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Recent Developments in the Stem Cells Loaded Natural Polymeric Hydrogel Scaffolds for Skin Tissue Engineering Applications.

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ABSTRACT

The skin is essential for performing sensory and homeostasis functions, including protecting deeper tissues from the external environment and regenerating damaged tissues. However, the dermal system as a whole and the extracellular matrix, in particular, have limited capacity for regeneration, which makes the effects of trauma, ischemia, and degenerative disease devastating and often irreversible. Currently, there is no effective treatment for functional scarless recovery after a skin injury, as new therapeutic strategies for enhancing endogenous repair mechanisms of the dermal system have become ineffective. One of the most promising approaches to address these issues is associated with the use of hydrogels, the three-dimensional (3D) networks formed by hydrophilic polymers containing up to 90% (w/w) of water. The role of stem cells loaded hydrogels in general skin tissue system regeneration and skin tissue defect treatment, in particular, has been widely reviewed in our study. Due to their ideal immunomodulatory, biomimetic, biocompatible, and fibroblast proliferative characteristics, the stem cells loaded with hydrogel have demonstrated tremendous potential for regenerating skin tissue defects.

Keywords: Hydrogel, Adipose Stem Cells, Mesenchymal Stem Cells, Skin, Alginate, Gelatin, Chitosan.

INTRODUCTION

The skin is essential for performing sensory and homeostasis functions, including protecting deeper tissues from the external environment and regenerating damaged tissues. However, the dermal system as a whole and the extracellular matrix, in particular, have limited capacity for regeneration, which makes the effects of trauma, ischemia, and degenerative disease devastating and often irreversible. Several factors contribute to the development of this disease, including a lack of progenitor cells in dermal parenchyma, a slower regeneration of epidermal cells, and a microenvironment formed by the tissue defect. Further, in the dermal tissues, such a hostile microenvironment can only promote partial self-regeneration resulting in the formation of scars. It leads to the destruction of the vascular system, cytotoxicity, and inflammation.[1,2]

Currently, there is no effective treatment for functional scarless recovery after a skin injury, as new therapeutic strategies for enhancing endogenous repair mechanisms of the dermal system have become ineffective. It is mainly due to improper angiogenesis, lack of microenvironment support, and systemic effects of various topical drug delivery systems. One of the most promising approaches to address these issues is associated with the use of hydrogels, the three-dimensional (3D) networks formed by hydrophilic polymers containing up to 90% (w/w) of water.[3]

Hydrogels are of great interest for future clinical applications in skin tissue regeneration as they deal with both mentioned problems (insufficiency of progenitor cells and injury-induced microenvironment): they can serve as local transport systems for the delivery of drugs and signaling molecules directly to the injury site, and as scaffolds providing ideal physical support, substrates for adhesion, and protection to host and graft cells, thereby facilitating extracellular matrix formation. The primary role of hydrogels in skin tissue regeneration is to exert control over the host dermal tissue and grafted cell fate by supporting attachment such as by epidermal cells, fibroblasts and keratinocytes proliferation, migration, and differentiation.[4]

Role of stem cells loaded hydrogel in the treatment of skin tissue defects.

It has taken many studies up to this point to develop the stem cells loaded hydrogels that would modulate fibroblast behavior to hasten the healing process while also preventing tissue necrosis. Due to their ideal immunomodulatory, biomimetic, biocompatible, and fibroblast proliferative characteristics, the stem cells loaded with hydrogel have demonstrated tremendous potential for regenerating skin tissue defects.[5]

Wound healing involves an organized, dynamic, and interactive process involving a favorable microenvironment and appropriate angiogenesis. The platelet-derived growth factor-BB (PDGF-BB) is essential for the healing of wounds. However, the PDGF-BB and bone marrow-derived mesenchymal stem cells (BMSCs) were delivered to the wound simultaneously using an injectable hydrogel that was successfully developed using sodium alginate (SA) and dextran (Dex). Zhang et al. reveal that PDGF-BB protein improved BMSC survival, migration, and EC differentiation in vitro. The PDGF-BB/SA/Dex hydrogels had outstanding biocompatibility and could sustainably release PDGF-BB both in vitro and in vivo. Additionally, these composite hydrogels loaded with BMSCs could hasten wound healing by enhancing epithelialization and collagen deposition. In addition, the hydrogels made of PDGF-BB/SA/Dex encouraged the proliferation of hair follicle stem cells in the wound and the EC differentiation of transplanted BMSCs. Additionally, there was an elevated expression of angiogenesis-specific markers in the PDGF-BB/SA/Dex/BMSCs group, including PDGFR-, p-PI3K, p-Akt, and p-eNOS. In conclusion, the PDGF-BB/SA/Dex injectable hydrogels may offer a new therapeutic approach for stem cell therapy in wound healing by boosting angiogenesis through activating the PDGF-BB/PDGFR-mediated PI3K/Akt/eNOS pathway.[6]

Hsu et al. examined the wound healing abilities of a gelatin-based hydrogel (GBH) wound dressing in combination with adipose-derived stem cells (ADSCs) using mouse and porcine models. The ADSCs offered the potential for wound and injury healing through skin regeneration. The analytical findings demonstrated that, in vitro, compared to ADSCs extracted from mice, ADSCs from porcine considerably boosted cell proliferation and promoted cell differentiation. Additionally, the in vivo outcomes showed that the GBH wound dressing, in combination with ADSCs and its culture medium, would be able to hasten wound healing in mouse and porcine models. The use of GBH wound dressings for skin regeneration has been demonstrated in vitro and in vivo, and ADSCs is an alternative therapy that could prove beneficial.[7]

Complete regeneration following skin damage continues to be a significant clinical concern. By enhancing the bioactivity of synthetic matrices, hydrogels treated with growth factors or mimicking peptides have been used for functional tissue regeneration. Li et al. created the CS-IGF-1C hydrogel, a chitosan-based hydrogel with IGF-1C immobilization that serves as a biomimetic scaffold, encourages dermal cell survival and wound closure, enhances ECM remodeling by supporting angiogenesis, and attests to its function in quickening the healing of cutaneous wounds. The beneficial CS-IGF-1C hydrogel is a practical substitute for commercial wound dressings and offers valuable insights for ischemia disease research.[8]

Natural Polymers involved in the formulation of Stem cells loaded hydrogel scaffold

Alginate

Alginates, natural hetero-polysaccharides obtained from brown sea algae, are of particular interest among hydrogel biomaterials because of their distinctive qualities, such as biodegradability and biomimetic characteristics. Alginate can offer a three-dimensional (3-D) scaffold that makes it easier for stem cells to distribute in space, creating a structural arrangement similar to the in vivo native microenvironments.[9]

Although stem cell transplantation is a promising treatment for wound healing, its use is restricted by the limited retention and survival of transplanted stem cells. Injectable hydrogels have positive effects on the engineering of skin tissue. The injection of sodium alginate (SA) and collagen type I (Col) into a full-thickness excision wound model increased the effectiveness of stem cells. According to Zhang et al. findings, SA/Col hydrogel was injectable, biodegradable, and had low immunogenicity, all of which could help hUC-MSCs be retained and survive in vivo. Injection of hUC-MSCs into SA/Col reduced wound size ($p < 0.05$). SA/Col loaded with hUC-MSCs also showed considerable reductions in the expression of NLRP3 inflammasome-related proteins ($p < 0.05$). Finally, these findings suggest the possibility of treating skin wounds by suggesting that SA/Col loaded with hUC-MSCs enhances skin wound healing by partially blocking the NLRP3 pathway.[10]

Most conventional wound dressings only support some clinical requirements because they lack multifunctionality. Bilayer wound dressings with several uses may be desirable for efficient skin regeneration. By using methacrylate gelatin (GM), alginate (Al), tannic acid (TA), chitosan, and polycaprolactone, Asadi et al. developed a multifunctional bilayer scaffold. Moreover, the GM/Al/TA hydrogel was applied to PC nanofibers to create a bilayer nanocomposite scaffold (Bi-TA). The hydrogel layer of Bi-TA that is composed of GM/Al/TA demonstrated antibacterial, free radical scavenging, and biocompatibility capabilities. Additionally, PC nanofiber was a barrier to stop bacteria from entering the hydrogel layer and causing moisture loss. A full-thickness wound model was used to examine the Bi-TA scaffold's ability to repair wounds. Additionally, the tumor necrosis factor (TNF-α) and transforming growth factor (TGF)–β1 immunohistochemistry (IHC) stainings were evaluated. Compared to other groups, the Bi-TA scaffold showed improved wound closure rates, effective collagen deposition, rapid re-epithelialization, more skin appendages, and replacement of problem areas with normal skin tissue. Additionally, Bi-TA dressing was found to regulate TGF-β and TNF-α. Overall, with the necessary structural and multifunctional qualities, the Bi-TA can be a great candidate for creating dressings that work well for wound healing applications.[11]

Patients who have excessive scarring experience negative physiological and psychological repercussions; as a result, there is an urgent need for a therapeutic approach that promotes speedy wound healing and minimizes scarring. Shen et al. developed bilayered thiolated alginate/PEG diacrylate (BSSPD) hydrogels to promote quick and scar-free wound healing. These hydrogels allowed for the sequential release of tiny extracellular vesicles (sEVs), which were active at various stages of wound healing. By increasing the proliferation and migration of fibroblasts and endothelial cells during early inflammation and proliferation phases, bone marrow-derived mesenchymal stem cells (B-sEVs) promoted angiogenesis and collagen deposition in the hydrogels. While, sEVs released from the top layer of the hydrogels by mesenchymal stem cells generated from bone marrow and enriched in miR-29b-3p inhibited excessive capillary proliferation and collagen deposition during the late proliferation and maturation phases. The wound healing rate, angiogenesis, and collagen deposition after treatment with BSSPD loaded with B-sEVs were assessed at various time intervals in a full-thickness skin

defect model in rat and rabbit ears. Interestingly, tissues in the group treated with BSSPD loaded with sEVs for sequential release (SR-sEVs@BSSPD) displayed more uniform distributions of vascular structures and collagen arrangements and fewer hyperplastic scars than tissues in the other groups at the end of the maturation phase. As a result, the skin repair phases-based SR-sEVs@BSSPD was effectively constructed and had much potential as a cell-free therapy for scarless wound healing.[12]

Gelatin

Gelatin, a naturally occurring collagen degradation product, is a readily accessible source of biocompatible and biodegradable raw materials for hydrogel production. It makes a variety of tissue engineering applications possible, including those for osteogenesis and skin restoration. The lack of rigidity caused by thermal instability at physiological temperatures is a severe drawback of gelatin-based hydrogels, which is frequently overcome by cross-linking gelatin chains. Cross-linking boosts thermal and mechanical stability while slowing in vivo deterioration.[13]
Diabetes patients' decreased angiogenesis is caused by endothelial dysfunction, which delays the healing of diabetic wounds. Extracellular vesicles, often known as exosomes or EVs, have gained attention as potential therapeutic delivery systems for drugs to sick cells. According to Wang et al. By delivering VH298 to endothelial cells, EVs were described in the present work as a novel therapy for diabetic wounds. Moreover, the results demonstrated that human umbilical vein endothelial cells (HUVECs) in vitro demonstrated positive effects from VH-EVs by activating the HIF-1 signaling pathway. Additionally, it was identified that VH-EVs had therapeutic effects on angiogenesis and wound healing in vivo. We also designed a gelatin methacryloyl (GelMA) hydrogel for VH-EVs that was highly biocompatible and had suitable mechanical characteristics. GelMA hydrogel containing VH-EVs (Gel-VH-EVs) accelerated wound healing in diabetic mice by improving local angiogenesis and blood flow. The stimulation of the HIF-1/VEGFA signaling pathway was possibly related to the underlying mechanism for increased angiogenesis. Eventually, these findings provide a new bioactive dressing for treating diabetic wounds and point to a viable EV-based approach for delivering VH298 to endothelial cells.[14]

As a substitute for free cell injection wound dressings containing cell-laden bulk hydrogel or scaffold were primarily used to promote cell engraftment. However, for deep or chronic wounds with limited blood supply, dressing of cells laden in biomaterials on the wound surface may not effectively and promptly exert functions. Zeng et al. developed injectable gelatin microgels (GMs) that could load cells for improved cell distribution and therapy. In this study, human adipose-derived stem cells (hASCs) loaded with GMs were compared with traditional two-dimensional (2D) cell culture in a variety of biological changes, including cell phenotype markers, stemness genes, differentiation, secretion of growth factors, cell apoptosis, and cell memory by FACS, QRT-PCR, and ELISA. These comparisons showed the GMs' priming effects on the upregulation of stemness genes and improved growth factor production by hASCs for potentially enhanced wound healing. Unlike free cell injection, multisite injection and dressing of hASCs-laden GMs could considerably speed healing in a full-thickness skin wound model in nude mice. Protein analysis and bioluminescence imaging showed enhanced cell retention and growth factor secretion. Additionally, GMs as primed injectable 3D micro-niches provide a novel cell delivery technique for skin wound healing. These GMs may not only aid in the repair of the wound bed but may also directly impact the basal layer of the wound, promoting faster wound healing. For refractory wounds like diabetic ulcers or radiating skin wounds, injectable GMs may offer a new minimally invasive treatment approach as an easy multisite cell delivery method.[15]

A severe consequence of diabetes is diabetic wounds. Stem cells are a promising treatment for diabetic skin tissue defects. The hydrogel can provide a niche for cell adhesion and survival to increase the effectiveness of stem cell therapy; however, creating hydrogel with the right qualities is still quite a challenge. In order to treat a full-thickness diabetic wound, Xu et al. used human umbilical cord-derived mesenchymal stem cells (hUMSCs) and a hydrogel made of gelatin methacrylate (GelMA) and chitosan-catechol (Chi-C). These findings identified that the hydrogel with tunable mechanical properties provides a platform for introducing stem cells to treat diabetic wounds. The hydrogel with the optimal mechanical stiffness demonstrated excellent biocompatibility and preserved the stemness, proliferation, and adhesion of hUMSCs in vitro. The therapeutic system encouraged wound closure, reduced inflammation, sped up collagen synthesis and vascular regeneration in vivo, and ultimately enhanced diabetic wound healing. This study offered a brand-new alternate method for fastening the wound healing activity in deep tissue injury.[16]

Chitosan

Chitosan's biocompatibility, biodegradability, and muco-adhesiveness have led to extensive research into its potential for use in tissue engineering concepts. By adjusting the chitosan concentration, it is possible to customize the mechanical properties of chitosan hydrogel (CS). Due to these benefits, CS has received much attention in developing stem cell-loaded formulations for skin tissue regeneration studies.[17]

In addition to cytokines and growth factors, mesenchymal stem cells from human umbilical cords (hUCMSCs) can aid wound healing. Hydrogel is an appropriate biomaterial to provide a niche for cell adherence and survival. In order to treat a full-thickness cutaneous wound, Xu et al. developed an injectable thermo-sensitive hydrogel containing hUCMSCs composed of chitosan, glycerol phosphate sodium, and cellulose nanocrystals (CS/GP/CNC). The CS/GP system's addition of CNC increased the gelling speed while significantly enhancing its mechanical characteristics and delaying its degradation rate. The innovative hydrogel was non-toxic and injectable. The combination of hydrogel and hUCMSCs dramatically accelerated wound closure, microcirculation, tissue remodeling, re-epithelialization, and hair follicle regeneration, as well as reduced over-inflammation in the central and surrounding wounds, according to histological analysis. The combination of hydrogel and hUCMSCs increased the expression of the keratinocyte maturity marker K1 and inhibited the release of inflammatory factors, including TNF- α and IL-1. The current data offer a feasible course for treating chronic cutaneous wounds.[18]

For use as wound treatment, hydrogels have attracted much interest. The "optimal dressing" criteria included adhering to the tissue and preventing wound infection. Tian et al. fabricated (l-DOPA) - (((Poly-l-lysine)-HBC hydrogels by modifying thermosensitive

hydroxybutyl chitosan (HBC) with l-DOPA and -Poly-l-lysine (eLHBC). The eLHBC showed a nearly 1.5-fold (P 0.01) higher wet adhesion strength than HBC. When eLHBC was incorporated into-Poly-l-lysine, it developed an innate antibacterial activity that stopped inflammation and wound infection. The paracrine secretion of cytokines and growth factors by bone marrow mesenchymal stem cells (BMSCs) contained in the eLHBC could facilitate the migration of fibroblast cells. By encouraging collagen deposition and preventing infection and inflammation in vivo, BMSC-loaded eLHBC improved complete skin-thickness wound healing, with a wound closure rate of more than 99% after 15 days. The tissue-adhesive, bioinspired eLHBC may be used as advanced wound dressings to facilitate effective tissue regeneration at the skin injury site.[19]

One of the most challenging clinical problems is delayed wound healing in diabetic patients because it increases the risk of gangrene, amputation, and even death. Therefore, there is currently a great deal of interest in a unique way to enhance diabetic wound healing. Exosomes produced from gingival mesenchymal stem cells (GMSCs) were isolated by Shi et al. to load them onto a chitosan/silk hydrogel sponge to assess the effects of this unique non-invasive technique on skin abnormalities in diabetic rats. In the Streptozocin (STZ)-induced diabetic rat model, the combination of exosomes and hydrogel might accelerate skin wound healing by encouraging the re-epithelialization, deposition, and remodeling of ECM, as well as by boosting angiogenesis. These findings offer fresh insight into the function of GMSC-derived exosomes in wound healing and a cutting-edge non-invasive technique for applying exosomes with the potential for skin repair. Furthermore it was emphasised that the precise mechanism through which GMSC-derived exosomes improve skin regeneration.[20]

CONCLUSION

The role of stem cells loaded hydrogels in general skin tissue system regeneration and skin tissue defect treatment, in particular, has been widely reviewed. The 'plain' hydrogel matrices are rarely sufficient for skin tissue engineering. Even modified hydrogels impregnated with cells are not deprived of significant drawbacks like the probability of side effects. Thus, the future design of hydrogels must target the production of complex hybrid systems involving bioprinting technologies, exploring other biocompatible and naturally occurring polymers, and possibly developing new *in vitro* and *ex vivo* models of skin tissue regeneration.

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REFERENCES

1. Tavakoli S, Klar AS. Advanced Hydrogels as Wound Dressings. *Biomolecules*. 2020; 10(8):1169.
2. Narauskaitė D, Vydmantaitė G, Rusteikaitė J, Sampath R, Rudaitytė A, Stašytė G, Aparicio Calvente MI, Jekabsone A. Extracellular Vesicles in Skin Wound Healing. *Pharmaceuticals*. 2021; 14(8):811.
3. Fan F, Saha S and Hanjaya-Putra D (2021) Biomimetic Hydrogels to Promote Wound Healing. Front. Bioeng. Biotechnol. 9:718377.
4. Mantha S, Pillai S, Khayambashi P, Upadhyay A, Zhang Y, Tao O, Pham HM, Tran SD. Smart Hydrogels in Tissue Engineering and Regenerative Medicine. *Materials*. 2019; 12(20):3323.
5. Lukomskyj AO, Rao N, Yan L, Pye JS, Li H, Wang B, Li JJ. Stem Cell-Based Tissue Engineering for the Treatment of Burn Wounds: A Systematic Review of Preclinical Studies. *Stem Cell Rev and Rep.* 2022; 18: 1926–1955.
6. Zhang Z, Li Z, Wang Y, Wang Q, Yao M, Zhao L, Shi J, Guan F, Ma S. PDGF-BB/SA/Dex injectable hydrogels accelerate BMSC-mediated functional full thickness skin wound repair by promoting angiogenesis. J Mater Chem B. 2021;9(31):6176-6189.
7. Hsu LC, Peng BY, Chen MS, Thalib B, Ruslin M, Tung TDX, Chou HH, Ou KL. The potential of the stem cells composite hydrogel wound dressings for promoting wound healing and skin regeneration: In vitro and in vivo evaluation. J Biomed Mater Res B Appl Biomater. 2019;107(2):278-285.
8. Li Q, Cui J, Huang H, Yue Z, Chang Y, Li N, Han Z, Han ZC, Guo Z, Li Z. IGF-1C domain-modified chitosan hydrogel accelerates cutaneous wound healing by promoting angiogenesis. Future Med Chem. 2020;12(13):1239-1251.
9. Ahmad Raus R, Wan Nawawi WMF, Nasaruddin RR. Alginate and alginate composites for biomedical applications. Asian J. Pharm. 2021; *16*(3):280-306.
10. Zhang Z, Li Z, Li Y, Wang Y, Yao M, Zhang K, Chen Z, Yue H, Shi J, Guan F, Ma S. Sodium alginate/collagen hydrogel loaded with human umbilical cord mesenchymal stem cells promotes wound healing and skin remodeling. Cell Tissue Res. 2021;383(2):809-821.
11. Asadi N, Mehdipour A, Ghorbani M, Mesgari-Abbasi M, Akbarzadeh A, Davaran S. A novel multifunctional bilayer scaffold based on chitosan nanofiber/alginate-gelatin methacrylate hydrogel for full-thickness wound healing. Int J Biol Macromol. 2021;193(Pt A):734-747.
12. Shen Y, Xu G, Huang H, Wang K, Wang H, Lang M, Gao H, Zhao S. Sequential Release of Small Extracellular Vesicles from Bilayered Thiolated Alginate/Polyethylene Glycol Diacrylate Hydrogels for Scarless Wound Healing. ACS Nano. 2021;15(4):6352-6368.
13. Tondera C, Hauser S, Krüger-Genge A, Jung F, Neffe AT, Lendlein A, Klopfleisch R, Steinbach J, Neuber C, Pietzsch J. Gelatin-based Hydrogel Degradation and Tissue Interaction *in vivo*: Insights from Multimodal Preclinical Imaging in Immunocompetent Nude Mice. Theranostics. 2016; 6(12):2114-2128.
14. Wang Y, Cao Z, Wei Q, Ma K, Hu W, Huang Q, Su J, Li H, Zhang C, Fu X. VH298-loaded extracellular vesicles released from gelatin methacryloyl hydrogel facilitate diabetic wound healing by HIF-1α-mediated enhancement of angiogenesis. Acta Biomater. 2022;147:342-355.
15. Zeng Y, Zhu L, Han Q, Liu W, Mao X, Li Y, Yu N, Feng S, Fu Q, Wang X, Du Y, Zhao RC. Preformed gelatin microcryogels as injectable cell carriers for enhanced skin wound healing. Acta Biomater. 2015;25:291-303.

16. Xu H, Wang J, Wu D, Qin D. A hybrid hydrogel encapsulating human umbilical cord mesenchymal stem cells enhances diabetic wound healing. J Mater Sci Mater Med. 2022;33(8):60.
17. Sánchez-Cid P, Jiménez-Rosado M, Rubio-Valle JF, Romero A, Ostos FJ, Rafii-El-Idrissi Benhnia M, Perez-Puyana V. Biocompatible and Thermoresistant Hydrogels Based on Collagen and Chitosan. Polymers 2022; 14:272.
18. Xu H, Huang S, Wang J, Lan Y, Feng L, Zhu M, Xiao Y, Cheng B, Xue W, Guo R. Enhanced cutaneous wound healing by functional injectable thermo-sensitive chitosan-based hydrogel encapsulated human umbilical cord-mesenchymal stem cells. Int J Biol Macromol. 2019; 137:433-441.
19. Tian MP, Zhang AD, Yao YX, Chen XG, Liu Y. Mussel-inspired adhesive and polypeptide-based antibacterial thermo-sensitive hydroxybutyl chitosan hydrogel as BMSCs 3D culture matrix for wound healing. Carbohydr Polym. 2021; 261:117878.
20. Shi Q, Qian Z, Liu D, Sun J, Wang X, Liu H, Xu J, Guo X. GMSC-Derived Exosomes Combined with a Chitosan/Silk Hydrogel Sponge Accelerates Wound Healing in a Diabetic Rat Skin Defect Model. Front Physiol. 2017; 8:904.

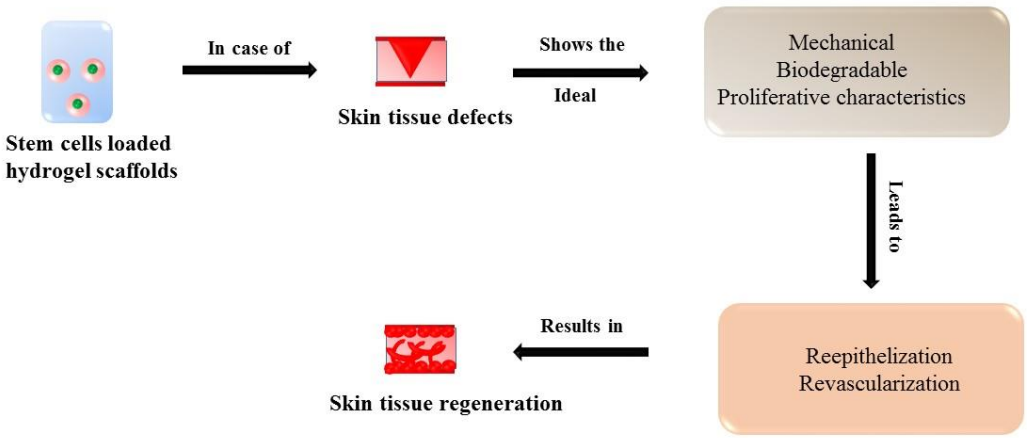

Figure 1. Demonstrates the importance of the stem cells loaded hydrogel scaffold in skin tissue regeneration.

Table 1. Represents the significance of stem cells loaded polymeric hydrogel scaffolds in the regeneration of the skin tissue defects.

S. No	Formulated by	Name of the Formulation	Significance of the Study	References
1.	Zhang et al.	PDGF-BB And Bone Marrow-Derived Mesenchymal Stem Cells (Bmscs) Loaded Sodium Alginate –Dextran Hydrogels	Hydrogels had outstanding biocompatibility and could sustainably release PDGF-BB both in vitro and in vivo.	6
2.	Hsu et al.	Adipose Stem Cells Loaded Gelatin Hydrogel.	Boosted cell proliferation and promoted cell differentiation.	7
3.	Li et al.	IGF-1C Domain-Modified Chitosan Hydrogel	Chitosan-based hydrogel with IGF-1C immobilization that serves as a biomimetic scaffold, encourages dermal cell survival and wound closure, enhances ECM remodeling by supporting angiogenesis.	8
4.	Zhang et al.	Sodium Alginate/Collagen Hydrogel Loaded With Human Umbilical Cord Mesenchymal Stem Cells	Enhances skin wound healing by partially blocking the NLRP3 pathway.	10
5.	Asadi et al.	Chitosan Nanofiber/Alginate-		11

		Gelatin Methacrylate Hydrogel	Demonstrated antibacterial, free radical scavenging, and biocompatibility capabilities.	
6.	Shen et al.	Small Extracellular Vesicles loaded Bilayered Thiolated Alginate/Polyethylene Glycol Diacrylate Hydrogels	Displayed more uniform distributions of vascular structures and collagen arrangements and fewer hyperplastic scars than tissues in the other groups at the end of the maturation phase.	12
7.	Wang et al.	VH298-Loaded Extracellular Vesicles Released From Gelatin Methacryloyl Hydrogel	Accelerated wound healing in diabetic mice by improving local angiogenesis and blood flow. The stimulation of the HIF-1/VEGFA signaling pathway was possibly related to the underlying mechanism for increased angiogenesis.	14
8.	Zeng et al.	Gelatin microcryogels	Showed the Gelatin hydrogels priming effects on the upregulation of stemness genes and improved growth factor production by hASCs for potentially enhanced wound healing.	15
9.	Xu et al.	Human Umbilical Cord-Derived Mesenchymal Stem Cells (hUMSCs) and a Hydrogel Made Of Gelatin Methacrylate (GelMA) and Chitosan-Catechol (Chi-C).	Hydrogel with the optimal mechanical stiffness demonstrated excellent biocompatibility and preserved the stemness, proliferation, and adhesion of hUMSCs in vitro.	16
10.	Xu et al.	Human Umbilical Cord-Mesenchymal Stem Cells loaded Chitosan Hydrogel	Increased the expression of the keratinocyte maturity marker K1 and inhibited the release of inflammatory factors, including TNF- α and IL-1.	18
11.	Tian et al.	Fabricated (l-DOPA) - (((Poly-l-lysine)-HBC hydrogels by Modifying Thermosensitive Hydroxybutyl Chitosan (HBC) with l-DOPA and -Poly-l-lysine (eLHBC).	Developed an innate antibacterial activity that stopped inflammation and wound infection.	19
12.	Shi et al.	GMSC-Derived Exosomes Combined with a Chitosan/Silk Hydrogel	Accelerated skin wound healing by encouraging the re-epithelialization, deposition, and remodeling of ECM, as well as by boosting angiogenesis.	20