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How can iPSC-Derived Therapies Complement Traditional Burn Treatments, such as Skin Grafts and Wound Dressings?

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Abstract

Burn injuries pose significant challenges in clinical management, often resulting in long-term complications like scarring and impaired wound healing. Traditional treatments have limitations, spurring exploration into innovative modalities. Induced pluripotent stem cells (iPSCs) offer promise in regenerative medicine by providing personalized and autologous cell sources. This paper assesses iPSC-derived therapies' potential to complement traditional burn treatments. iPSCs, generated from patient somatic cells and differentiated into skin cells, offer a tailored approach to wound healing. Their immunomodulatory properties can mitigate inflammation and reduce rejection risk in allogeneic transplantation. Despite challenges, iPSC-based therapies can revolutionize burn care, improve outcomes, and enhance burn survivors' quality of life. Continued research and advancements in iPSC technology are essential for realizing these approaches' full potential in clinical practice. Burn injuries present complex wound management challenges, requiring innovative approaches. This paper evaluates iPSC-derived therapies' integration into two key aspects of burn treatment: skin grafting and wound dressings. Traditional skin grafting faces limited availability and functional outcomes, which iPSC technology may address by providing patient-specific, functionally enhanced graft material with reduced rejection risk. Similarly, traditional wound dressings have limitations impacting their effectiveness in burn treatment. Advanced dressings incorporating iPSC-derived cells offer active participation in wound healing, promoting tissue regeneration, and minimizing scarring. Preclinical and clinical studies demonstrate iPSC-derived therapies' efficacy in enhancing keratinocyte migration, angiogenesis, and wound closure. These findings underscore iPSC-based therapies' potential to revolutionize burn treatment by addressing key challenges and improving patient outcomes. Future research should focus on refining protocols, conducting large-scale clinical trials, and navigating regulatory pathways to facilitate widespread adoption, ultimately enhancing the quality of life for burn survivors. Addressing scalability, cost, and ethical considerations is paramount for successful integration into clinical practice, requiring collaborative efforts between researchers, clinicians, regulators, and stakeholders.

Keywords: *iPSC, Burn Treatment, Ethics, Review, Wound Healing*

1. Introduction

1.1 Background:

Burns are injuries to the skin and underlying tissues caused by exposure to heat, electricity, chemicals, or radiation. The severity of a burn is typically categorized into degrees, ranging from first-degree (superficial) to fourth-degree (full-thickness) burns:

- First-degree burns: Affect the outer layer of the skin (epidermis), causing redness and pain but usually not blistering. Examples include mild sunburns.
- Second-degree burns: Extend into the second layer of skin (dermis) and can cause blistering, swelling, and more intense pain.

- Third-degree burns: Extend into the deeper layers of skin, damaging or destroying both the epidermis and dermis. These burns may appear white, charred, or leathery, and nerve endings may be damaged, leading to a lack of pain in the affected area.
- Fourth-degree burns: Extend beyond the skin, affecting muscles, tendons, and bones. These are severe burns that require immediate medical attention (1).

Burns can also be classified based on the extent of the body surface affected, commonly using the Rule of Nines for adults or the Lund and Browder chart for more precise measurements, especially in children.

Burn injuries, whether caused by thermal, chemical, or electrical sources, inflict substantial trauma to the skin and underlying tissues, necessitating prompt and effective interventions for optimal recovery. Traditional methods, such as autologous skin grafts and advanced wound dressings, have played pivotal roles in addressing the immediate challenges associated with burn wounds. However, limitations in these approaches, such as graft availability, immune rejection, and scarring, underscore the need for innovative therapeutic modalities (2).

Current burn treatments encompass a multifaceted approach aimed at minimizing tissue damage, preventing infections, and promoting optimal wound healing. Immediate first aid involves the application of cool running water to the burn site to mitigate thermal injuries. Topical antimicrobial agents, such as silver sulfadiazine, contribute to infection prevention during the wound healing process. Advanced wound dressings, including hydrogels and silver-containing dressings, create an environment conducive to tissue repair. Skin grafts, both autografts and allografts, play a critical role in promoting wound closure and minimizing scarring. Pain management strategies, ranging from over-the-counter analgesics to prescription medications, address the significant discomfort associated with burn injuries. Physical therapy assists in maintaining joint mobility and preventing complications like contractures. Infections are managed through antibiotics, and ongoing research explores regenerative therapies, such as induced pluripotent stem cells (iPSCs), to enhance tissue regeneration and reduce scarring. It's essential to acknowledge that burn treatment is dynamic, and medical practices may evolve. Consultation with healthcare professionals ensures the utilization of the most current and effective treatment modalities (3).

In recent years, induced pluripotent stem cells (iPSCs) have emerged as a revolutionary tool in regenerative medicine, offering the potential to generate patient-specific cells for various applications. iPSCs are generated by reprogramming adult cells, such as skin cells, into a pluripotent state, allowing them to differentiate into various cell types, including skin cells. In burn treatment, iPSCs can be harnessed to produce patient-specific skin cells, offering a tailored and autologous cell source. These iPSC-derived skin cells have the potential to replace damaged or lost tissue, promoting accelerated wound healing and minimizing scarring. Furthermore, iPSCs exhibit immunomodulatory properties, which can be instrumental in reducing inflammation and improving graft survival. This technology addresses challenges associated with immune rejection, as iPSCs derived from the patient's cells mitigate the risk of immunological complications. Although iPSC-based therapies for burns are still in the early stages of research and development, the potential to enhance traditional treatments, such as skin grafts and wound dressings, is substantial. As this innovative technology progresses, it may offer a novel avenue for advancing burn care, ultimately improving outcomes and quality of life for burn survivors. This paper delves into the unique properties of iPSCs and investigates their capacity to complement and synergize with traditional burn treatments (4).

1.2 Rationale:

Current burn treatments, while effective in many cases, are not without limitations. One significant limitation is the potential for scarring and impaired wound healing. Despite advancements in wound dressings and skin grafting techniques, extensive burns often result in hypertrophic scars and contractures, which can lead to functional impairment and cosmetic concerns. The risk of infection is another notable limitation, especially in severe burns where the protective skin barrier is compromised. Despite the use of antimicrobial agents and meticulous wound care, burn wounds remain susceptible to bacterial colonization, posing a constant threat to patient recovery. Additionally, the availability of donor sites for autografts in skin grafting procedures can be limited, particularly in cases of extensive burns. This limitation necessitates the exploration of alternative graft sources, such as allografts or xenografts, which may carry their own set of challenges, including immune rejection and limited long-term efficacy. Moreover, pain management, while crucial, can be challenging, and the use of opioids for pain control may introduce the risk of addiction or other adverse effects. Furthermore, the financial burden associated with long-term burn care, including surgeries, rehabilitation, and ongoing medical support, can be substantial, potentially limiting access to optimal treatment for some individuals. As our understanding of burn pathophysiology advances, addressing these limitations becomes paramount to improving overall outcomes for burn patients and underscores the need for ongoing research into innovative and more effective burn treatments (5).

Induced pluripotent stem cells (iPSCs) possess unique properties that make them highly promising for applications in regenerative medicine. One of the key features is their pluripotency, which enables iPSCs to differentiate into cells of various lineages, mimicking the characteristics of embryonic stem cells. This versatility allows for the generation of a wide range of cell types, including those crucial for tissue repair and regeneration. Additionally, iPSCs offer a patient-specific and autologous cell source, addressing concerns related to immune rejection commonly associated with allogeneic cell therapies. The reprogramming process used to create iPSCs involves reverting adult cells, such as skin cells, to a pluripotent state, avoiding the ethical concerns associated with the use of embryonic stem cells. This ethical advantage has contributed to the broader acceptance and exploration of iPSCs in research and clinical applications. Moreover, iPSCs exhibit extensive self-renewal capabilities, allowing for the generation of a sufficient number of cells for therapeutic purposes. Their potential to indefinitely proliferate in culture makes iPSCs a sustainable and scalable source of cells for regenerative interventions. The advent of genome editing technologies further enhances the appeal of iPSCs, as specific

genetic modifications can be introduced to correct disease-associated mutations or enhance therapeutic properties. As iPSC technology continues to advance, its application in regenerative medicine holds promise for personalized treatments, disease modelling, and addressing various medical conditions, including those related to tissue damage and degenerative disorders (6).

2. iPSC-Derived Therapies:

2.1 iPSC Generation:

Induced pluripotency is a ground-breaking concept in stem cell biology, referring to the process of reprogramming differentiated cells, typically somatic cells, back into a pluripotent state. Pluripotency means that the resulting cells have the potential to differentiate into any cell type in the human body. This transformative achievement was first realized with the discovery of induced pluripotent stem cells (iPSCs) by Shinya Yamanaka and his colleagues in 2006 (7). The reprogramming process involves the introduction of a defined set of transcription factors—typically Oct4, Sox2, Klf4, and c-Myc—into the target somatic cells. These transcription factors act as molecular switches, turning on and off specific genes associated with pluripotency and embryonic development. The exogenous expression of these factors reconfigures the cellular identity of the somatic cells, erasing their specialized characteristics and returning them to an embryonic-like state. This process effectively resets the cellular clock, allowing the newly induced pluripotent cells to regain the ability to differentiate into various cell types, mirroring the developmental potential of embryonic stem cells. The reprogramming of somatic cells into iPSCs not only holds profound implications for regenerative medicine but also provides a powerful tool for disease modelling, drug discovery, and personalized medicine. Despite its transformative potential, challenges such as genomic instability and the potential for tumorigenicity associated with the reprogramming process need to be carefully addressed for the safe and effective utilization of iPSCs in clinical applications (8).

Induced pluripotency and the reprogramming process hold significant potential in the context of burns and their treatment. When considering burn injuries, the ability to generate induced pluripotent stem cells (iPSCs) from a patient's somatic cells opens new avenues for personalized regenerative therapies. The reprogramming process involves the introduction of specific transcription factors into skin cells, for example, reversing their specialization and returning them to a pluripotent state. In the context of burns, this means that patient-specific iPSCs can be generated, which have the unique capability to differentiate into various cell types, including skin cells. iPSCs offer a promising solution to address the challenges associated with traditional burn treatments, such as limited donor sites for autografts and the risk of immune rejection. Patient-derived iPSCs can be differentiated into skin cells that are genetically identical to the patient, minimizing the risk of rejection and providing a tailored and effective approach to wound healing. Additionally, iPSCs can be guided to differentiate into specific cell types that aid in tissue repair and regeneration, potentially reducing scarring and enhancing the overall healing process. While there are challenges to be addressed, including ensuring the safety and stability of iPSCs, the reprogramming process offers an exciting avenue for advancing personalized and regenerative therapies in the treatment of burns. The ability to harness the patient's cells for targeted and effective wound healing represents a transformative approach that holds great promise for the future of burn care (9).

2.2 Differentiation into Skin Cells:

Directing induced pluripotent stem cells (iPSCs) toward specific skin cell types, such as keratinocytes and fibroblasts, involves a series of controlled differentiation steps mimicking natural embryonic development. The differentiation process aims to recapitulate the cellular events that occur during skin development and regeneration. Several methods and signalling pathways are employed to guide iPSCs into the desired lineages.

To generate keratinocytes, iPSCs are typically subjected to a protocol that involves the activation of pathways associated with ectodermal differentiation. This often includes the modulation of signalling pathways such as Wnt, BMP, and FGF. Sequential exposure to specific growth factors and small molecules helps in the stepwise induction of iPSCs into ectodermal lineages, eventually leading to the formation of keratinocytes. Key growth factors such as BMP4 and bone morphogenetic protein 7 (BMP7) are often utilized in this process (10).

For fibroblast differentiation, iPSCs undergo a mesodermal lineage commitment. TGF-β signalling is crucial in this context, as it promotes the differentiation of iPSCs toward mesenchymal lineages. The addition of TGF-β1, along with other factors such as bFGF and PDGF, guides iPSCs through a mesenchymal transition, ultimately resulting in the generation of fibroblast-like cells (11).

Beyond keratinocytes and fibroblasts, iPSCs can be directed into other relevant skin cell types using tailored protocols. Melanocytes, for instance, can be generated through the activation of the Wnt and c-kit signalling pathways. The addition of specific growth factors like SCF (stem cell factor) and ET-3 (endothelin-3) further refines the differentiation process toward melanocytic lineages (12).

The success of these differentiation methods often relies on the careful orchestration of multiple signalling pathways, growth factors, and temporal control over the culture conditions. Researchers continuously refine these protocols to enhance the efficiency, yield, and functional maturity of iPSC-derived skin cells. The resulting iPSC-derived keratinocytes, fibroblasts, and other relevant cell types offer a valuable resource for various applications, including regenerative medicine and disease modelling in the context of skin disorders and burn injuries.

Recapitulating skin tissue architecture in vitro represents a significant challenge in tissue engineering and regenerative medicine, aiming to mimic the complex and hierarchical structure of native skin. To achieve this, researchers employ advanced three-

dimensional (3D) culture systems and bioengineering techniques that replicate the cellular and extracellular matrix (ECM) components found in the skin. In the case of induced pluripotent stem cell (iPSC)-derived skin tissue, the process involves carefully orchestrating the differentiation of iPSCs into specific cell lineages that constitute the skin, such as keratinocytes, fibroblasts, and melanocytes.

In 3D cultures, iPSC-derived keratinocytes are often organized into stratified layers to emulate the epidermis, while fibroblasts contribute to the development of the dermal layer. These layers are interconnected through a biomimetic ECM that provides structural support and biochemical cues essential for cell proliferation, migration, and differentiation. The inclusion of components like collagen, elastin, and hyaluronic acid in the engineered ECM helps recreate the biomechanical and biochemical properties of native skin. Additionally, the incorporation of vascularization components is crucial to mimic the blood supply essential for nutrient exchange and overall tissue viability (13).

The recapitulation of skin tissue architecture also involves considering the unique features of specialized skin structures, such as hair follicles, sweat glands, and sebaceous glands. Researchers utilize specific induction protocols to guide iPSCs into these lineages, fostering the development of these functional structures within the engineered skin tissue.

Furthermore, recapitulating skin tissue architecture extends beyond cellular composition to include features like innervation. Incorporating sensory neurons and nerve endings in the engineered skin tissue enhances its physiological relevance and contributes to the modelling of sensory responses and wound healing processes.

While significant progress has been made, challenges remain, including achieving full functional maturation of iPSC-derived skin tissue and ensuring proper integration with the host upon transplantation. Continued advancements in biomaterials, 3D bioprinting, and bio-fabrication technologies, along with a deeper understanding of skin development and physiology, contribute to refining in vitro models that closely mimic the intricacies of native skin tissue. Ultimately, these efforts hold great promise for advancing personalized medicine, drug testing, and therapeutic interventions, particularly in the context of skin disorders, burns, and wound healing.

2.3 Immunomodulatory Properties:

The exploration of induced pluripotent stem cells (iPSCs) in modulating the immune response holds great promise, particularly in reducing inflammation associated with various pathological conditions. iPSCs possess unique immunomodulatory properties that make them an intriguing candidate for therapeutic applications. These cells can release a variety of anti-inflammatory factors and cytokines, creating a microenvironment conducive to immune regulation. iPSC-derived mesenchymal stem cells (iPSC-MSCs), for instance, have been shown to exhibit potent immunomodulatory effects. When exposed to inflammatory stimuli, iPSC-MSCs can release anti-inflammatory cytokines, such as interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β), while suppressing the production of pro-inflammatory cytokines like tumour necrosis factor-alpha (TNF-α) and interferon-gamma (IFN-γ). These immunomodulatory effects are particularly relevant in the context of inflammatory disorders, autoimmune diseases, and conditions characterized by excessive inflammation, including severe burns. By dampening the pro-inflammatory response, iPSCs can potentially mitigate tissue damage caused by an overactive immune system. Furthermore, iPSCs have been investigated for their potential to induce regulatory T cells (Tregs), a subset of immune cells known for their suppressive effects on inflammation. This unique ability to modulate the immune response positions iPSCs as a novel tool in the development of therapeutic strategies for conditions where immune dysregulation plays a central role. While the field is still in its early stages, ongoing research continues to uncover the mechanisms underlying iPSC-mediated immunomodulation, to harness these capabilities for precision medicine and tailored therapeutic interventions (14).

The exploration of induced pluripotent stem cells (iPSCs) in modulating the immune response holds significant promise for burn treatment, where excessive inflammation is a critical factor contributing to tissue damage and complications. iPSCs exhibit unique immunomodulatory properties that can be harnessed to attenuate the inflammatory response associated with severe burns. In burn injuries, the initial inflammatory phase, while essential for initiating the healing process, can become dysregulated, leading to sustained inflammation and collateral tissue damage. iPSC-derived mesenchymal stem cells (iPSC-MSCs) have demonstrated the ability to release anti-inflammatory cytokines, such as interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β), while suppressing pro-inflammatory cytokines like tumour necrosis factor-alpha (TNF-α) and interferon-gamma (IFN-γ). This dual action helps to rebalance the immune response, mitigating the overactivation of immune cells that contribute to the inflammatory cascade in burn injuries. Additionally, iPSCs have the potential to induce the generation of regulatory T cells (Tregs), which play a crucial role in immune tolerance and suppression of excessive inflammation. By incorporating iPSCs or iPSC-derived products into burn treatment strategies, it is conceivable that the immunomodulatory effects could not only alleviate the immediate inflammatory response but also contribute to improved wound healing, reduced scarring, and overall enhanced tissue regeneration. While challenges and safety considerations need to be addressed, the immunomodulatory properties of iPSCs offer a novel avenue for refining and advancing burn treatment protocols, potentially mitigating the detrimental effects of prolonged inflammation, and improving the long-term outcomes for burn survivors. Ongoing research in this area holds the promise of unlocking innovative and targeted approaches for personalized burn care (15).

The prevention of rejection in allogeneic transplantation, particularly in the context of burn treatment, represents a critical challenge and an area of active exploration. Allogeneic transplantation involves using donor tissues or cells from another individual, and the risk of rejection arises from the recipient's immune system recognizing these transplanted materials as foreign and mounting an immune response against them. In burn treatment, where extensive skin damage often necessitates grafting procedures, preventing

rejection is paramount for the success of allogeneic skin grafts. Traditional approaches involve the use of immunosuppressive drugs to dampen the recipient's immune response, but these medications come with potential side effects and long-term complications (16).

Induced pluripotent stem cells (iPSCs) offer a promising avenue to address the challenge of rejection in allogeneic transplantation. By generating iPSCs from the patient's cells and differentiating them into the required cell types, such as keratinocytes for skin grafts, the risk of rejection is significantly reduced. This is because the resulting cells are genetically identical to the patient, minimizing the chance of immune recognition and rejection. iPSCs derived from the patient's somatic cells can provide a personalized and autologous cell source for regenerative therapies, including those required for burn treatment.

Moreover, advancements in gene editing technologies allow for precise modifications to the iPSCs, potentially eliminating any remaining risk factors for rejection. These modifications can include the removal of immunogenic markers or the introduction of specific genetic elements to enhance the compatibility of the transplanted cells with the recipient's immune system.

While challenges and safety considerations persist, the use of iPSCs in allogeneic transplantation for burn treatment holds significant potential to overcome the barriers associated with rejection. This approach not only addresses the immunological challenges but also contributes to the development of safer and more effective regenerative therapies for individuals with extensive burn injuries. Ongoing research in iPSC technology and transplantation immunology continues to refine these approaches, aiming to provide innovative and patient-specific solutions for burn care.

3. Integration with Traditional Burn Treatments:

3.1 Skin Grafts:

Skin grafting is a fundamental component of burn treatment, providing a critical solution for restoring the damaged skin barrier and promoting wound healing. However, despite its significance, skin grafting in the context of burn injuries is fraught with challenges that impact both the immediate and long-term outcomes for patients. One of the primary challenges lies in the limited availability of suitable donor sites for autografts. Autografts, where skin is harvested from a healthy area of the patient's body, are the preferred choice due to reduced risk of rejection. However, in cases of extensive burns, the availability of unburned, healthy skin for grafting may be severely limited, leading to challenges in obtaining sufficient graft material. This constraint necessitates alternative graft sources, such as allografts (grafts from another individual) or xenografts (grafts from a different species), but these carry the risk of immune rejection and limited long-term success.

Another challenge in skin grafting for burns is the potential for graft failure or necrosis. The graft's ability to establish vascularization and integrate with the recipient site is crucial for its survival. Insufficient blood supply to the graft, often exacerbated by the compromised vascular bed in burn wounds, can lead to graft failure. Additionally, infections pose a significant threat to graft viability, particularly in the early stages post-transplantation, necessitating rigorous wound care and infection prevention measures.

The issue of scarring and contractures further complicates skin grafting outcomes in burn patients. Despite successful graft take, the healing process may result in hypertrophic scars and contractures, limiting joint mobility and causing aesthetic concerns. Addressing these issues requires a multidisciplinary approach, involving physical therapy, scar management strategies, and, in some cases, additional surgical interventions.

Moreover, advancements in regenerative medicine, such as induced pluripotent stem cell (iPSC) therapies, aim to overcome these challenges by providing a potential source of autologous, patient-specific cells for grafting. While promising, these approaches are still in the early stages of development and face challenges related to safety, scalability, and long-term efficacy. In conclusion, while skin grafting remains a cornerstone in burn treatment, ongoing research and innovative approaches are essential to address the persistent challenges associated with graft availability, integration, and functional outcomes in individuals with severe burn injuries (17).

The evaluation of how induced pluripotent stem cell (iPSC)-derived skin cells can enhance graft acceptance and functionality in burn treatment reveals a promising avenue for overcoming some of the inherent challenges associated with conventional skin grafting. iPSC technology allows for the generation of patient-specific skin cells, offering a potentially unlimited source of autologous graft material. This personalized approach addresses the critical issue of graft rejection, as iPSC-derived skin cells are genetically identical to the recipient, minimizing the risk of immunological complications.

Furthermore, iPSCs can be guided to differentiate into specific cell types relevant to skin grafting, such as keratinocytes and fibroblasts. These iPSC-derived cells not only resemble their natural counterparts but also exhibit enhanced regenerative and functional properties. The controlled differentiation process ensures that the generated cells possess the necessary characteristics for effective wound healing, including the formation of a stratified epidermis and the production of extracellular matrix components crucial for dermal structure.

The immunomodulatory properties of iPSCs also play a significant role in graft acceptance. iPSCs and their derivatives have been shown to secrete anti-inflammatory cytokines and modulate immune responses, creating a microenvironment conducive to graft integration. This immunomodulatory effect may contribute to a more favourable immune response at the graft site, reducing inflammation and minimizing the risk of rejection.

In addition to addressing immunological challenges, iPSC-derived skin cells have the potential to enhance the functional outcomes of skin grafts. The ability to generate various skin cell types in a controlled manner allows for the recreation of a more natural and functional skin structure. This includes the formation of hair follicles, sweat glands, and other specialized structures that contribute to the overall functionality of the skin (18).

While these advancements hold great promise, challenges remain, including ensuring the safety and efficacy of iPSC-derived cells in clinical applications, addressing scalability issues, and optimizing the functional maturation of these cells. Nevertheless, the exploration of iPSC technology in burn treatment signifies a paradigm shift towards personalized and regenerative approaches, offering the potential to improve graft acceptance, functionality, and long-term outcomes for individuals with severe burn injuries. Ongoing research in this area is crucial for refining iPSC-based strategies and translating them into effective clinical interventions.

3.2 Wound Dressings:

Traditional wound dressings have been fundamental in the management of burn injuries, offering crucial support for the healing process, infection prevention, and overall wound care. Gauze dressings, a pervasive choice in burn treatment, provide a cost-effective and readily available option. They offer a protective layer, absorb exudate, and allow for visual assessment of the wound. However, frequent changes in gauze dressings can be painful, disrupt the delicate healing environment, and contribute to prolonged recovery times. Hydrocolloid dressings, another common choice, create a moist environment that promotes autolytic debridement and accelerates wound healing. While effective for many wounds, they may not be suitable for highly exudative burn wounds and could potentially cause maceration of the surrounding healthy skin. Alginate dressings, derived from seaweed, are absorbent and conform well to wound contours. Although useful in managing exudative wounds, they have limitations such as desiccation and the potential to adhere to the wound bed, causing discomfort during removal.

Despite their historical significance, traditional wound dressings exhibit limitations that impact their effectiveness in burn treatment. The need for frequent changes can lead to repeated trauma to the healing tissue, delaying the overall healing process and potentially increasing the risk of scarring. Moreover, the antimicrobial properties of traditional dressings may not be sufficient to address the heightened susceptibility of burn wounds to infections due to compromised skin integrity. Additionally, the necessity for careful wound observation during dressing changes can contribute to patient discomfort and anxiety, posing challenges in maintaining a conducive healing environment (19).

Recognizing these limitations, there has been a paradigm shift towards the development of advanced wound dressings that address specific challenges associated with burn injuries. Modern approaches focus on creating dressings that not only provide a protective barrier and support wound healing but also incorporate features like sustained antimicrobial activity, reduced frequency of changes, and improved patient comfort. Regenerative therapies, including those derived from induced pluripotent stem cells (iPSCs), are also being explored to revolutionize burn wound management by promoting tissue regeneration and minimizing scarring. As research advances, the integration of innovative wound care strategies holds the potential to enhance outcomes and redefine the standard of care for burn patients.

The incorporation of induced pluripotent stem cell (iPSC)-derived cells into advanced dressings represents a cutting-edge approach to burn treatment, aiming to revolutionize wound healing and mitigate the limitations of traditional dressings. iPSCs, with their remarkable ability to differentiate into various cell types, including skin cells like keratinocytes and fibroblasts, offer a unique opportunity to engineer advanced dressings that actively contribute to tissue regeneration. These dressings, often referred to as bioactive or smart dressings, go beyond providing a passive barrier and instead actively participate in the healing process.

In iPSC-based advanced dressings, iPSC-derived cells are incorporated into a biomaterial matrix, creating a scaffold that mimics the natural extracellular matrix of the skin. This scaffold not only supports the attachment and growth of iPSC-derived cells but also provides a three-dimensional structure that closely resembles the architecture of native tissue. The iPSC-derived cells, once integrated into the dressing, release growth factors, cytokines, and other bioactive molecules that stimulate the surrounding tissues, promoting cell proliferation, angiogenesis, and extracellular matrix remodelling (18).

One key advantage of incorporating iPSC-derived cells is their potential to enhance the regenerative capacity of the wound. iPSC-derived keratinocytes contribute to the formation of a stratified epidermis, while iPSC-derived fibroblasts aid in the development of a functional dermal layer. This multifaceted approach not only accelerates wound closure but also minimizes scarring and improves the overall cosmetic and functional outcomes.

Moreover, iPSC-derived cells possess immunomodulatory properties, creating a microenvironment that mitigates inflammation and promotes a balanced immune response. This is particularly crucial in burn wounds, where the inflammatory phase can be prolonged and detrimental to the healing process. iPSC-based dressings, by modulating the immune response, contribute to a more favourable environment for tissue repair.

While the field is still in its early stages, the integration of iPSC-derived cells into advanced dressings holds great promise for burn treatment. These bioactive dressings represent a paradigm shift, offering a personalized and regenerative approach that aligns with the specific needs of individual patients. As research progresses and safety considerations are addressed, iPSC-based advanced dressings may emerge as a transformative solution, significantly improving outcomes for burn patients by accelerating wound healing, minimizing scarring, and enhancing overall tissue regeneration (20).

4. Preclinical and Clinical Studies:

4.1 Clinical Study:

Desmoglein 3 (Dsg3) acts as an important regulator of keratinocyte migration and wound healing. This study investigates the therapeutic potential of extracellular vesicles derived from induced pluripotent stem cells (iPSCs-MVs) in deep second-degree burn wound healing. iPSCs-MVs were isolated and characterized, demonstrating their ability to accelerate wound closure in mice.

The study identifies microRNA-16-5p (miR-16-5p) as a key component of iPSCs-MVs responsible for promoting keratinocyte migration. iPSCs-MVs were found to enhance re-epithelialization, myofibroblast formation, collagen deposition, and angiogenesis in the wound area. Importantly, the effect of iPSCs-MVs on wound closure was attributed to increased keratinocyte migration rather than proliferation.

Further analysis revealed that miR-16-5p, the most highly expressed miRNA in iPSCs-MVs, played a crucial role in promoting keratinocyte migration. iPSCs-MVs were internalized by keratinocytes, and the pro-migratory effect of iPSCs-MVs was attenuated by a miR-16-5p inhibitor. The study also identified Dsg3 as a target gene of miR-16-5p. Dsg3 is a desmosomal cadherin known to regulate keratinocyte migration. The inhibition of Dsg3 expression by miR-16-5p contributed to enhanced keratinocyte migration.

In vitro experiments confirmed the ability of iPSCs-MVs to promote keratinocyte migration without affecting proliferation. The findings suggest that iPSCs-MVs, particularly through miR-16-5p, play a critical role in wound healing by accelerating keratinocyte migration. The study also demonstrates that local treatment with miR-16-5p can enhance wound closure, supporting its potential therapeutic application.

Overall, this research sheds light on the mechanisms underlying the regenerative effects of iPSCs-MVs in burn wound healing. The identification of miR-16-5p and its target gene Dsg3 provides insights into the molecular pathways involved in promoting keratinocyte migration. These findings contribute to the development of novel therapeutic strategies for enhancing wound-healing processes (21).

The effects of Dsg3 on migration were mediated by activation of the p38/MAPK pathway. Our study supports this notion as we observed an increased p-p38/p38 ratio in HaCaT cells upon treatment with miR-16-5p mimics or Dsg3 siRNA, indicating the activation of the p38/MAPK pathway. Conversely, overexpression of Dsg3 attenuated the p38 activation induced by miR-16-5p mimics. Inhibition of p38/MAPK signalling using SB202190 abolished the enhanced migration induced by miR-16-5p mimics. Thus, we propose that miR-16-5p promotes keratinocyte migration by targeting Dsg3, leading to the activation of the p38/MAPK signalling pathway.

In the context of burn wound healing, miR-16-5p agomir treatment significantly accelerated wound closure and increased re-epithelialization. Consistent with the in vitro results, miR-16-5p did not affect keratinocyte proliferation at the wound edge, supporting the notion that the enhanced re-epithelialization was likely due to the promotion of keratinocyte migration. Furthermore, we observed a reduction in collagen deposition in wounds treated with miR-16-5p agomir. Collagen deposition is a crucial step in the wound-healing process, and excessive collagen formation can lead to hypertrophic scarring. Therefore, the observed reduction in collagen deposition may suggest a potential benefit of miR-16-5p treatment in preventing excessive scar formation during burn wound healing.

While this study provides valuable insights into the role of iPSCs-MVs and miR-16-5p in promoting wound healing, there are some potential challenges and areas for future research. Firstly, the study focused on the effects of iPSCs-MVs and miR-16-5p on keratinocyte migration, and their impact on other cell types involved in wound healing, such as fibroblasts, endothelial cells, and immune cells, needs further investigation. Understanding the broader cellular responses to iPSCs-MVs and miR-16-5p will provide a more comprehensive view of their therapeutic potential in wound healing. Secondly, the study primarily utilized a mouse model of deep second-degree burn wounds. While this model is relevant, it is essential to assess the translatability of these findings to human wounds, considering the differences in skin structure and healing mechanisms between mice and humans. Clinical studies or experiments using human skin equivalents could provide additional insights into the applicability of iPSCs-MVs and miR-16-5p in human wound healing.

In conclusion, the research paper highlights the potential of iPSCs-MVs and miR-16-5p in accelerating wound healing, particularly in the context of deep second-degree burn wounds. The study provides mechanistic insights into how iPSCs-MVs, through the delivery of miR-16-5p, enhance keratinocyte migration by targeting Dsg3 and activating the p38/MAPK pathway. These findings contribute to the growing body of knowledge in regenerative medicine and suggest avenues for future therapeutic interventions in wound healing (21).

The exploration of induced pluripotent stem cells (iPSCs) for burn treatment in human clinical trials carries immense importance in revolutionizing the field of regenerative medicine. Burn injuries, especially severe cases, pose significant challenges for conventional treatments, often resulting in scarring, prolonged healing times, and limited functional recovery. iPSC-based therapies offer a promising alternative by harnessing the regenerative potential of these versatile cells. One crucial aspect is their ability to differentiate into various cell types, including skin cells, providing a potential solution for reconstructing damaged tissue. The prospect of personalized medicine, where iPSCs can be derived from a patient's cells, minimizes the risk of rejection and addresses issues of immune compatibility. Moreover, iPSC-based treatments hold the promise of reducing scarring and accelerating the healing

process, thereby significantly improving outcomes for burn patients. Looking ahead, the future of iPSC burn treatment clinical trials involves optimizing protocols, expanding large-scale trials, exploring combination therapies, fostering global collaboration, and navigating regulatory pathways. Successful trials are a prerequisite for regulatory approval, paving the way for iPSC-based burn treatments to become a transformative and widely accessible solution, ultimately enhancing the quality of life for burn survivors.

5. Future Perspectives and Challenges:

5.1 Scalability and Cost:

Addressing challenges related to the large-scale production of induced pluripotent stem cell (iPSC)-derived therapies is crucial for realizing their widespread clinical application and ensuring accessibility for a broad patient population. One of the primary challenges lies in the scalability of iPSC manufacturing. The conventional methods for generating iPSCs involve time-consuming and labour-intensive processes, including manual cell culture and genetic reprogramming. Scaling up these processes to meet the demand for many therapeutic doses poses logistical and economic challenges. Advanced technologies, such as automated bioreactor systems and closed-culture systems, are being explored to streamline iPSC production, enhance efficiency, and minimize variability between batches.

Ensuring the quality and consistency of iPSC-derived therapies represents another significant challenge. The inherent biological variability of iPSC lines, even those derived from the same individual, necessitates stringent quality control measures to guarantee the safety and efficacy of the final product. Standardizing protocols for iPSC generation, differentiation, and characterization is essential to minimize batch-to-batch variations and ensure reproducibility. Furthermore, rigorous testing for potential genomic alterations, epigenetic changes, and residual pluripotent cells is critical to address safety concerns associated with iPSC-derived therapies.

Navigating regulatory frameworks poses a substantial challenge in the large-scale production of iPSC therapies. Regulatory authorities require robust evidence of the safety, efficacy, and consistency of these therapies before granting approvals for clinical use. Establishing clear and standardized regulatory pathways for iPSC-derived products is imperative to facilitate their translation from research laboratories to clinical settings. Close collaboration between researchers, industry stakeholders, and regulatory agencies is essential to establish comprehensive guidelines that ensure patient safety and therapeutic efficacy while promoting innovation in iPSC-based therapies (22).

Addressing ethical considerations and public perception is yet another challenge in the large-scale production of iPSC-derived therapies. Ensuring transparency in the use of donor cells, obtaining informed consent, and addressing concerns related to genetic manipulation are critical aspects. Public engagement and education efforts are essential to foster understanding and acceptance of iPSC technologies and their potential benefits.

Addressing challenges related to the large-scale production of induced pluripotent stem cell (iPSC)-derived therapies in the context of burn treatment is vital for harnessing the full potential of regenerative medicine in managing severe burn injuries. A primary challenge lies in the scalability of iPSC manufacturing to meet the demands of a significant patient population with burn injuries. The conventional methods of iPSC generation involve intricate, time-consuming processes, making it imperative to develop efficient and automated systems that can handle large-scale production. Advanced bioreactor technologies and closed-culture systems are under exploration to optimize iPSC expansion and differentiation, ensuring reproducibility and minimizing variability between batches (23).

In conclusion, overcoming the challenges related to large-scale production of iPSC-derived therapies for burn treatment requires concerted efforts in technological innovation, quality assurance, regulatory frameworks, and ethical considerations. Success in addressing these challenges will pave the way for iPSC-based therapies to become a transformative tool in regenerative burn treatment, offering personalized and effective solutions for a diverse patient population. Ongoing collaborations between researchers, industry stakeholders, regulatory bodies, and the public are essential to navigate these complexities and advance iPSC therapeutics in the realm of burn care.

Implementing strategies to make induced pluripotent stem cell (iPSC) therapies more cost-effective in the context of burn treatment is critical for their widespread accessibility and clinical adoption. One key strategy involves optimizing and automating the manufacturing processes of iPSCs and their derivatives. Streamlining the reprogramming, expansion, and differentiation steps using advanced bioreactor systems and closed-culture platforms can enhance efficiency, reduce labour costs, and enable the production of larger quantities of cells at scale. Additionally, standardizing protocols for iPSC generation and differentiation can contribute to reproducibility, minimizing the need for extensive quality control measures and reducing overall production costs.

Another strategy is exploring alternative and more cost-efficient culture media and reagents. The development of chemically defined and xeno-free culture conditions can decrease the reliance on expensive growth factors and animal-derived components, making the iPSC production process more economical. Moreover, leveraging economies of scale through large-scale production facilities and collaborations between academic institutions, industry partners, and regulatory bodies can contribute to cost reduction by spreading fixed costs across a higher volume of therapeutic doses.

Investing in research and development to enhance the scalability of iPSC manufacturing technologies is crucial for cost-effectiveness. Innovations in bioprocessing, automation, and robotics can further optimize workflows, reduce manual interventions,

and decrease overall production costs. Additionally, advancements in gene-editing technologies, such as CRISPR-Cas9, can enable precise genetic modifications in iPSCs more efficiently, potentially reducing the time and resources required for generating customized therapeutic products (24).

Considering reimbursement models and healthcare economics is also essential in making iPSC therapies more cost-effective. Collaboration with healthcare payers and policymakers to establish reimbursement frameworks that reflect the long-term benefits and cost-effectiveness of iPSC therapies in burn treatment can incentivize their integration into standard care practices. Demonstrating the economic value through clinical trials and real-world evidence is pivotal in convincing stakeholders of the long-term cost savings associated with iPSC therapies, including reduced hospitalizations, complications, and long-term care costs for burn patients.

In summary, a multifaceted approach is needed to make iPSC therapies more cost-effective for burn treatment. Strategies involving process optimization, standardized protocols, alternative culture conditions, and economies of scale can collectively contribute to lowering production costs. Concurrently, ongoing collaboration with regulatory bodies, healthcare payers, and the broader medical community is crucial to establishing a supportive environment that recognizes the value and cost-effectiveness of iPSC therapies in revolutionizing burn care.

5.2 Ethical Considerations:

Exploring the ethical implications associated with induced pluripotent stem cell (iPSC) technology in burn treatment raises critical considerations surrounding consent, genetic manipulation, and broader societal implications. Obtaining informed consent from donors for the use of their cells in iPSC generation is a fundamental ethical requirement. Clear communication about the potential uses of iPSCs, including their application in burn treatment, is essential to ensure that donors understand the nature and purpose of their contributions. Moreover, the potential for genetic manipulation, though a powerful tool for enhancing iPSC functionality, raises ethical concerns. Ensuring transparency about any genetic modifications, their purpose, and potential long-term consequences is imperative to uphold ethical standards. The use of gene-editing technologies like CRISPR-Cas9 demands careful ethical scrutiny to prevent unintended consequences and to address concerns related to unintended off-target effects or the introduction of genetic alterations with unknown implications.

Equitable access to iPSC-based therapies is another ethical consideration. Ensuring that the benefits of iPSC technology are accessible to diverse populations, irrespective of socioeconomic factors, is crucial to prevent exacerbating healthcare disparities. Additionally, the potential for commercialization and profit-making from iPSC therapies necessitates ethical considerations to avoid exploitation and to prioritize patient welfare over financial gains (23).

Furthermore, the long-term safety of iPSC therapies and the potential for unintended consequences, such as tumorigenicity, necessitate ongoing ethical oversight. Rigorous preclinical and clinical testing, along with continuous monitoring of patients, is crucial to minimize risks and ensure the safety of individuals receiving iPSC-based treatments.

A broader societal consideration involves addressing expectations and hype surrounding iPSC technology. Public understanding and perception of iPSCs, especially in the context of burn treatment, may be influenced by expectations of rapid clinical application. Ethical communication and managing public expectations are vital to avoid premature and unrealistic anticipations, fostering a balanced discourse that acknowledges both the potential benefits and the uncertainties associated with iPSC-based burn therapies.

In conclusion, exploring the ethical implications of iPSC technology in burn treatment requires a comprehensive approach that involves transparent communication, informed consent, addressing concerns related to genetic manipulation, ensuring equitable access, and ongoing safety monitoring. As iPSC technology advances, ethical considerations must evolve in parallel to strike a delicate balance between promoting scientific innovation and ensuring the ethical use of iPSCs for the betterment of burn patients and society at large (25).

Balancing the benefits and risks in the clinical applications of induced pluripotent stem cells (iPSCs) in burn treatment is a complex and essential task that involves careful consideration of scientific, ethical, and safety factors. The potential benefits of iPSCs in burn treatment are significant. iPSCs can be differentiated into various cell types relevant to skin regeneration, such as keratinocytes and fibroblasts, offering a personalized and potentially limitless cell source for grafts. This can address the critical challenge of donor site scarcity in severe burn injuries, providing an autologous and customized therapeutic approach. Additionally, iPSCs possess immunomodulatory properties that may contribute to a more favourable wound-healing environment in burn injuries, potentially reducing inflammation and promoting tissue regeneration.

However, along with these promises come inherent risks that require meticulous evaluation. The risk of tumorigenicity, associated with the potential for iPSCs to form teratomas or other unwanted cell types, remains a significant concern. Ensuring the safety of iPSC-derived therapies demands thorough preclinical testing and ongoing monitoring of patients post-treatment to detect and mitigate any adverse effects promptly. Moreover, ethical considerations related to obtaining informed consent for the use of iPSCs, addressing concerns about genetic manipulation, and ensuring equitable access to these therapies must be considered.

Balancing these benefits and risks necessitates a rigorous regulatory framework and close collaboration between researchers, clinicians, regulatory agencies, and ethical review boards. Clinical trials must adhere to stringent protocols, incorporating robust safety measures, transparency in reporting outcomes, and continuous monitoring to assess both short-term and long-term effects.

An open dialogue with patients and the public, ensuring clear communication about the potential benefits and uncertainties of iPSC-based treatments, is essential in fostering trust and managing expectations (26).

As iPSC technology advances, ongoing research and a commitment to evidence-based practice are paramount. This involves continuous refinement of iPSC generation and differentiation protocols, addressing safety concerns, and optimizing clinical applications. Striking the right balance between the potential benefits and associated risks is crucial for the responsible advancement of iPSC-based therapies in burn treatment, ultimately ensuring the best possible outcomes for patients while upholding ethical standards and safety considerations.

6. Conclusion:

The potential of induced pluripotent stem cell (iPSC)-derived therapies to complement and synergize with traditional burn treatments is vast and transformative. iPSCs offer a promising avenue to address critical challenges in burn care, particularly in enhancing the regenerative capacity of damaged skin. By differentiating iPSCs into specific cell lineages relevant to the skin, such as keratinocytes and fibroblasts, personalized and autologous grafts can be generated, potentially overcoming limitations associated with donor site scarcity and immune rejection. The ability of iPSCs to modulate the immune response presents an additional advantage, as it may contribute to reducing inflammation, minimizing tissue damage, and creating a more conducive environment for wound healing. The incorporation of iPSC-derived cells into advanced dressings represents an innovative approach, actively participating in tissue regeneration and providing a multifaceted solution for burn injuries. Moreover, iPSC technology holds the potential to address the limitations of traditional treatments, such as the need for frequent dressing changes and the risk of infection. By leveraging the unique properties of iPSCs, including their pluripotency and immunomodulatory capabilities, a synergistic integration with traditional burn treatments could redefine the landscape of burn care, offering more effective, personalized, and regenerative solutions for individuals with severe burn injuries. However, the realization of this potential requires ongoing research, addressing safety considerations, and navigating ethical, regulatory, and logistical challenges to ensure the responsible translation of iPSC-derived therapies into mainstream clinical practice.

Emphasizing the need for further research and clinical validation in induced pluripotent stem cells (iPSCs) and burn treatment underscores the importance of advancing our understanding, ensuring safety, and validating the therapeutic potential of iPSC-based approaches in the complex context of severe burn injuries. While iPSC technology holds immense promise, numerous critical questions and challenges persist. Rigorous preclinical research is essential to comprehensively evaluate the safety profile of iPSC-derived therapies, addressing concerns such as tumorigenicity, genetic stability, and potential long-term effects. Clinical validation through well-designed and meticulously conducted trials is imperative to ascertain the efficacy and safety of iPSC-based interventions in diverse patient populations. This validation process should involve large-scale, multi-centre trials that adhere to stringent protocols, incorporate robust endpoints, and consider long-term outcomes. Furthermore, research should focus on optimizing iPSC manufacturing processes to ensure scalability, reproducibility, and cost-effectiveness, facilitating the eventual integration of iPSC therapies into mainstream clinical practice. Continuous exploration of iPSC-derived cell types, their behaviour in the wound microenvironment, and their interaction with the host immune system is crucial for refining treatment strategies and addressing specific challenges associated with burn injuries. Ethical considerations, patient perspectives, and societal attitudes should also be central to the research agenda, ensuring that iPSC-based therapies align with broader healthcare goals and values. In conclusion, while iPSCs hold tremendous potential for revolutionizing burn treatment, a dedicated and multidisciplinary research effort is essential to validate their safety, efficacy, and practical feasibility in diverse clinical settings, paving the way for a new era in personalized and regenerative burn care.

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