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REVIEW

# Skin Organoids in Diabetic Chronic Wounds: Current Status and Future Perspectives

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**Abstract:** Diabetes is one of the most prevalent chronic metabolic diseases worldwide, and its incidence continues to rise. Diabetes-related complications have become a major public health concern, with diabetic chronic wounds—particularly diabetic foot ulcers—representing one of the most challenging and clinically significant manifestations. These non-healing wounds often require prolonged recovery, severely impair patients' quality of life, and impose substantial economic and psychological burdens on healthcare systems and families. Conventional therapeutic approaches are limited by insufficient reparative capacity, scarcity of functional tissue sources, and the inability to achieve durable structural and functional restoration, frequently resulting in suboptimal outcomes. Recent advances in stem cell engineering and three-dimensional tissue technologies have enabled the development of organoids—emerging biomimetic regenerative constructs—allowing their increasing application in tissue repair, including diabetic ulcers. This review provides an integrated summary of the major barriers to diabetic wound healing, the regenerative mechanisms of skin organoids, and recent progress in this field. Unlike previous reviews that address organoids or wound healing separately, this work specifically focuses on diabetic chronic wounds while emphasizing engineering strategies, regenerative potential, and translational considerations. We further analyze the key challenges that hinder clinical translation, including model consistency, vascularization capacity, long-term functional stability, immune compatibility, potential tumorigenicity, and interactions with the local microenvironment. Collectively, this work aims to provide a structured framework and future research directions for the application of skin organoids in diabetic chronic wound repair, supporting their responsible transition from experimental research toward clinical practice.

**Keywords:** skin organoids, diabetic foot ulcer, diabetes, wound healing, regenerative medicine, tissue engineering

## Background

Both the prevalence of diabetes and diabetes-related mortality have steadily increased globally. According to the International Diabetes Federation (IDF) 2021 report, an estimated 537 million people worldwide were living with diabetes, with projections indicating this number will rise to 783 million by 2045.[1] In 2019, more than 4 million adults died from diabetes and its complications, underscoring its significant public health burden. The economic impact is also profound, with global diabetes-related healthcare expenditures exceeding USD 760 billion, accounting for approximately 10% of annual health spending among adults.[2] Among individuals with diabetes, nearly 25% will develop chronic diabetic ulcers, of which at least one-quarter fail to achieve effective healing. Once progression to amputation occurs, the five-year mortality rate can reach as high as 70%, a risk particularly pronounced in elderly patients.[3] Despite multi-disciplinary standard care, recurrence remains common, and long-term wound stability is often difficult to achieve, underscoring the persistent clinical management challenges of diabetic foot ulcers.

Current conventional therapies for diabetic chronic wounds, such as debridement and negative pressure wound therapy (NPWT), remain limited by several shortcomings, including inadequate infection control, modest efficacy in wound repair, prolonged treatment courses, and significant invasiveness. For example, randomized controlled trials of NPWT in diabetic foot ulcers have reported complete healing rates of approximately 50–60% at 12–16 weeks, with substantial recurrence rates, highlighting the limited and variable therapeutic benefit in complex chronic wounds.[4] These

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approaches also fail to address the multifactorial pathophysiology underlying complex chronic wounds. Moreover, the absence of precision strategies tailored to individual pathological conditions means that standardized interventions often cannot accommodate patient heterogeneity, resulting in suboptimal healing outcomes. Although advanced approaches such as bioengineered skin substitutes, cell sheet therapies, and stem cell–based dressings have shown incremental improvements, their clinical benefits remain constrained by limited durability, high costs, and variable long-term outcomes. By contrast, organoid technology has demonstrated considerable therapeutic potential in the management of diabetic chronic wounds. In 2021, Lee et al engineered complex skin organoids containing skin appendages and provided preliminary evidence supporting their utility in tissue reconstruction and wound healing.[5] Similarly, Diao et al[6] successfully generated sweat gland organoids from murine paw pad epithelial cells, which not only accelerated dorsal wound healing in vivo but also regenerated functional sweat glands in thermally injured paw pads. More recently, in 2025, researchers developed skin organoids with integrated appendages and fully functional neural circuits, achieving superior repair outcomes compared with conventional treatments in full-thickness frostbite wounds of nude mice.[7] To provide a clearer overview of current experimental advances, representative skin organoid studies with demonstrated in vivo relevance to wound repair are summarized in Table 1. It should be noted that these studies were conducted in preclinical animal models, and to date, no skin organoid–based therapies have entered human clinical trials.

From a manufacturing perspective, skin organoids are primarily generated from pluripotent stem cells (iPSCs), adult stem cells (ASCs), or tissue-derived cells that self-organize within three-dimensional culture systems. Their construction typically involves several key steps, including stem-cell induction and differentiation, staged three-dimensional culture, scaffold or matrix support, and mechanical or chemical microenvironmental modulation. In recent years, bioreactor platforms—such as dynamic rotary systems and biomechanical stimulation modules—have been introduced to improve organoid uniformity and tissue maturation. In addition, three-dimensional bioprinting technologies enable more precise spatial patterning and structural reconstruction, further enhancing integration after transplantation. With the continued advancement of these engineering strategies, skin organoids are increasingly recognized for their potential in functional tissue restoration, promoting vascularization, alleviating chronic inflammation, and facilitating neural regeneration.

Organoids, as highly biomimetic miniaturized organ-like structures formed through the self-organization of stem cells or tissue-specific cells under three-dimensional conditions, are capable of recapitulating tissue development, structural organization, and functional characteristics in vitro. Compared with traditional two-dimensional culture systems, three-dimensional organoids demonstrate markedly greater physiological relevance in terms of cellular heterogeneity, spatial architecture, and functional simulation. However, despite promising preclinical findings, clinical translation of skin organoids remains in an early exploratory stage, facing substantial regulatory, manufacturing, and safety-related challenges, including insufficient maturation, limited long-term functional stability, risks of immune rejection, and potential tumorigenicity. Therefore, this review synthesizes recent advances in organoid technology within regenerative medicine and organ transplantation, and further examines the potential applications and future directions of skin organoids in the treatment of diabetic chronic wounds.

# Diabetic Chronic Wounds

## Mechanisms and Challenges

Wound healing is a natural physiological process in response to tissue injury, involving the coordinated actions of multiple cytokines, growth factors, chemokines, and metabolites. This process is typically divided into four continuous yet overlapping stages: hemostasis, inflammation, proliferation, and remodeling. In patients with diabetes, wound healing capacity is markedly impaired due to a series of pathological alterations in the local microenvironment, including chronic inflammation, impaired angiogenesis, hypoxia-induced oxidative stress, neuropathy, accumulation of advanced glycation end-products (AGEs), and dysregulated neuropeptide signaling.

During the inflammatory phase, neutrophils are prone to undergo neutrophil extracellular trap formation (NETosis), thereby aggravating chronic inflammation and tissue damage. Macrophage polarization is also disrupted, with sustained dominance of the pro-inflammatory M1 phenotype and reduced M2 subsets, resulting in excessive expression of pro-inflammatory mediators and insufficient activation of anti-inflammatory pathways. In the proliferative phase, dysfunction

**Table 1** Representative Skin Organoid Studies with Demonstrated in vivo Relevance to Wound Repair

| First Author (Year) | Organoid Type/ Structure | Cell Source | Key Fabrication/Culture Strategy | In vivo Model | Main Regenerative Outcomes |
|---|---|---|---|---|---|
| Diao et al[6] | Sweat gland organoids | Mouse sweat gland epithelial cells | 3D culture of isolated sweat gland epithelial cells to form gland-like organoids | Mouse full-thickness skin wounds and burned paw pads | Accelerated wound closure and regenerated functional sweat glands |
| Lee et al[8] | Human skin organoids with appendages | hPSCs | TGF-β/BMP/FGF modulation combined with long-term 3D suspension culture | Proof-of-concept model | Generated epidermis, dermis and pigmented hair follicles, providing a platform for complex skin regeneration |
| Lee et al[5] | Advanced appendage-forming skin organoids | hPSCs | Optimized signaling cues and 3D culture to enhance appendage maturation | Preclinical skin repair model | Improved structural complexity and enhanced translational relevance |
| Kwak et al[9] | Multilayered epidermal organoids | iPSC-derived keratinocyte progenitors | 3D stratified epidermal culture and application of organoid secretome | Full-thickness rodent wound | Promoted re-epithelialization, collagen deposition and neovascularization |
| Wang et al[7] | Neural-integrated skin organoids | hPSC-derived skin organoids | Engineering of appendages and neural circuits followed by transplantation into defects | Frostbite-induced full-thickness defects | Improved healing compared with conventional therapy, enhanced appendage regeneration and reduced scarring |


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of endothelial progenitor cells (EPCs) impairs neovascularization, while hypoxia further exacerbates oxidative stress and inflammation. Fibroblasts exhibit diminished activity, leading to reduced collagen deposition and insufficient secretion of growth factors, which together hinder extracellular matrix (ECM) synthesis, cell migration, and proliferation. In the remodeling phase, dysregulated collagen metabolism and aberrant expression of matrix metalloproteinases (MMPs) disrupt ECM architecture and degradation balance. These defects, compounded by the persistent inflammatory microenvironment, prevent proper tissue repair and scar maturation.[2] Taken together, the development of diabetic chronic wounds represents a multifactorial and stage-dependent pathological process, in which persistent inflammation, impaired angiogenesis, and extracellular matrix dysregulation reinforce one another to form a self-perpetuating vicious cycle that ultimately culminates in refractory ulceration. The therapeutic challenges of diabetic chronic wounds mainly stem from persistent chronic inflammation and uncontrolled infection. Endothelial injury initiates inflammatory cell infiltration and NETosis-mediated release of cytotoxic components, directly impairing tissue repair.[10] Meanwhile, the wounds are highly susceptible to polymicrobial infections, predominantly *Staphylococcus aureus* (50–80%), among which approximately 15% are drug-resistant strains such as MRSA.[11] Under conditions where necrotic tissue and pathogens cannot be completely eradicated, sustained secretion of TNF-α, IL-1β, and MMPs leads to aberrant ECM degradation. In parallel, fibroblast dysfunction results in reduced synthesis of fibronectin, tenascin, and type III collagen, thereby compromising the formation and functionality of the ECM scaffold.[12–14] This vicious cycle of inflammation and infection markedly delays ulcer healing. Although effective infection control has been shown to significantly reduce the risk of amputation,[3] current therapeutic strategies remain insufficient for long-term management.

In normal wound healing, M1 macrophages dominate during the initial 1–3 days and subsequently transition toward the M2 phenotype, which peaks around day 7. In diabetic wounds, however, impaired resolution is primarily driven by sustained M1 polarization. Evidence shows that diabetic mice maintain high expression of CCR7, an M1 marker, even three days after injury. The M1 phenotype is induced by pro-inflammatory mediators such as TNF and lipopolysaccharide (LPS), leading to secretion of IL-12, IL-23, and reactive oxygen species (ROS), which are strongly pro-inflammatory. In contrast, the M2 phenotype is induced by IL-4 and IL-10, producing repair-associated factors including TGF and IGF. Moreover, the hyperglycemic microenvironment markedly upregulates the expression of at least 13 pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6.[15] Persistently elevated TNF-α further activates the NF-κB signaling pathway,[16] thereby reinforcing chronic inflammation and establishing a positive feedback loop that sustains M1 polarization.

Impaired angiogenesis in diabetic chronic wounds further complicates their management. The core mechanism involves dysfunction of the HIF-1α/VEGF signaling pathway, characterized by reduced transcriptional activity of hypoxia-inducible factor-1α (HIF-1α) and a diminished responsiveness of vascular endothelial growth factor (VEGF) to ischemic stimuli.[16] Additionally, the accumulation of AGEs contributes to angiogenic impairment by compromising EPC function, disrupting the SDF-1/CXCR4 signaling axis (with CXCR4 expression significantly suppressed when AGEs $\geq$ 500 μg/mL),[17] and downregulating VEGF and FGF-2 expression.[18] Collectively, these alterations hinder neovascularization and delay wound repair.

Dysfunction of the TGF-β signaling pathway is a key mechanism underlying impaired healing in diabetic chronic wounds. Maione et al employed a 3D ECM tissue model to systematically compare the ECM-forming capacity of fibroblasts derived from diabetic foot ulcers (DFUF), non-ulcerated diabetic foot tissue (DFF), and healthy controls (non-diabetic foot fibroblasts, NFF). Their study demonstrated that, although DFUF could still upregulate α-SMA (ACTA2) expression in response to TGF-β stimulation, the expression of ECM-related genes such as FN1 and COL1A1 was markedly restricted. Furthermore, DFUF exhibited pronounced defects in collagen secretion, resulting in abnormal ECM deposition. These findings reveal a selective functional impairment of the TGF-β signaling pathway in DFUF, suggesting that simple exogenous supplementation of TGF-β is insufficient to effectively promote healing in diabetic chronic wounds.[19]

Diabetic foot ulcers (DFUs), a specific subtype of diabetic chronic wounds, are closely associated with peripheral neuropathy. The pathological features manifest as a triad of neural impairments: sensory neuropathy results in loss of protective pain sensation, delaying the detection of injuries; autonomic dysfunction causes dry skin and fissures, compromising the integrity of the epidermal barrier; and motor neuropathy leads to altered plantar biomechanics, producing abnormal pressure distribution. This multifaceted neural damage markedly increases the risk of infection and delayed ulcer healing.[20] Although current clinical management strategies—including microcirculation improvement

and infection control—effectively reduce amputation rates and improve clinical outcomes, curative interventions targeting neuropathy remain lacking, leaving patients' quality of life largely unaddressed.

## Current Therapeutic Approaches and Limitations

Current therapeutic strategies for diabetic chronic wounds include anti-infective therapy, off-loading, debridement, NPWT, and growth factor-based treatments. Studies have shown that, in the absence of acute soft tissue infection, prolonged systemic antibiotic therapy (up to 90 days) yields outcomes comparable to surgical debridement.[21] However, long-term use of broad-spectrum antibiotics increases the risk of drug resistance and reduces patient adherence, limiting their effectiveness in controlling the persistent chronic inflammation characteristic of diabetic chronic wounds. Off-loading therapy redistributes mechanical pressure to significantly reduce stress on ulcerated areas and promote wound healing. Evidence indicates that specialized off-loading devices, such as total contact casts (TCC) and knee-high walking boots, can decrease pressure at the ulcer site by 80–90%.[22] Nonetheless, these devices have notable clinical limitations: TCCs are highly restrictive, impairing daily activities, while walking boots, though adjustable, are cumbersome and often poorly tolerated, particularly by elderly patients, ultimately constraining therapeutic efficacy.

Debridement can rapidly remove necrotic tissue, disrupt bacterial biofilms, alleviate inflammation, and promote the transition of macrophages from the M1 to the M2 phenotype. By releasing pro-repair factors such as VEGF, FGF, and TGF-β, debridement improves the local microenvironment—enhancing oxygen tension, activating HIF-1α and stem cell function, and regulating ECM remodeling and MMP activity—to accelerate angiogenesis and tissue regeneration.[23] However, for extensive or deep wounds, or in cases with poor granulation tissue formation, adjunctive therapies such as flap transplantation or NPWT are often required.[24] NPWT mechanically stimulates integrin-mediated mechanotransduction, promoting fibroblast proliferation and neovascularization.[25] It also removes exudate, reduces edema, improves local perfusion, and decreases levels of inflammatory mediators, including TNF-α and MMPs. Nevertheless, its clinical application is limited by a lack of high-quality randomized controlled trials, long treatment durations, poor patient adherence, and high economic costs. Moreover, given the frequent coexistence of high infection risk, vascular insufficiency, and delayed healing in diabetic chronic wounds, combination therapies remain invasive and often yield suboptimal outcomes.

To overcome the limitations of invasive approaches such as debridement and NPWT, current research has focused on minimally invasive regenerative medicine strategies, particularly advanced therapies including growth factor-based treatments and stem cell therapy. These approaches aim to selectively regulate cellular proliferation, differentiation, and molecular signaling pathways. Growth factors have shown considerable potential in the repair of diabetic chronic wounds by promoting cell proliferation, migration, and angiogenesis. Exogenous PDGF activates fibroblasts and endothelial cells, VEGF improves hypoxia and induces neovascularization, SDF-1 enhances recruitment of EPCs, and FGF-2 together with TGF-β synergistically stimulate fibroblast proliferation and ECM remodeling.[10] However, the protease-rich environment of diabetic chronic wounds (eg, elevated MMP-9) accelerates growth factor degradation, and the accumulation of AGEs impairs receptor function[26] Coupled with inherent limitations of growth factors—such as short half-life and low bioavailability—these factors substantially compromise therapeutic stability and efficacy, leading to suboptimal outcomes Stem cell therapy, delivered via local injection or scaffold-based approaches, utilizes mesenchymal stem cells (MSCs) or iPSCs. Through paracrine secretion of VEGF, FGF, and other cytokines, stem cells promote angiogenesis, anti-inflammation, and immunomodulation, thereby enhancing tissue repair. Despite advantages including multi-modal mechanisms, broad availability, safety, and potential for personalized treatment, stem cell therapy faces significant challenges: transplanted cells have limited survival and functional persistence in vivo, making it difficult to reconstruct the three-dimensional architecture and functional microenvironment of tissues. Furthermore, efficacy in complex diabetic wounds remains uncertain, and both safety and reproducibility require further validation.

In addition, researchers have explored various novel therapies, including dehydrated human amnion/chorion allografts (dHACM), hyperbaric oxygen therapy, and umbilical cord-derived mesenchymal stem cell-derived exosomes (UC-MSC-Exo). These interventions can improve wound healing by suppressing inflammation, promoting angiogenesis, and accelerating epithelialization.[27,28] However, due to the lack of large-scale clinical trials assessing their long-term safety and efficacy, these approaches have not yet been widely adopted in clinical practice.

Current therapies for diabetic chronic wounds are limited by suboptimal efficacy, invasiveness, and poor patient adherence, highlighting the urgent need for novel strategies that are safe, effective, and personalized. Organoid technology has demonstrated significant potential in wound repair. Organoids can precisely mimic host-specific inflammatory responses and directly modulate immune pathways,[29] offering highly individualized treatment without relying on antimicrobial mechanisms, thereby circumventing issues of antibiotic resistance. Vascularized organoids promote in vivo engraftment, differentiation, and functional reconstruction, substantially improving graft survival rates,[30] making them particularly suitable for complex, hard-to-heal wounds. Furthermore, organoids possess unique self-organizing capabilities, differentiating into functional cell types while continuously secreting bioactive factors.[31] This allows them to integrate with host tissue, provide an extracellular matrix scaffold,[32] and partially substitute for lost tissue function. Importantly, their preserved cellular heterogeneity and three-dimensional microenvironment more accurately recapitulate physiological conditions in vivo, further enhancing the advantages of personalized therapy. The main treatment methods and limitations for diabetic chronic wounds currently are summarized in Table 2.

# Skin Organoids

## Introduction and Mechanisms

Organoids are complex three-dimensional structures that self-organize in vitro They are formed by cells grown in a defined three-dimensional environment, which aggregate into miniature cellular clusters capable of self-organization and differentiation into functional cell types, thereby mimicking the architecture and functions of native organs. The constituent cells can be derived from iPSCs or tissue-derived primary cells (TDPCs), including adult stem/progenitor cells, differentiated cells, and cancer cells.[31] The self-organizing property of organoids refers to the ability of cells to arrange themselves into intricate structures without strict external guidance. This process relies on the interplay between intrinsic developmental programs and external microenvironmental cues, such as intercellular signaling, biochemical factors within the niche, and the physical properties of the ECM, enabling the transition from disordered cell aggregates to functional organ-like models.

The history of organoid research can be traced back to the early 20th century. In 1907, Henry demonstrated through sponge regeneration experiments that "plasmodial masses" possessed a complete regenerative capacity independent of their original structure.[32] In 1960, Weiss and colleagues, using chicken embryo cell suspension transplantation, provided the first evidence that highly differentiated cells retained the ability to reconstruct organ-like structures.[33] By 1987, scientists had begun modifying culture conditions to better mimic the in vivo microenvironment. For instance, Li et al cultured mammary epithelial cells in an EHSECM extract and successfully induced the formation of three-dimensional ducts and lumenal structures in vitro, which were capable of synthesizing and secreting milk proteins. Similarly, alveolar type II epithelial cells cultured within ECM maintained their differentiated state.[34] Collectively, these early studies underscored the critical role of cell–ECM interactions in sustaining organoid functionality and cellular differentiation. A major breakthrough came in 2009, when Sato et al established a three-dimensional culture system based on Lgr5+ intestinal stem cells. Within an ECM hydrogel microenvironment, they successfully generated intestinal organoids displaying a complete crypt–villus architecture, with both histological and functional features closely resembling those of the native intestine.[35] This achievement marked a pivotal milestone in the birth of modern organoid technology and laid the foundation for subsequent advances in diverse organoid systems. Since 2010, organoid technology has undergone rapid and transformative development. Researchers have successfully generated organoids modeling adenomas, Barrett's esophagus,[36] brain tissue,[37] prostate cancer, and many other systems, extending its application across a wide spectrum of stem cell–based culture models. As a physiologically relevant and highly versatile three-dimensional culture platform, organoid technology has demonstrated substantial value in disease modeling, drug discovery, regenerative medicine, and transplantation research.[36]

The successful development of multi-system organoid models has provided a novel platform for studying skin organoids within more complex physiological contexts. Since 2019, skin organoid technology has undergone rapid advancement, evolving from basic structural construction to functional simulation. Diao et al successfully generated mouse sweat gland organoids,[6] offering the first insights into the potential of organoids in skin biology. This was

**Table 2** The Main Treatment Methods and Limitations for Diabetic Chronic Wounds

| Therapeutic Approach | Key Advantages | Major Limitations | Optimization Strategies |
|---|---|---|---|
| Anti-infective Therapy[21] (Antibiotics/Topical Dressings) | Rapid infection control<br>Clinically well-established | Repeated use may increase antibiotic resistance<br>Limited efficacy when used alone | Precisely modulate local immune responses<br>Anti-inflammatory and reparative |
| Off-loading Therapy[22] | Non-invasive<br>Effectively reduces pressure on wound | Inconvenient to use<br>Poor patient adherence<br>No direct tissue repair function | Combine with other therapies to promote tissue regeneration and functional recovery |
| Debridement[23,24] | Activates reparative factors<br>Rapid removal of necrotic tissue<br>Improves microvascular perfusion | Slow healing and invasive<br>Limited efficacy for large wounds | Support tissue regeneration<br>Suitable for extensive wound repair |
| Skin/Flap Transplantation[23,24] | Widely applied clinically<br>Well-established techniques<br>Can cover large wound areas | Low graft survival<br>High risk of infection<br>Insufficient local blood supply | Control inflammation<br>Modulate immune responses<br>Enhance graft vascularization |
| Negative Pressure[24,25] Wound Therapy (NPWT) | Promotes angiogenesis<br>Accelerates granulation tissue formation<br>Rapidly removes inflammatory mediators | Restricts mobility<br>Long treatment durationDifficulty closing complex wounds | Enhance tissue regenerative capacity |
| Growth Factor Therapy[10] | Activates cell migration and proliferation<br>Alleviates hyperglycemia-induced signaling impairments | Easily degraded<br>Activates only single signaling pathway<br>Reduced efficacy in hyperglycemia | Continuous growth factor–secreting grafts<br>Precise regulation of signaling pathways |
| Stem Cell Therapy[27,28] (MSC/iPSC) | Promotes angiogenesis<br>Immunomodulatory<br>Potential for personalized therapy | Short in vivo survival<br>Safety concerns | Reconstruct 3D tissue architecture<br>Restore functional tissue microenvironment |
| Exosome Therapy[27,28] (eg, UC-MSC-Exo) | Low immunogenicity<br>Promotes angiogenesis<br>Anti-inflammatory and high safety profile | Limited clinical research<br>Safety still under evaluation<br>Weak targeting and rapid clearance | More stable in vivo effects<br>Grafts that continuously release exosomes and bioactive factors |
| Placental Membrane[27,28] (eg, dHACM) | ECM scaffold supports repair<br>Angiogenic and epithelializing<br>Reparative and anti-inflammatory | Lacks dynamic tissue regulation<br>Limited clinical data and safety concerns<br>ECM function limited to structural support | ECM supports tissue repair<br>Continuous secretion of reparative factors |
| Hyperbaric Oxygen Therapy[27,28] | Improves local hypoxia<br>Enhances vascularization and collagen | Limited RCT evidence<br>Long treatment duration and high cost | Mimic hyperoxia<br>Improve wound oxygenation and perfusion simultaneously |

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followed by a series of breakthroughs: in 2020, the first nearly complete human skin organoids were developed, incorporating appendages such as hair follicles and sebaceous glands;[8] in 2021, Lee et al established more complex organoids with diverse appendage structures and demonstrated their potential applications in tissue repair.[5] In 2024, Kwak et al constructed multilayered epidermal organoids capable of promoting re-epithelialization, collagen deposition, and angiogenesis.[9] By 2025, researchers had successfully engineered skin organoids containing fully functional neural circuits in vitro. These progressive breakthroughs in both structure and function highlight the immense potential of skin organoids in regenerative medicine and transplantation. Current research is increasingly focused on developing mature skin organoids that can accurately recapitulate in vivo physiological processes and immune responses, underscoring their broad prospects in clinical translation. Due to differences in preparation protocols and culture systems among various research teams, the generated skin organoids exhibit some variability in their structural composition. Therefore, this study presents a schematic diagram of a skin organoid structure based on representative models from the literature in Figure 1, to visually demonstrate its typical features.

## Advances of Organoids in Regenerative Medicine and Organ Transplantation

With their remarkable biomimetic properties, organoids have emerged as a central tool in regenerative medicine. In 2012, Yui et al successfully transplanted colon organoids derived from single adult Lgr5+ intestinal stem cells into a superficially injured mouse colon model, where they generated functional crypt structures containing all normal colonic cell types.[38] In 2013, Huch et al demonstrated that liver organoids derived from mouse Lgr5+ hepatic stem cells could restore liver function in mice with hereditary (eg., tyrosinemia type I) or chemically induced damage, thereby prolonging survival.[39] In 2014, Watson et al transplanted human pluripotent stem cell (hPSC)-derived intestinal organoids under the mouse kidney capsule, which developed crypt–villus structures and exhibited absorptive functions such as permeability and peptide uptake, highlighting their therapeutic potential for intestinal failure disorders such as short bowel syndrome.[34] In 2015, Huch and colleagues established bipotent progenitor cell–derived organoids from adult human intrahepatic bile ducts. When transplanted into retrorsine/$CCl_4$-induced immunodeficient mice under specific induction

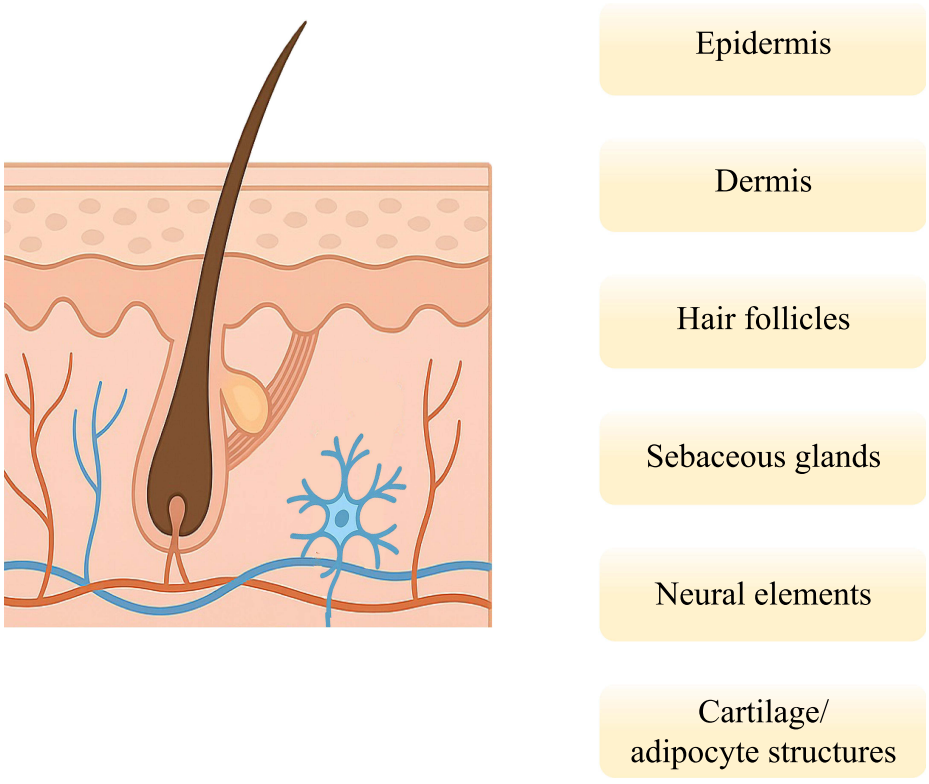


**Figure 1** Schematic representation of a pluripotent stem cell–derived skin organoid (based on published models).

conditions (eg., BMP7, DAPT, FGF19), these organoids differentiated into mature hepatocytes, expressing key functional genes such as *Albumin, CYP3A4, APOB*, and *C3*. They performed essential hepatic activities, including glycogen storage, LDL uptake, bile acid secretion, ammonia detoxification, and drug metabolism, thereby closely mimicking authentic hepatocyte functions.[40] In 2017, Sampaziotis et al engineered extrahepatic cholangiocyte organoids, which, when transplanted into the mouse gallbladder, formed barrier-functional biliary epithelium and successfully repaired experimentally induced bile duct damage.[34] In 2018, van den Berg et al generated hPSC-derived kidney organoids and transplanted them under the renal capsule of mice, where they promoted vascularization and maturation of critical structures such as glomerular basement membranes, filtration slits, and proximal tubules, approaching physiological kidney function.[41] In the same year, Nie et al showed that hPSC-derived liver organoids transplanted into the spleen of mice with acute liver failure survived and performed key hepatic functions, significantly improving survival rates.[42] Also in 2018, Prior et al developed second-generation mouse liver organoids, which, after 103 days of transplantation, repopulated approximately 80% of the hepatic parenchyma, demonstrating robust engraftment and regenerative capacity.[43] In 2020, Shi et al created vascularized human cortical organoids (vOrganoids) that, upon transplantation into the mouse S1 cortex, established functional circulatory networks, indicating that vascularization enhances neuronal organoid maturation and long-term survival in vivo.[30] In 2021, Sampaziotis et al directly injected cholangiocyte-derived organoids into peripheral intrahepatic bile ducts under normothermic mechanical perfusion, which increased bile output and pH, thereby restoring biliary function.[44] In 2022, Zhang et al isolated endometrial stem cells from mouse uterine tissue and generated endometrial organoids (EMOs) using a three-dimensional culture system. When transplanted into the basal layer of intrauterine adhesion (IUA) mouse models, these organoids developed columnar epithelium–like and glandular structures, showing robust proliferative and secretory capacity as well as hormonally responsive behavior. Remarkably, 75% of the treated mice regained fertility.[45] In the same year, Sugimoto et al engineered organoids derived from normal human intestinal tissue and transplanted them into de-epithelialized colons of immunodeficient mice. The engrafted organoids maintained epithelial structure and function long-term without tumorigenic growth, demonstrating safety and stability in tissue repair. In a short bowel syndrome model, transplanted organoids reconstructed villi and lacteals, restored digestive and absorptive functions, and significantly improved survival and nutritional uptake.[46] In 2023, Hirami et al used clinical-grade iPSC lines from Kyoto University's iPSC bank, free of pathogenic mutations, to generate retinal organoid sheets. Three sheets were transplanted into the subretinal space of two patients with advanced retinitis pigmentosa (RP). Over 24 months of follow-up, no signs of graft rejection, excessive proliferation, or tumorigenesis were observed. OCT imaging revealed >10% thickening of the transplanted retinal area, with good tissue integration and partial improvement in functional indices.[47]

Multiple types of organoids—including those derived from the liver, kidney, endometrium, intestine, retina, and brain—have been successfully generated and transplanted in vivo, where they recapitulate native organ architecture and function, thereby promoting functional repair of damaged tissues. Studies have demonstrated that organoids exhibit excellent safety and stability in tissue regeneration, with remarkable potential for reconstructing complex structures and restoring physiological function. Building on these advantages, researchers are now exploring the application of organoid technology in the treatment of diabetic chronic wounds aiming to overcome the limitations of current therapies, which are often associated with limited efficacy and significant invasiveness. The progress of organoids in regenerative medicine and organ transplantation is summarized in Table 3.

# Diabetic Chronic Wounds and Skin Organoids

## Biological Basis and Regenerative Potential of Skin Organoids in Diabetic Chronic Wound Healing

The treatment of diabetic ulcers remains highly challenging; however, skin organoid transplantation addresses multiple core pathophysiological mechanisms of diabetic chronic wounds, offering therapeutic potential through a synergistic, multi-mechanistic approach.

Organoids offer a multidimensional platform for treating chronic inflammation through immune modulation and gene–cell integrated therapy. Studies have shown that co-culturing organoids with immune cells can reshape the immune

**Table 3** The Progress of Organoids in Regenerative Medicine and Organ Transplantation

| Study | Year | Organoid Type | Disease Model | Therapeutic Outcome |
|---|---|---|---|---|
| Yui et al[38] | 2012 | Colonic organoids | Mouse model with superficial colon injury | Formation of functional crypt structures |
| Huch et al[39] | 2013 | Liver organoids | Fah(-/-) mice (hereditary tyrosinemia type I) | Generation of functional stem cells; prolonged survival |
| Watson et al[34] | 2014 | Intestinal organoids | Mouse renal capsule | Formation of crypt-villus structures; restored permeability and peptide absorption |
| Huch et al[40] | 2015 | Cholangiocyte organoids | Immunosuppressed Balb/c nude mice | Expression of key liver genes; recapitulation of liver cell function |
| Sampaziotis et al[34] | 2017 | Extrahepatic bile duct organoids | Mouse extrahepatic bile duct injury model | Formation of barrier-function bile duct epithelium; successful bile duct repair |
| Van den Berg et al[41] | 2018 | Kidney organoids | Immunodeficient mice under renal capsule | Generation of neovasculature; promoted maturation of key kidney structures |
| Nie et al[42] | 2018 | Liver organoids | Acute liver failure mouse model | Restored liver function; improved survival of diseased mice |
| Prior et al[43] | 2018 | Liver organoids | Fah(-/-) mice (hereditary tyrosinemia type I) | Hepatic parenchyma regeneration; treatment of liver failure |
| Shi et al[30] | 2020 | Vascularized human cortical organoids | Immunodeficient mice S1 cortex | Reduced apoptosis; improved survival |
| Sampaziotis et al[44] | 2021 | Bile duct organoids | MDA-injured mice; ex vivo perfused human livers | Repair of damaged bile duct epithelium; validated in human organs |
| Zhang et al[45] | 2022 | Endometrial organoids | Mouse model of intrauterine adhesion | Recapitulated endometrial proliferation and secretory function; 75% of mice restored fertility after transplantation |
| Sugimoto et al[46] | 2022 | Intestinal organoids | Immunodeficient mice (NOG) colon model | Reconstruction of human colonic crypts; long-term tumor-free |
| Hirami et al[47] | 2023 | Retinal organoids | Patients with advanced retinitis pigmentosa (RP) | >10% retinal thickening in transplant area; no hyperproliferation or immune rejection |

microenvironment—for example, intestinal organoids enhance barrier integrity and coordinate antimicrobial immune responses via epithelial–macrophage signaling.[29] From a biomaterials perspective, synthetic ECMs (eg., PEG hydrogels) can be engineered to deliver anti-inflammatory drugs such as dexamethasone in a controlled-release manner, while natural ECMs (eg., decellularized matrices) contain components like collagen V that directly suppress pro-inflammatory pathways. Furthermore, engineered biomaterial scaffolds (eg., functionalized hydrogels) can support organoid transplantation at injury sites, where organoids alleviate inflammation and promote repair by secreting paracrine anti-inflammatory factors (eg., IL-10) and enhancing epithelial regeneration.[48] In addition, organoids can serve as vehicles for gene–cell integrated therapy. For instance, cerebellar organoid models derived from iPSCs of patients with CDK5RAP2 mutations demonstrated that electroporation-mediated delivery of wild-type CDK5RAP2 via adeno-associated virus (AAV) during neuroepithelial formation significantly expanded the neuroepithelium and increased radial glial cell numbers, thereby achieving gene correction.[48] This strategy could be extended to deliver anti-inflammatory genes such as IL-10 or TGF-β, providing a novel avenue for the gene therapy of inflammation-associated diseases. Previous studies have also indicated that immune regulatory pathways play a key role in tissue repair and inflammatory responses in various diseases, and the differences in their microenvironment can significantly impact the regenerative process.[49]

In 2023, a study demonstrated that transplantation of organoids derived from intestinal crypts of Lgr5-EGFP-IRES-CreERT2 transgenic mice promoted repair of intestinal ischemia–reperfusion (I/R) injury. Researchers found that L-malic acid (MA) was enriched in the cecal contents of recipient mice and played a pivotal role by activating the suppressor of cytokine signaling 2 (SOCS2) pathway. This activation specifically upregulated M2 macrophage markers (CD206, Arg1, Ym1/2) and the anti-inflammatory cytokine IL-10, while suppressing pro-inflammatory mediators such as IL-6 and IL-

1β. As a result, macrophages were polarized toward the M2 phenotype, leading to intestinal mucosal repair and an improved injury microenvironment. The mechanism was shown to depend on organoid-secreted MA, which modulates macrophage behavior via SOCS2 signaling.[50] These findings highlight the regulatory potential of organoids in driving macrophage polarization toward the M2 phenotype.

Organoid technology has also shown tremendous potential in addressing angiogenic impairments. In June 2025, a study reported a novel approach for rapidly generating vascular organoids (VOs) by orthogonal activation of the transcription factors ETV2 and NKX3.1. This method produced large numbers of size-uniform VOs within just five days, each exhibiting lumen polarization and mature endothelial/smooth muscle cell populations, effectively recapitulating vascular cell interactions and organ-specific microenvironments. In a streptozotocin (STZ)-induced diabetic immunodeficient mouse model of hindlimb ischemia, VO transplantation significantly enhanced blood flow recovery (achieving ~50% reperfusion in ischemic limbs within two weeks), reduced tissue necrosis, and outperformed single-cell transplantation controls, underscoring the superior advantage of VOs in vascularized tissue repair.[51] Beyond this, exogenous upregulation of HIF-1α has been shown to further enhance organoid vascularization and alleviate hypoxic microenvironments. In a 2023 study, renal progenitor cells were subjected to either plasmid-based HIF-1α overexpression or treatment with DMOG (dimethyloxallyl glycine, a stabilizer of HIF-1α). The resulting renal organoids displayed a marked increase in $CD31^+$ endothelial cells, denser and more continuous vascular networks, and well-developed vessel structures extending from the periphery to the core. AngioTool analysis confirmed significant improvements in vascular area, branching points, and mean vessel length. Importantly, these effects were abrogated by VEGFR inhibitors (eg., semaxanib, axitinib), indicating that exogenous HIF-1α promotes vascularization via VEGF pathway activation.[52] By integrating vascularization strategies such as targeting the HIF-1α/VEGF axis, it is possible to engineer vascular-rich "skin–vascular" composite organoids, offering a promising new therapeutic avenue for the treatment of diabetic chronic wounds.

Disruption of TGF-β signaling leads to reduced collagen synthesis in diabetic chronic wounds, thereby delaying healing. Organoid technology offers a potential strategy for targeting this pathway. In 2020, Lee et al established an hPSC-based culture system for generating skin organoids. Through temporally regulated modulation of TGF-β and FGF signaling, they co-induced cranial surface ectoderm and cranial neural crest cells (CNCCs) within spherical cell aggregates. Human pluripotent stem cells were first aggregated into spheroids and co-cultured with the TGF-β inhibitor SB431542 and bone morphogenetic protein 4 (BMP4), which promoted surface ectoderm induction while suppressing neuroectodermal differentiation. On day 3, the investigators added the BMP inhibitor LDN and FGF to induce CNCCs—the precursors of dermis, nerves, and pigment cells. Once both surface ectoderm and CNCCs had been successfully induced, the aggregates were transferred to a shaker platform for long-term culture, and exogenous TGF-β inhibitors were withdrawn. During 4–5 months of culture, a cystic skin organoid formed, consisting of stratified epidermis, an adipocyte-rich dermis, and pigmented hair follicles with sebaceous glands. Single-cell RNA sequencing (scRNA-seq) revealed a $VIM^+$ dermal fibroblast cluster at day 48, with high expression of fibroblast markers such as DPT, TWIST2, and LUM, and multiple collagen genes including COL1A1/2, COL3A1, COL5A3, COL6A3, COL12A1, and COL21A1. Moreover, WNT pathway regulators showed compartment-specific expression patterns between epidermal (WNT6, LEF1) and dermal (SFRP2, TCF4, WIF1, APCDD1) cell populations, while dermal FGF7 (keratinocyte growth factor) appeared to drive epidermal stratification[8] This work provides mechanistic insights relevant to diabetic skin chronic ulcers (DSCU): impaired TGF-β signaling leads to reduced FN1 and COL1A1 expression and defective collagen secretion—key contributors to non-healing wounds. The successful regeneration of collagen-rich dermal tissue within organoids underscores their therapeutic potential. In addition, endogenous expression of BMP and related signaling molecules suggests that organoids can partially recapitulate the skin's immune microenvironment, offering opportunities for immunomodulatory interventions when combined with biomaterial strategies. Other studies further indicate that co-culture with T cells can simulate the activation or suppression of immune pathways, facilitating the screening of immunoregulatory agents.[29] Fibroblasts derived from diabetic foot ulcers (DFUFs) exhibit reduced responsiveness to TGF-β signaling, resulting in limited upregulation of downstream ECM genes. Co-culture of DFUFs with immune cells may help reconstruct TGF-β pathway impairment and enable screening of immunomodulatory factors for skin scaffold design. Organoid platforms can also model the immune microenvironment through co-culture systems, integrate gene-editing approaches to regulate immune pathways, and support disease-specific immunophenotyping. Specific

biomaterials can further enhance immunomodulation—silver nanoparticle hydrogels regulate local immunity and reduce infection through ion release, while PEG-based hydrogels can deliver immune-related factors such as TGF-β or BMP to modulate immune-cell recruitment and polarization within organoids.[48] Altogether, these strategies establish organoid technology as a robust platform for immunotherapeutic development, including gene-based interventions and drug screening for diabetic ulcer treatment.

In addition, organoid transplantation shows promise in alleviating the characteristic triad of sensory, motor, and autonomic neuropathies associated with DFUs. In current skin organoid models, sensory neurons and Schwann cells form nerve bundle–like structures that target $KRT20^{+}/TUJ1^{+}$ Merkel cells within hair follicles, thereby establishing a human-like tactile transmission pathway and conferring primitive tactile perception potential. In skin organoids cultured for over 100 days, $ISL1^{+}/TUJ1^{+}$ axons were observed to form an intricate neural network in which neurons interacted with $S100B^{+}$ Schwann-like cells and satellite glial-like cells to coordinately innervate hair follicles. The morphology and spatial organization of this network closely resembled that of native human neural structures, further supporting the organoids' potential to mediate tactile sensation. Moreover, neurons were found to extend into epithelial layers and encircle hair follicles, where $KRT20^{+}/TUJ1^{+}$ Merkel cells were distributed along the outer root sheath, suggesting the ability to form de novo mechanosensitive tactile complexes and providing a morphological foundation for tactile function in organoids.[8] Beyond structural insights, recent studies suggest that injectable drug-loaded skin scaffold systems may offer therapeutic interventions targeting key pathogenic mechanisms of DFUs—including peripheral neuropathy, peripheral arterial disease, and immunosuppression[32]—thereby improving associated neural dysfunction. The major pathophysiological mechanisms underlying diabetic chronic wounds are summarized in Figure 2.

## In-vitro Modeling and Application Strategies of Skin Organoids for Diabetic Wound Repair

In recent years, researchers have been continuously working to develop more mature organoid models to advance their applications in disease therapy. In 2020, a research team successfully generated nearly complete human skin organoids from pluripotent stem cells for the first time. These organoids exhibited a multicellular and structurally complex

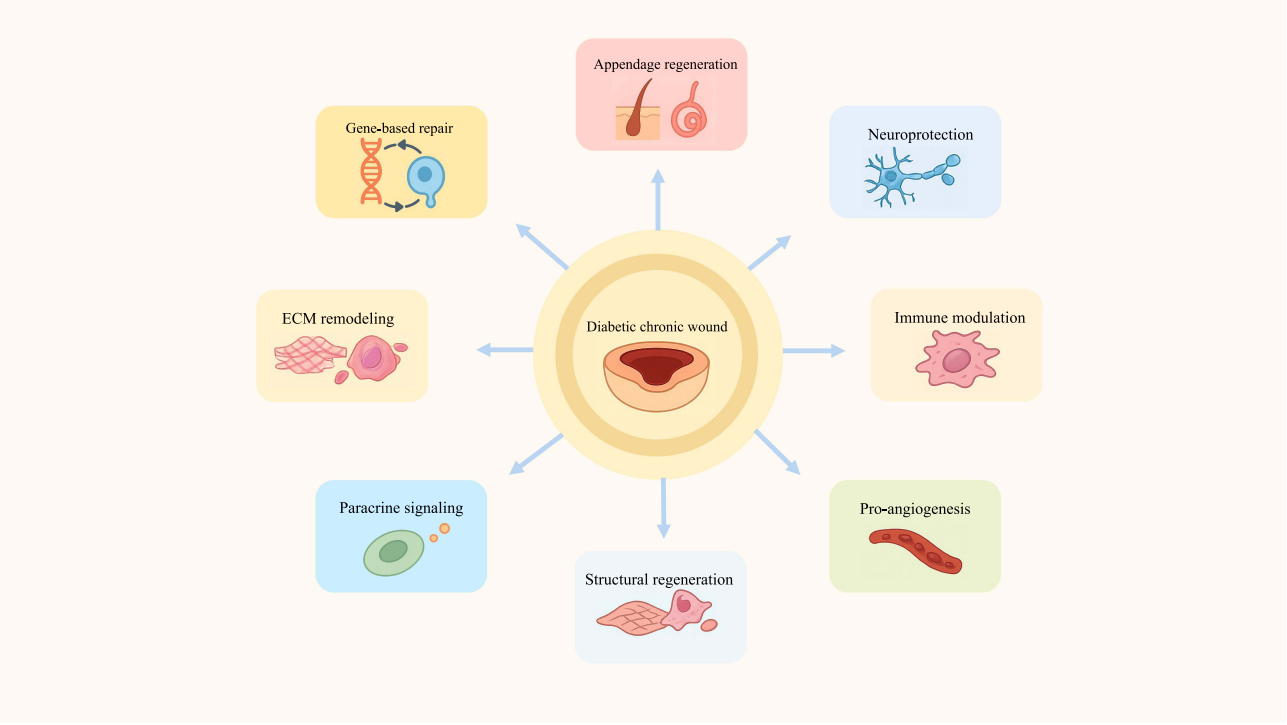


**Figure 2** Schematic representation of key pathophysiological mechanisms in diabetic chronic wounds.

architecture, comprising stratified epidermis, adipocyte-rich dermis, and pigmented hair follicles with associated sebaceous glands, thereby forming a functional skin unit. The hair follicles demonstrated melanogenesis and displayed morphological features resembling human fetal hair (lanugo or vellus hair). The dermis contained adipocytes and cartilage-like structures, recapitulating deeper layers of human skin. Furthermore, the organoids developed sensory neurons (eg., Aβ/δ low-threshold mechanoreceptors, LTMRs), Schwann cells, and Merkel cells, together forming a neural network analogous to human tactile circuits. To evaluate whether these organoids could integrate, survive, and function in vivo—thus assessing their therapeutic potential as grafts for skin defect repair—the researchers transplanted the skin organoids into immunodeficient mice (NU/J nude mice). The transplanted organoids fused seamlessly with host epidermis, forming structures with a stratum corneum and rete ridges resembling those of adult human facial skin, and were also capable of generating hair. Importantly, no tumor-like overgrowth or ulceration was observed during the transplantation process, indicating favorable biocompatibility and controlled engraftment.[8] This work represents the first successful de novo generation of full-thickness human skin organoids with appendages, such as hair follicles, from pluripotent stem cells that could integrate and function in vivo. These findings provide direct experimental evidence and strong support for the future application of such organoids in the repair of diabetic chronic ulcers, severe burns, and extensive skin defects. The schematic overview of the fabrication and in vivo maturation of skin organoids is shown in Figure 3.

However, these skin organoids lack key immune cell populations, which limits their application in immunology-related studies. This deficiency may be attributable to their scaffold composition, which consists of exogenously supplied Matrigel combined with ECM secreted by stem cells, without the co-culture of stem cells and immune cells or the incorporation of immunomodulatory factors into the scaffold. To address this fundamental limitation, researchers have attempted to develop immunocompetent organoids or organoid–immune cell co-culture systems to enable organoids to more faithfully recapitulate human inflammatory responses. In 2020, Tran et al developed several complex co-culture models. In one system, primary human macrophages were co-cultured with intestinal organoids, where macrophages enhanced the expression of epithelial tight junction proteins, thereby improving barrier integrity. In another model, microglia derived from human induced pluripotent stem cell (hiPSCs)—the intrinsic immune cells of the brain—were co-

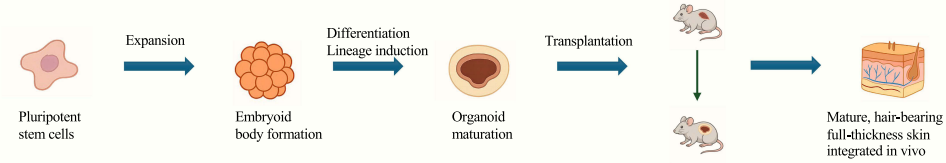


**Figure 3** Schematic overview of the fabrication and in vivo maturation of skin organoids.


https://doi.org/10.2147/DMSO.S598026

cultured with cerebral organoids. The microglia successfully integrated into the organoids and exhibited typical morphological and functional characteristics.[29] These findings demonstrate that co-culture with immune cells allows organoids to more accurately reproduce the in vivo microenvironment. The integration of organoids with immune cells can reconstruct functional immune responses, faithfully modeling both inflammatory and anti-inflammatory processes, thereby providing a theoretical foundation for this fusion strategy. Immune-enhanced skin organoids may therefore offer a precise regulatory platform for the treatment of diabetic chronic wounds.

In 2024, Kwak et al successfully generated multilayered epidermal organoids (iEpiOs) from iPSCs. These organoids not only expressed epidermal stem cell markers such as Itga6, Sca1, and CD34, with capacities for self-renewal and multilineage differentiation, but also activated key signaling pathways—including MAPK, WNT, and Hippo—under 3D culture conditions. In addition, iEpiOs enhanced the activity of the AP-1 transcription factors (c-Jun/c-Fos), thereby promoting the expression of epidermal differentiation genes such as p63, Filaggrin, and Loricrin. To further assess the therapeutic potential of 3D skin organoids in wound healing, the researchers compared the efficacy of extracellular vesicles (EVs) derived from self-organized iEpiOs with those from 2D-cultured cells. iEpiOs were dissociated into single cells, transitioned into 2D culture, and EVs were extracted from both 2D and 3D systems. A full-thickness skin defect model was established in BALB/c nude mice using a 6-mm punch biopsy with silicone ring placement to prevent contraction. Local injections of PBS, 2D-EVs, or 3D-EVs were administered, and the outcomes were compared. Results showed that the 3D-EV group exhibited significantly accelerated wound closure on days 3, 5, and 7, with nearly complete healing by day 7. Histological analysis further confirmed more complete re-epithelialization, orderly and mature collagen fiber deposition, and immunohistochemistry demonstrated markedly enhanced VEGF expression, indicating active angiogenesis.[9] This study demonstrated that 3D iEpiOs markedly enhance the repair of full-thickness skin defects by promoting re-epithelialization, collagen remodeling, and angiogenesis, thereby providing supportive evidence for their potential application in the treatment of diabetic chronic wounds.

In studies aimed at constructing mature skin organoids, researchers have focused on enhancing their functional properties—such as anti-inflammatory capacity, vascularization, and innervation—to more comprehensively recapitulate complex physiological mechanisms and thereby promote the repair and regeneration of hard-to-heal wounds, including frostbite, burns, and diabetic ulcers. In 2025, Wang et al generated multilayered skin organoids from hiPSCs, comprising epidermal, dermal, neuronal, and hair follicle cell populations. These organoids were encapsulated in gelatin hydrogel and transplanted into full-thickness frostbite wounds in mice, demonstrating superior repair outcomes compared to conventional treatments. The organoids effectively reduced infiltration of monocytes, macrophages, and Langerhans cells, modulated Toll-like receptor, NOD-like receptor, and chemokine signaling pathways, and significantly down-regulated pro-inflammatory cytokines such as CCL4 and IL-6, thereby mitigating excessive inflammation and preventing the establishment of a chronic inflammatory microenvironment. Concurrently, the organoids significantly increased the proportion of $KRT14^{+}$ epidermal stem cells, restored their normal differentiation trajectories into various epidermal layers, and activated stem cell regulatory pathways including Cd63 and Map3k5, promoting epidermal regeneration. At the ECM level, the organoids enhanced MMP3 expression while reducing scar-associated collagen (Col1a1, Col3a1), facilitating ECM degradation and remodeling, which contributes to scar inhibition.[11] Given that diabetic chronic wounds similarly exhibit persistent inflammation, epidermal stem cell dysfunction, and ECM remodeling abnormalities, these findings provide a strong theoretical and practical basis for the application of organoids in regenerative medicine for complex skin injuries, including diabetic chronic ulcers.

Although organoid construction techniques have matured, a common limitation remains: the lack of intrinsic vascular networks. Vascularization is crucial for ensuring long-term organoid survival, promoting functional maturation, and achieving integration with host tissues. In June 2025, Gong et al successfully generated VOs from iPSCs, featuring lumen-polarized structures and mature endothelial cell populations. To evaluate their therapeutic potential in diabetic vascular injury, the researchers established a severe hindlimb ischemia model in diabetic immunodeficient nude mice by surgically ligating and excising the unilateral femoral artery. Subsequently, 1,000 VOs or an equivalent mixture of 2D-cultured induced endothelial cells (iECs) and induced smooth muscle cells (iMCs) were injected into the ischemic muscle region. Results showed that the VO-treated group achieved a 50% restoration of blood flow by day 14 post-surgery, markedly superior to the minimal recovery observed in the control group. Histological analysis further confirmed

abundant human $CD31^+$ microvessels in the ischemic muscle of the VO group, whereas vessels in the control group were predominantly murine, indicating successful engraftment and survival of transplanted iECs.[51] Moreover, VO treatment significantly reduced both the severity and incidence of limb necrosis, demonstrating that VOs can promote neovascularization and restore perfusion in regions with diabetic angiogenesis deficits.[51] This study highlights the potential of multifunctional organoid transplantation as a promising strategy for diabetic chronic wounds. Co-transplantation of VOs with pancreatic islets may further accelerate islet vascularization and functional normalization, offering a novel approach toward diabetes remediation. In summary, vascular organoids derived from forward-programmed stem cells could potentially be co-cultured with epidermal organoids to enhance vascularization, providing a stable, reliable, and functional platform for cell-based therapies targeting ischemic diseases and diabetes.

Meanwhile, some studies are focused on developing vascularized neural organoid models. A core limitation of current neural organoids and assembloids is the absence of functional vascular systems, which leads to incomplete maturation of neurons and glial cells, thereby restricting physiological functionality and post-transplant integration. Researchers have proposed that the current technical integration direction involves combining vascular organoid technology (eg., blood-brain barrier models) with multi-organoid assembloids, introducing endothelial cells and pericytes into various organoids to establish functional vascular networks. Concurrently, strategies such as co-transplantation of vascular progenitor cells or induction of host angiogenesis (eg., via VEGF modulation) are being investigated to enhance vascularization within the grafts.[53] In 2020, the construction of vascularized organoids demonstrated that the proportions of HIF-$1\alpha^+$ cells and cleaved Caspase-$3^+$ cells were significantly lower compared to non-vascularized controls, indicating reduced hypoxia and apoptosis. vOrganoids exhibited larger overall volume, thicker neuroepithelium, and were enriched with outer radial glia (oRGs) and excitatory neurons, suggesting that vascularization significantly promotes organoid growth, differentiation, and maturation.[30] Upon transplantation of vOrganoids into the S1 cortex of mice, the endogenous vascular network successfully integrated with host cerebral vessels, establishing a functional circulatory system. This demonstrates that vascularization not only facilitates neural organoid development in vitro but also enables integration with host vasculature in vivo, enhancing functional maturation and long-term survival. The success of vascularized neural organoids marks a significant milestone in constructing highly integrated composite organoids or assembloids. Future strategies for developing neuro-vascularized mature skin organoids may include: (1) co-culturing skin organoids with iPSC-derived endothelial cells and neurons/Schwann cells within a single 3D system to guide self-organization into composite structures; (2) independently generating skin, vascular, and neural organoids and utilizing microfluidic platforms to support their mutual infiltration and functional connectivity; (3) employing gene editing or bioengineered scaffolds to direct axonal growth or promote vascularization within skin organoids. The creation of such neuro-vascularized composite skin organoids represents a major advancement for regenerative medicine in treating diabetic chronic wounds. Beyond providing physical barrier coverage, these organoids could rapidly restore vascular supply, recover sensory function, and modulate inflammatory responses, enabling multi-mechanistic, synergistic therapy for diabetic chronic wounds. The pathophysiological mechanisms of diabetic chronic wounds are summarized in Figure 4.

The successful translation of new technologies into clinical practice depends heavily on the reproducibility of outcomes and the long-term stability of the model—principles that have been well validated across multiple clinical studies.[54] Although the aforementioned findings in mouse models are encouraging, substantial differences remain between animal hosts and human diabetic chronic wounds, including discrepancies in immune activation patterns, angiogenic capacity, inflammatory persistence, and metabolic status. These differences limit the direct extrapolation of therapeutic effects and underlying mechanisms to clinical settings. To address this gap, several engineered in vitro systems have recently been developed to more faithfully recapitulate the microenvironment of diabetic wounds. In 2025, Sharma et al introduced a microfluidic diabetic wound-on-a-chip platform that integrates human fibroblasts, macrophages, and endothelial cells within a perfusable microscale architecture. This system successfully reproduced key pathological features of impaired healing, including defective extracellular matrix remodeling, compromised angiogenesis, and endothelial-to-mesenchymal transition (EndMT).[55] Combining skin organoids with such microengineered platforms may provide a more physiologically relevant means to assess organoid integration, immunomodulatory effects,

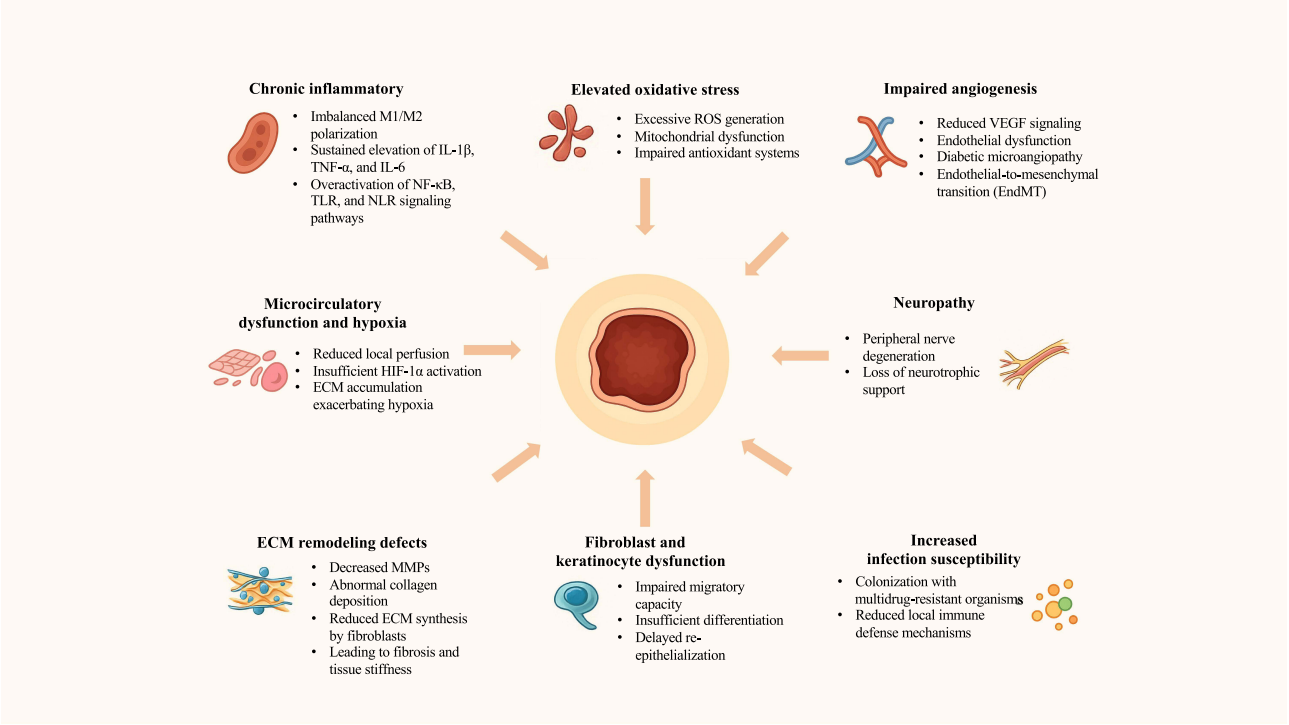


**Figure 4** Schematic representation of the pathophysiological mechanisms underlying diabetic chronic wounds.

and regenerative potential. This approach offers a robust framework for preclinical validation, thereby strengthening the foundation for the future clinical application of skin organoid-based therapies.

## Limitations and Translational Challenges of Current Skin Organoid Systems

Despite the substantial progress in skin organoid engineering, current systems still face several critical limitations that constrain their therapeutic potential for diabetic chronic wounds. The foremost challenge is insufficient vascularization. Most skin organoids lack perfusable vascular networks, resulting in restricted nutrient and oxygen delivery and consequently poor long-term survival and structural integration after transplantation—an issue that becomes even more pronounced within the ischemic and metabolically compromised microenvironment characteristic of diabetic wounds.[51] Although recent advances in vascular organoid construction offer new avenues for improving blood supply, achieving fully mature, functional vasculature within skin organoids remains an unresolved hurdle. A second major limitation is the absence of key immune cell populations, including macrophages, dendritic cells, and Langerhans cells, all of which are essential for regulating inflammation, clearing pathogens, and orchestrating tissue remodeling.[29,56] While co-culture approaches incorporating immune cells have been explored, they still fall short of recapitulating the persistent and dysregulated inflammatory state that defines diabetic chronic wounds. Moreover, organoids derived from pluripotent stem cells continue to carry risks of tumorigenicity and off-target differentiation. Incomplete differentiation or the presence of residual undifferentiated cells may lead to aberrant proliferation or the formation of tumor-like structures.[57] Long-term 3D culture can also induce non–skin-lineage subpopulations, potentially compromising tissue functionality and integration.[58]

In addition, current organoid systems rely heavily on Matrigel and other mouse tumor–derived extracellular matrices, which are compositionally undefined, exhibit substantial batch-to-batch variability, and possess uncontrollable mechanical and biochemical properties. Their xenogeneic origin also presents inherent safety and regulatory barriers. These matrices not only limit the reproducibility of organoid models but also pose a major obstacle to clinical translation.[59] At the same time, various scaffold materials may generate potential toxicity during degradation, including increased oxidative stress, cellular injury, or exacerbated inflammatory responses—issues repeatedly highlighted in biomaterial toxicology studies.[60,61] Lastly, full-thickness human skin consists of highly complex structures such as hair follicles,

sweat glands, neural networks, vascular beds, and multiple fibroblast subpopulations; yet current skin organoids are still unable to faithfully reconstruct all of these essential functional units.[5] Therefore, despite continual advancements in organoid technology, its overall maturity and functional complexity remain insufficient to fully meet the demands of diabetic chronic wound repair.

Beyond structural and functional limitations, skin organoids also encounter multiple translational barriers on the path toward clinical application. A major challenge lies in their limited stability and adaptability in vivo. Diabetic chronic wounds exist in a hostile microenvironment characterized by hyperglycemia, hypoxia, and persistent inflammation, accompanied by abnormal tissue tension, heightened oxidative stress, and elevated bacterial load. Even when organoids are successfully transplanted, these conditions severely compromise their early viability and impede effective integration with host tissues.[62] Furthermore, current organoids lack clinically suitable physical forms and mechanical properties. Most exist as free-floating three-dimensional clusters that are structurally loose, difficult to secure, and unable to maintain stable positioning on chronic wounds with heavy exudation or high contamination risk. Compared with standard clinical dressings, artificial dermis, or skin substitutes, organoids remain far less operable—a limitation increasingly emphasized in recent materials science research.[63] In addition, the standardization of organoid production remains inadequate. Variability in stem cell sources, induction conditions, and culture parameters within the same system leads to functional heterogeneity, making it difficult for organoid-based products to achieve the batch-to-batch consistency and quality control required for clinically compliant tissue-engineering materials. Without stable manufacturing processes and predictable structural and functional outcomes, substantial challenges will arise during regulatory approval, scale-up, and clinical trial design.[64] Lastly, the lack of clinically compatible delivery systems represents another key bottleneck in translation. Diabetic chronic wounds are frequently associated with infection, excessive exudation, and fragile tissue architecture. Organoids alone cannot provide adequate protective barriers, nor can they supply antimicrobial activity, moisture regulation, or structural support—factors essential for enabling their regenerative potential.[65] This laboratory-to-clinic gap mirrors a long-standing challenge across stem cell and regenerative medicine research, where promising biological constructs often fail to transition into clinically workable therapies. In summary, for skin organoids to transition from laboratory research to clinical practice, they must not only achieve greater structural complexity and functional maturity but also be supported by compatible engineered scaffolds, delivery systems, and standardized quality frameworks. These developments are essential to ensure their practicality and predictability within the challenging microenvironment of chronic wounds.

## Emerging Strategies and Future Directions for Clinical Translation

Overall, current skin organoids still exhibit notable limitations in structural maturation, functional stability, and the level of operability required for clinical use, directly constraining their further translational applicability in diabetic chronic wounds. Therefore, future research should focus on advancing supporting biomaterial systems, developing more physiologically relevant functional validation models, and optimizing culture platforms, with the goal of establishing an organoid technology pipeline capable of transitioning smoothly from laboratory settings to clinical applications.

In the field of scaffold materials and delivery systems, existing evidence indicates that the clinical translation of emerging technologies largely depends on rigorous validation of their operability and stability—an established principle demonstrated across various minimally invasive therapies and tissue-replacement strategies.[66]

From a translational perspective, these advances can be distilled into several key design principles for clinically viable organoid-supporting materials. These include: (i) antibacterial and biofilm-resistant properties to manage infection risk; (ii) mechanically robust materials with tunable elasticity to withstand physiological stress; (iii) moisture-retentive and exudate-regulating capacity to stabilize the wound microenvironment; and (iv) adhesive and integrative interfaces that facilitate graft fixation and vascular integration. With continued advances in materials science, research on chronic wound repair has begun to shift from traditional dressings toward more programmable and functional material platforms. Representative studies illustrate how these design principles are implemented in practice. For example, Prince et al evaluated the clinical benefits of advanced bioactive dressings in pressure ulcer care, highlighting the necessary pathway for translating tissue substitutes into clinical use.[67] Uyama and colleagues further outlined the antibacterial properties, biodegradability, and tunable structural characteristics of chitosan, cellulose, alginate, and their nanocomposites in chronic wounds, providing a material framework capable of

delivering both regulatory compliance and physical support for skin organoids.[68,69] By tuning pore architecture, surface energy, and mechanical modulus, these sustainable biopolymers offer stable interfaces for organoid adhesion, fixation, and post-transplant tissue integration. In addition, studies by Kalarikkal and Ghosal demonstrated the potential of electrospun nanofibers, porous aerogels, and plasma-modified biomaterials in regulating moist wound healing, modulating immune responses, and enabling drug delivery, thereby supporting the feasibility of composite strategies that integrate organoids with functional materials.[70] The antibacterial nanofibers and drug-loaded constructs developed by Ninan et al provide further solutions for managing infection and biofilm formation in diabetic wounds, offering a protective barrier that can be incorporated into organoid-based patches.[71]

In terms of organoid functional validation and chronic pathological modeling, existing mouse models fall short of faithfully recapitulating the persistent inflammation, ECM imbalance, and angiogenic impairment characteristic of diabetic wounds, creating inherent limitations for cross-species verification. The diabetic wound-on-a-chip microfluidic model developed by Sharma and colleagues offers an important avenue for organoid evaluation, as it simultaneously reproduces key pathological features such as hyperglycemia, hypoxia, AGEs-induced stimulation, and endothelial stress.[56] This platform enables real-time monitoring of cell migration, EndMT, angiogenic deficits, and ECM remodeling failure, thereby providing physiologically relevant readouts for assessing organoid integration and immunoregulatory effects. Future developments may further incorporate organoid-on-chip hybrid systems to mimic the temporal dynamics of the host–graft interface.[29] Studies by Ninan et al[71] and Ghosal[72] similarly point out that insufficient angiogenesis, dysregulated immune responses, and abnormal mechanical microenvironments represent the three major bottlenecks limiting regenerative efficiency in chronic wounds—complexities that cannot be fully addressed by organoid construction strategies alone. Consequently, future directions may involve assembling multi-organoid constructs, developing multi-cellular compartmentalized architectures, and applying biophysical gradient-guided engineering—such as stiffness gradients across dermal–epidermal interfaces or oxygen tension gradients within vascularized constructs—to better recapitulate the spatial and mechanical heterogeneity of native skin. Emerging evidence suggests that controlled mechanical and hypoxic gradients can regulate lineage specification, vascular patterning, and extracellular matrix remodeling, thereby enhancing structural maturation and functional integration of engineered tissues.[73]

In the areas of large-scale manufacturing, quality consistency, and regulatory compliance, current organoid production systems remain heavily dependent on xenogeneic matrices such as Matrigel, which have undefined compositions, marked batch-to-batch variability, and uncontrollable mechanical properties—factors that fall short of clinical-grade quality requirements. To address these limitations, materials scientists have proposed replacing Matrigel with degradable polysaccharides or synthetic polymers that possess defined compositions, tunable mechanical properties, and improved reproducibility profiles, thereby facilitating standardization and regulatory alignment.[68] Moreover, because diabetic chronic wounds are frequently associated with infection and heavy exudation, delivery systems must exhibit greater structural stability and resistance to environmental stressors.[71] Consequently, future organoid-based therapies will need to integrate engineered materials that are amenable to sterilization, fixation, and scalable production under Good Manufacturing Practice (GMP)-compatible conditions, ensuring suitability for clinical application. From a manufacturing perspective, it will be essential to establish GMP-compliant production workflows that are traceable, scalable, and parametrically controlled, ensuring batch-to-batch consistency and enabling organoid products to meet regulatory requirements for clinical-grade bioengineered tissues rather than remain limited to laboratory prototypes.

On this basis, safety becomes the central determinant of whether organoids can advance into clinical use, and it is closely tied to the degree of engineering within the manufacturing system. Given the potential tumorigenicity and genomic instability of pluripotent stem cell–derived organoids, several studies have suggested incorporating genetic circuit controls—such as suppression of MYC (v-myc avian myelocytomatosis viral oncogene homolog) or gating of the p53 (tumor protein 53) pathway—alongside residual pluripotent cell elimination strategies (eg., FACS-based removal, suicide-gene systems) and high-resolution genomic surveillance methods (including long-read sequencing and single-cell karyotyping) to ensure controlled proliferation and lineage stability during long-term culture and after ectopic transplantation.[74] In the highly inflamed microenvironment of diabetic chronic wounds, transplanted organoids may also trigger acute immune rejection or progressive structural fibrosis. Thus, strategies such as human leukocyte antigen (HLA)-I/II editing, immunomodulatory scaffolds (eg., interleukin-10 (IL-10)/colony-stimulating factor 1 receptor

(CSF1R)-tuned matrices), and antigen-presentation assessment platforms are needed to establish a predictable immune-compatibility framework.[75,76] Moreover, long-term culture may lead to off-target differentiation and lineage drift, necessitating future reliance on dynamic pathway regulation (BMP/WNT/FGF programming), spliceosome modulation —which may enable fine-tuning of alternative splicing events to stabilize lineage commitment and prevent aberrant differentiation— and multidimensional microenvironmental engineering to maintain stable multicellular composition.[77] As these risk-mitigation systems mature, converging international regulatory frameworks for tissue-engineered products similarly emphasize the need for multidimensional preclinical evaluation—including toxicity, tumorigenicity, immunogenicity, in vivo biodistribution, and persistence—supported by single-cell lineage tracing, spatial molecular imaging, and long-term animal studies to establish a reliable clinical safety evidence chain. Taken together, the clinical translation of skin organoids for diabetic chronic wound repair will depend not only on enhancements in structural maturity and regenerative potential but also on a comprehensive engineering overhaul of manufacturing, material integration, and safety systems to meet clinical-grade standards of predictability, reproducibility, and regulatory compliance.

Finally, advancing clinical translation will require meeting three essential conditions: (1) mechanistic consistency must be validated on controllable platforms—such as organ-on-chip systems or human-derived co-culture models—to compensate for the limitations of animal studies; (2) clinically compliant delivery and fixation systems must be established, including sterilizable, storable, and structurally stable patches or composite scaffolds; (3) early-phase human trials will be necessary, with a focus on implantation stability, short-term safety, graft integration, and long-term regenerative function. In summary, the translation of skin organoids for the treatment of diabetic chronic wounds will not be achieved through a single breakthrough. Instead, it requires coordinated progress along a multidimensional pathway spanning materials engineering, pathological modeling, structural maturation, manufacturing systems, and clinical validation. Establishing controllability, reproducibility, and regulatory compatibility across these steps is the fundamental prerequisite for moving organoid technologies from the laboratory into true clinical application.

## Conclusion

As a leading-edge technology in regenerative medicine, skin organoid transplantation has made substantial progress in recent years in the context of tissue reconstruction and organ replacement research. Compared with traditional skin substitutes or single-cell transplantation, skin organoids can recapitulate key developmental programs to generate three-dimensional structures composed of multiple cell types—including epidermis, dermis, hair follicles, and neural elements —thereby providing a physiologically relevant platform for modeling and repair. For diabetic chronic wounds, skin organoids offer multimodal therapeutic potential by suppressing chronic inflammation, promoting angiogenesis, improving local oxygenation, and partially correcting ECM remodeling defects; they may also support immunomodulation when combined with drug-loaded scaffolds. Future systems with improved neural and vascular integration may enable more comprehensive functional restoration, representing a promising and potentially transformative direction; however, it should be noted that current evidence remains largely preclinical. Nevertheless, clinical translation is constrained by multiple factors, including incomplete tissue maturation, limited long-term functional stability, suboptimal vascularization, and uncertainties regarding immune rejection. Potential risks such as tumorigenicity, off-target differentiation, and post-transplant microbiome dysbiosis must also be carefully addressed. Achieving clinical deployment will require improving structural integrity, immune compatibility, and long-term safety without compromising manufacturing scalability and reproducibility. To tackle these challenges, emerging strategies include biomaterial scaffolds, controlled-release factors, gene editing, microenvironmental and microbiome modulation, mechanical stimulation, and organ-on-chip systems. Meanwhile, high-throughput single-cell omics, spatial transcriptomics, and multimodal in vivo imaging provide powerful tools not only for precisely characterizing organoid development and post-implantation behavior, but also for standardization and quality assurance/quality control (QA/QC) of organoid batches, including identity, maturation state, and batch-to-batch consistency. Overall, skin organoids hold considerable promise for future clinical translation, provided that standardized fabrication workflows, rigorous safety evaluation frameworks, and robust in-process monitoring and release criteria are established to enable clinically deployable regenerative treatment modalities.

## Data Sharing Statement

Data sharing is not applicable to this article as no new data was analysed in this study.

## Author Contributions

Zhiyao Wang: Conceptualization; Data curation; Writing – original draft; Visualization.

Minjie Hou: Data curation; Writing – review & editing.

Jie Pei: Methodology; Writing – review & editing; Validation.

Fei Gao: Conceptualization; Supervision; Project administration; Writing – review & editing.

Zhi Li: Conceptualization; Supervision; Project administration; Writing – review & editing.

All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. Zhi Li is the primary corresponding author.

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## Disclosure

The authors declare that they have no competing interests.

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