G’°) and loss modulus (G”°) than SA. The above results could refer to the higher cross-linking density in the system of Sr²⁺-loaded hydrogels. There are two kinds of interactions or cross-linking in all hydrogels: the electrostatic interaction between the primary amine group of PEI and the carboxyl group of SAA and Schiff base cross-linking between the primary amine group and the aldehyde group. Both of these interactions exist in the AP and SAP systems. However, the introduction of a certain amount of Sr²⁺ could be attributed to another electrostatic interaction between Sr²⁺ and the carboxyl group, which increased the cross-linking density in the SAP system, leading to increased G’ and G” of the Sr²⁺-loaded SAP hydrogel.

To verify the self-healing behavior of SAP, rheology tests were also conducted under high and low shear strains (Figure 2d). Based on the strain amplitude sweep results, continuous
step strain measurements were performed to test the rheology recovery behavior of the SAP hydrogel. As the oscillatory shear strain stepped from 1 to 60% and was maintained for 100 s, $G'$ and $G''$ overlapped, while they immediately recovered their original values after the strain returned to 1%. The $G'$ of hydrogels showed a substantial decrease to a level below $G''$ under high strain, demonstrating that the hydrogel networks collapsed. The self-healing properties of the SAP hydrogel refer to aldime condensation. Based on the above results, these hydrogels possess excellent mechanical properties similar to those of human skin and can protect tissues from external force damage. Moreover, the rapid self-healing properties of these hydrogels could provide dynamic protection of the wound in orthopedic-related functional exercise. Furthermore, the morphologies of samples were also confirmed with SEM; as shown in Figure 2e, the SAP hydrogel had few pores compared to the AP hydrogel, which could also be due to the increased cross-linking density in the system of Sr$^{2+}$-loaded hydrogels.

**In Vitro Cell Responses to the Hydrogel.** First, the Sr$^{2+}$ release kinetics were assessed by immersing the SAP hydrogels in 5 mL of PBS for 21 days. The Sr$^{2+}$ release profiles of the SAP hydrogels are presented in Figure 3b. Generally, there was a quick initial Sr ion release, and the release rate decreased with time; 7 days later, the released Sr ion amounts were relatively constant. Fibroblasts and vascular endothelial cells are two key cells that construct skin. During wound healing and skin tissue repair, fibroblasts and vascular endothelial cells migrate into the wound site, shrink the wound, and form granulation tissue, providing the scaffold and blood supply for skin repair. Therefore, in vitro, we used human fibroblasts and vascular endothelial cells for research. During wound healing, fibroblasts and vascular endothelial cells need to proliferate in large quantities. In vitro, we used the CCK8 assay to detect the proliferation of the two cell types under hydrogel intervention (Figure 3c,d). The results showed that the AP group was not significantly different from the control group at
1, 3, and 7 days, which indicated that the hydrogel itself had no significant effect in promoting proliferation of the two cell types and was nontoxic. The SAP group showed a significant increase in proliferation capacity. In several tissue engineering studies, strontium ions are believed to have the ability to promote bone formation and angiogenesis.\textsuperscript{18,19} It has also been reported that strontium ions promote skin angiogenesis.\textsuperscript{20,21}

Migration is another important function of cell formation and tissue repair. We tested the chemotactic effect of the hydrogel on the two cell types by the Transwell assay (Figure 3a,f). The results showed that AP had chemotactic effects on the two cell types. We attribute this chemotaxis to the amino and aldehyde groups of the modified alginate.\textsuperscript{22} The two types of active groups bind to aldehyde and amino groups on the cell surface and have a certain adsorption effect.\textsuperscript{23,24} Therefore, they may chemoattract the two kinds of cells. For vascular endothelial cells, SAP exhibited stronger chemotactic effects than AP, which suggests that strontium ions have chemotactic effects on vascular endothelial cells.

The formation of vascular-like structures is a unique ability of vascular endothelial cells, and it is also a manifestation of the ability of vascular endothelial cells to form new blood vessels. We used a tube formation assay to test the ability of vascular endothelial cells to form vascular-like structures under hydrogel intervention. The results showed that SAP-pretreated vascular endothelial cells showed significantly increased vascular-like structure formation (Figure 3a,g). This result may be related to strontium-ion-induced promotion of angiogenesis gene expression in vascular endothelial cells. Therefore, we detected the expression of the angiogenesis-related gene VEGFA by qRT-PCR. The results showed that the expression of VEGFA was significantly upregulated after treatment with SAP, which is consistent with previous reports.

Figure 3. In vitro cell responses to hydrogel: (a) cell migration and tube formation; (b) strontium release curve; (c) HFF-1 viability via CCK8; (d) endothelial cell viability via CCK8; (e) VEGFA expression of the endothelial cell under different interfering conditions; (f) quantification of migrated cells; (g) quantification of tube formation. (*, p < 0.05; **, p < 0.01).
in the literature (Figure 3e). However, it is not clear how strontium ions promote the expression of genes related to angiogenesis, and we will further study this effect by proteomics in the future. The results of in vitro experiments suggested that hydrogels promote the migration and growth of cells, as well as proliferation and vascular differentiation. On the one hand, hydrogels provide cells with space for scaffolds and adhesion points; on the other hand, they can enhance cell activity and accelerate tissue repair.

**Hydrogel Promoted Skin Defect Healing in Rats.** The results of in vitro experiments suggest that hydrogels accelerate the rate of wound healing (Figure 4b,c). Therefore, we conducted in vivo experiments to further investigate this hypothesis. We chose a rat skin defect model for in vivo investigation. Skin defects were created on the back of the rat near the lower extremities, where there is more activity, which simulated skin stretch and deformation caused by rehabilitation exercises. During the study, we did not observed wound redness or ulceration of the wound, which means that the hydrogel treatment did not induce an obvious inflammatory reaction. We observed the adhesion and rupture of hydrogels and wound healing on skin defects at 0, 7, and 14 days. Gross observations showed that the hydrogel did not break or detach at the site of movement. Moreover, with the progression of

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**Figure 4.** Wound healing under different conditions: (a) ideograph of wound healing under the hydrogel; (b) wound healing process under different conditions; (c) quantification of the wound healing rate. (d) Histological observation of the wound: H&E staining for the wound healing rate; Masson’s trichrome staining for collagen deposition observation; immunohistochemistry (CD31) revealed wound angiogenesis. (*, p < 0.01).
healing, the AP and SAP groups exhibited faster healing rates, especially the SAP group. On the 14th day, the control group had a large, unhealed wound area, while the skin defects of rats in the SAP group were almost completely healed. The results of HE staining confirmed this (Figure 4d). The control group had a large non-epithelialized area that was occupied by fibrous tissue, while the skin defects in the SAP group were almost completely re-epithelialized. Masson’s staining results showed that the control group had thinner and finer fibrous deposits, while the SAP group showed denser, thicker collagen fibrous deposits (Figure 4d). This result is consistent with the in vitro results. SAP promoted the proliferation and growth of fibroblasts. More fibroblasts can secrete more collagen fibers, which cross-link to form collagen bundle, and deposit at the wound to form the basic scaffold and extracellular matrix of the skin. Angiogenesis is another important process for skin defect repair. The hydrogel designed in this study used strontium ions to promote angiogenesis. We observed the number of new blood vessels by immunohistochemistry. The results showed that the hydrogel group had significantly more new blood vessels than the control group, which may be related to the favorable vascular endothelial growth environment in the hydrogel (Figure 4d). The SAP group had significantly more neovascularization than the AP group, suggesting that strontium ions promote angiogenesis. These results are consistent with literature reports and in vitro results. Oxidized alginate combines with strontium ions to form a sustained release, which continuously affects vascular endothelial cells and promotes angiogenesis. With this hydrogel, the wound was well covered and protected. Sodium alginate has certain antibacterial properties and can prevent bacterial infections. At the same time, the self-healing and robust adhesion properties of hydrogels allow skin defects to be healed simultaneously with rehabilitation exercises. Strontium ions promote angiogenesis and accelerate the process of skin repair so that complex limb injuries can be managed well.

## CONCLUSIONS

Complex injuries are a common and difficult problem in the clinic. One complication is the compound damage to skin tissue, soft tissue, and bone tissue of the limb. The hydrogel of the present invention has good biocompatibility, adheres closely to tissues, and has self-healing abilities. At the same time, due to the slow release of strontium ions, this hydrogel protected rapidly angiogenesis of the skin tissue and accelerated the repair of defects. These characteristics make this hydrogel suitable for complex clinical situations, allowing rapid repair of skin defects in the case of limb rehabilitation exercises.

## EXPERIMENTAL SECTION

### Material Preparation and Synthesis

Sodium alginate, polyethyleneimine (PEI), sodium periodate (NaIO₄), ethylene glycol, and strontium nitrate were purchased from Shanghai Aladdin Industrial Co. Ltd.

Sodium Alginate Aldehyde (SAA) Synthesis. Briefly, 3 g of sodium alginate was dissolved in 100 mL of DI, and then 2.37 g of sodium periodate was added. The mixture was protected from light and stirred for 4 h. After that, an excess of ethylene glycol was added, and the solution was stirred for another 30 min to end the reaction. Finally, the solution was dialyzed against DI water for 72 h to remove undesired components, and the products were collected by freeze-drying and stored under 4 °C for further use. The obtained SAA were characterized by FTIR.

Preparation and Characterization of the Strontium-Ion-Doped SAA/PEI Hydrogel. Strontium ion (Sr²⁺)-doped PEI/SA and pure PEI/SA hydrogels were fabricated by simply blending the SAA solution with PEI solution with or without Sr²⁺ (1 mg/mL). Throughout the preliminary experiment, we used a ratio of PEI solution and SAA solution of 1:1 because when the content of SAA increases, the solution viscosity becomes too large, which is not good for injection. Hydrogel preparation with various formulations is shown in Table S1. The Sr²⁺ concentration affects injectability of composite hydrogels. We first screened Sr²⁺ concentration by measuring the gelling time. Briefly, 1 mL of composite sodium alginate gelling solution containing 0.25, 0.5, 1, and 1.5 mg/mL Sr²⁺ was injected into a 5 mL bottle at 37 °C. The bottle was tilted at 90° and reset every 5 s until the composite hydrogels did not change its liquid level with tilting the bottle. The corresponding time was taken as the gelling time. The number of parallel samples was 3. We used the selected concentration of strontium ions to do subsequent tests. The rheology properties were evaluated at 37 °C. The changes in time-dependent storage modulus (G′) and loss modulus (G″) rheology properties of the hydrogel were measured at 1% strain and 1 Hz. Also, the shear-thinning analysis was assessed through changing the strain (60, 200, and 600% with a 100 s interval) at 37 °C and 1 Hz. Moreover, the morphology of the hydrogels was observed by SEM after freeze-drying.

Sr Ion Release Determination. The Sr-loaded hydrogels (SAP, n = 3) were immersed in 5 mL of phosphate-buffered saline (PBS, pH 7.4) at 37 °C on a shaker table (100 rpm). The entire volume of PBS was collected using a pipette and replaced with fresh PBS after 1, 4, 7, 14, and 21 days. The PBS containing released Sr was analyzed using inductively coupled plasma atomic emission spectrometry (ICP-AES).

In Vitro Cell Responses to the Strontium-Ion-Doped SAA/PEI Hydrogel. Cell Culture. EA·hy926 cells were purchased from ATCC (USA) and were cultured in Dulbecco’s modified Eagle’s medium (DMEM) supplemented with 10% fetal calf serum (FCS), 100 U/mL penicillin, and 100 µg/mL streptomycin (Invitrogen). Human fibroblasts (HFF-1) were obtained from the Stem Cell Bank of the Chinese Academy of Sciences (Shanghai) and were cultured in Dulbecco’s modified Eagle’s medium (DMEM) supplemented with 15% FCS, 100 U/mL penicillin, and 100 µg/mL streptomycin (Invitrogen, Carlsbad, CA) at 37 °C.

Cell Migration. EA·hy926 cells and HFF-1 were cultured under three different culture conditions, which were divided into control group, AP group, and SAP group. AP group and SAP group culture media were collected from the AP- or SAP-soaked complete medium for 7 days. Two cells were cultured in 24-well plates. At 1, 3, and 7 days, 10% CCK-8 solution was added and reacted for 1 h. 100 µL of the reacted solution was transferred into a 96-well plate. The cell proliferation was determined using a spectrophotometric microplate reader (BioRad 680, USA) at 450 nm, with three replicates for each experimental group.

Cell Migration. EA·hy926 cell and HFF-1 migration under three different culture conditions was observed using the Transwell assay (Corning; pore size = 8 µm). EA·hy926 cells and HFF-1 were cultured in a complete medium and medium collected from the AP- or SAP-soaked complete medium for 48 h and then digested. 2 × 10⁶ EA·hy926 cells or HFF-1 were
added into the upper chamber of Transwell insertion with the basal culture medium, and 500 μL of complete medium and medium collected from the AP- or SAP-soaked complete medium were added into the lower compartment corresponding to different groups. After 24 h of culture, the cells of the upper compartment were erased, fixed, and stained with crystal violet. Optical microscopy (provided by Leica, Germany) was used to observe the cells.

**Tube Formation.** For observation of capillary-like structure formation of endothelial cells, the tube formation assay was applied. EA-hy926 cells and HFF-1 were cultured in three different conditions for 48 h and then digested. For the tube formation assay, briefly, 200 μL of Matrigel (Becton Dickinson) was added into a 24-well plate followed by gelling at 37 °C for 1 h. A 1.5 × 10⁴ suspension of cells was added onto the Matrigel. After incubation for 6 h, the tubes were observed under a light microscope.

**qRT-PCR.** qRT-PCR was applied to detect the expression levels of wound-repair-related genes VEGF. Cells were normally inoculated on each material for 3 and 7 days, and RNA was extracted with Trizol (Invitrogen). The obtained RNA was reversely transcribed into complementary DNA (cDNA) using Moloney mouse leukemia virus (m-mlv) reverse transcriptase (Takara). qRT-PCR analysis was performed using a sequence detection system (7900 HT, ABI). The relative expression of the primers used in this study and the genes of interest normalized the housekeeping gene, dog-actin. All samples were analyzed three times, and independent experiments were conducted.

**In Vivo Wound Healing Effects of the Strontium-Ion-Doped SAA/PEI Hydrogel.** The in vivo study was approved by the Ethics Committee of Jinzhou Medical University. For wound healing observation, the rat full-thickness skin wound model was used. 36 rats (2 months old; 240 ± 10 g) were used for the in vivo study. Briefly, after being anesthetized with pentobarbital, rats were shaved for the back fur. Two circular full-thickness skin wounds (18 mm) were created for each rat. The same method was used to establish the same wound surface on both sides of the rat’s back. Both wounds were treated in the same way. All of the rats were randomly divided into control group, AP group, and SAP group. 0.5 mL of normal saline or hydrogels was used to cover the wound, and the treatment was given only once at the beginning. All the full-thickness wounds were protected with a Tegaderm film and gauze. Wound healing was observed and photographed using digital cameras at days 0, 7, and 14. Hematoxylin and eosin (H&E) staining was applied to observe the wound healing rate. Masson’s trichrome staining was performed for collagen deposition observation. H&E staining and Masson’s trichrome staining were performed according to a previous study. Slides were then viewed under a light microscope (Nikon, Japan). CD31 immunohistochemistry was conducted according to previous reports and was used to evaluate angiogenesis in the healing stage.

**Statistics.** All the data were obtained from triple separated experiments. The results were expressed as mean ± SD (standard deviation). The analysis was performed using GraphPad 7.0 (Prism), and ANOVA analysis was used as the statistical method. P < 0.05 was considered as statistically significant.

**ASSOCIATED CONTENT**

**Supporting Information**

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.0c01108.

Table S1. Hydrogel preparation with various formulations. The gelation times of various SAP hydrogels were determined by the vial-tilting method (PDF)

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**Notes**

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