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Utilizing Stem Cells to Address Skin Tissue Immune Rejection

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ABSTRACT

The skin of the human body comprises three distinct layers — the epidermis, dermis, and hypodermis — each filled with diverse cells and structures vital for protection and temperature regulation. Acting as a shield against external elements, the skin is an integral part of the innate immune system. However, its protective nature also makes the skin highly immunogenic. As a result, traditional skin transplantation methods are complex procedures that have high risks of rejection and can increase susceptibility to infections. These challenges are further amplified by the difficulty in finding and verifying compatible transplants.

In recent years, advances in stem cell research and crafting artificial skin substitutes have shown promising results in wound healing (without the risks of immune rejection). Stem cells possess the unique ability to differentiate into various cell types and are classified based on their potency. By incorporating stem cells into biomaterial polymers, researchers can develop effective skin substitutes, allowing for promising treatment options for patients. This article will review what the skin is, how immune rejection occurs, and what recent advances in stem cells can help patients in the near future.

Introduction

Skin, the largest organ in the human body, is a complex structure that functions primarily as a protective barrier, aiding in temperature regulation, storage, sensation, and many other functions [1]. It is a significant factor in what defines a person externally (for example, in outer appearance) and internally (from a biological aspect). Everyone's skin is uniquely different from skin tone to the cellular makeup of the organ.

Since the skin plays a critical role in our day-to-day lives, damage from burns, wounds, or surgery, can lead to major complications. Severe injury often requires grafting or flaps from a different location on your body, but this is not always possible. If damage is too extensive, skin transplantation from another person might be required. This approach comes with major limitations, however, as the biggest hurdle to transplantation is our immune system – a complex "organ" programmed to recognize and attack foreign antigens, repair damaged tissue, and repel potential harm [7]. Though our immune system is essential to our health, it can “reject” transplanted tissue, stunting the survival of the transplant cells and possibly leading to further damage to the body. While steroids and other immunosuppressive drugs can slow this response, they are not curative and often must be taken chronically [14].

Recently, alternatives to transplants have emerged due to advances in stem cell research. These cells can regenerate and transform into many different types of tissues and organs, including the skin. While embryonic, pluripotent, and adult stem cells can differentiate into more than one cell type, their degree of potency impacts their effectiveness in skin tissue engineering. This article will introduce the structure of the skin and our immune system, what current types of skin transplants are used, why immune system rejection occurs, and finally, how stem cells can successfully replicate skin tissue (especially when scaffolds are used).

Function and Structure of the Skin

The human skin is a complex organ, characterized by its layered structure and diverse cell composition [1]. It is divided into three primary layers: the epidermis, dermis, and hypodermis, each offering unique functions and structural characteristics vital to maintaining overall skin health and body defense mechanisms [2].

The outermost layer is the epidermis – a dynamic environment that consists of keratinocytes, melanocytes, Langerhans cells, and Merkel cells. These cells work to offer a first line of defense against environmental stressors and are part of our immune system. Structurally, the epidermis is stratified into five sub-layers, including the stratum corneum (at the top) and the stratum basale (at the bottom). The stratum basale acts as the skin's regenerative source, housing the stem cells vital for continuous skin renewal [3].

Beneath the epidermis is the dermis, a structural layer that contains collagen and elastin. These proteins provide the skin with resilience and flexibility. Mixed in between are sweat glands, hair follicles, muscles, sensory neurons, and a network of blood vessels. This layer is divided into the upper papillary and lower reticular layers, each contributing to the skin's structural integrity [1,2].

The hypodermis, or subcutaneous tissue, attaches the skin to the underlying muscle and bone. Composed predominantly of fat, it serves dual functions in shock absorption and thermal insulation. The hypodermis also serves as a reservoir of energy [1,4].

In total, this elaborate composition ensures the skin's pivotal role in barrier function, sensory perception, thermoregulation, and metabolic regulation, showcasing the intricate synergy of cellular and structural elements working in concert to maintain skin health and systemic homeostasis.

The Body's Immune System

Our immune system comprises a complex network of cells, tissues, and organs that help protect us against harmful invaders, such as bacteria, viruses, and other pathogens. There are two main parts of the immune system: the innate and adaptive immune system.

The innate immune system is considered our first line of defense. It is responsible for providing a physical barrier against foreign attackers, attacking & "eating" foreign cells, and activating an alarm system (through other protein and chemical signals) to recruit other immune cells. It consists of the skin, mucous membranes, and specific immune system cells capable of phagocytosis (a process in which it allows certain cells to "eat" other cells). As a first line of defense, the innate immune system is fast, allowing it to quickly respond to invaders with the downside of being unable to change or adapt [5].

The adaptive immune system is composed of T and B lymphocytes, commonly known as T cells and B cells. These cells respond more slowly to pathogens and infections than the cells of the innate immune system but play a crucial role in immunological memory, enhancing the body's response to recurring attacks. In some situations, they can even accelerate the innate system's reaction to repeated exposures to pathogens [6].

T cells have multiple functions within the adaptive immune system. They are responsible for activating other immune cells during an attack, identifying and eliminating infected or cancerous cells, and forming immunological "memories" of pathogens to prepare the body for potential re-infections. Additionally, T cells are instrumental in moderating immune responses to prevent an overreaction once the threat is neutralized [7].

On the other hand, B cells, when activated by T cells, transform into plasma cells that manufacture precise and specific antibodies tailored to neutralize the identified invaders. These antibodies not only incapacitate pathogens but also trigger the activation of other immune cells and proteins to join the fight against the foreign intruders. In this way, the adaptive immune system contributes significantly to the body's defense mechanism, ensuring a swift and effective response to recognized pathogens and infections. [5,6,7].

Structurally, there are several key organs involved in our immune system. The bone marrow and thymus are considered primary lymphoid organs, which are responsible for the creation of lymphocytes. At the same time, the skin, spleen, tonsils, lymph nodes, and mucous membranes are secondary lymphoid organs in which immune system cells fight off antigens [8].

Skin Transplants

When layers of skin are damaged extensively – such as from burns, surgeries that require additional grafting for skin loss, injuries that cannot heal themselves, or other extensive wounds – one may require a skin transplant. Skin transplants consist of two major kinds: grafts and flaps. Grafts are patches of healthy skin often removed from one part of the body (autografts) or another person (allografts) and transplanted to the site of injury [9,10]. These surgeries are generally easier for surgeons to perform as they are completely removed from their original blood supply [9]. They are performed about 100,000 times annually in America [11]. Very rarely, another species may be used for grafting (called xenografts) [10].

Flaps are the more complex type of skin transplant as they contain their original blood supply and can comprise one or more tissue types. Examples include cutaneous flaps, fasciocutaneous flaps, and myocutaneous flaps [12]. These are transplanted from one part of the body to another and can comprise one or more tissue types. While requiring more complicated surgery than grafts, these transplants are more favorable due to better cosmetic outcomes and patient satisfaction [13].

Immune System Rejection

As described above, our immune system plays a pivotal role in identifying and combating harmful antigens and foreign invaders. This attribute isn't without its downsides, however. In the context of transplantation, the immune system can be a double-edged sword, potentially leading to complications or even death due to its rejection of transplanted tissues or organs. Skin transplants amplify this challenge, given the skin's high immunogenicity resulting from an abundance of antigen-presenting cells. These specialized cells expose foreign antigens to the T cells of the immune system, triggering a defense mechanism against the transplanted tissue. While autografts (transplants from the same individual's body) are typically safe from rejection, allografts (transplants between different individuals of the same species) and xenografts (transplants between different species) face a significant risk of being attacked and rejected by the recipient's immune system [14].

Types of rejection are based on time. Hyperacute rejection, a rare reaction, occurs within minutes to hours after transplantation, typically only occurring if the recipient has pre-existing antibodies against the donor tissue. Acute rejections, on the other hand, generally appear days to weeks after the transplantation and is the most common type of rejection. Chronic rejection usually occurs months to years after the transplant and is a long-term process, often resulting from the cumulative damage to the transplanted tissue caused by a low-grade persistent immune response against the graft [15].

To prevent strong immune responses and rejection, recipients of transplants are usually matched to donors that are screened via genetic testing and blood type compatibility. Though these screens can help, in most cases, recipients will still require immunosuppressants to inhibit the immune system and prevent a response to the foreign cells. These drugs (often corticosteroids (e.g., prednisone), calcineurin inhibitors, or mTOR inhibitors) reduce inflammation and suppress the immune system [16]. While effective in blocking immune rejection, they unfortunately come with serious side effects such as increasing the patient's risk of secondary infections [14].

Stem Cells

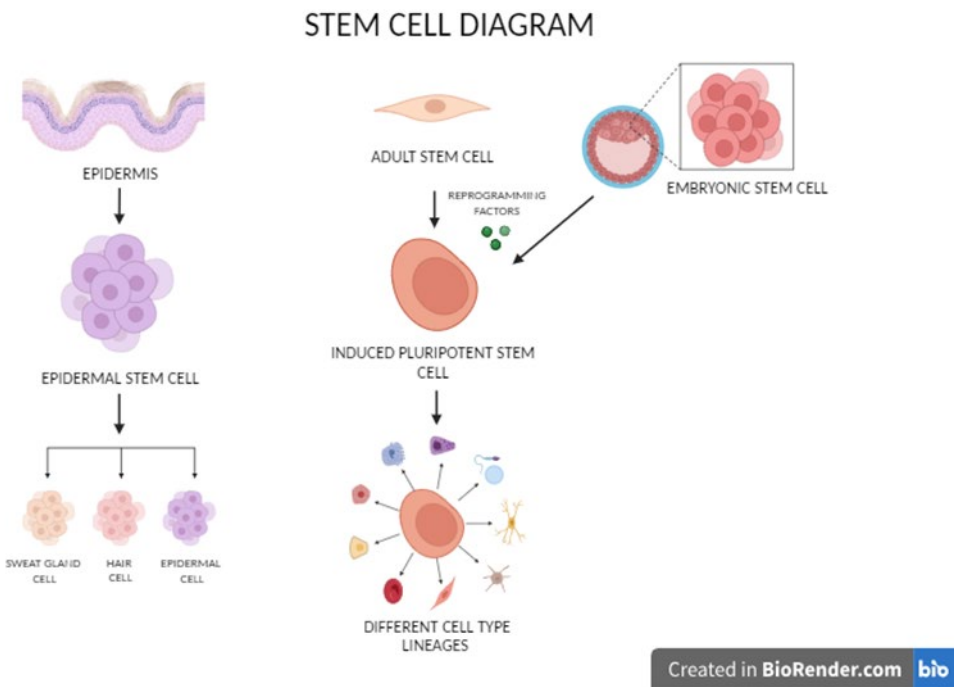
A solution to the strong immune response risks presented with transplantation may be found in the use of autologous stem cells (an individual's stem cells). Stem cells are categorized into adult (somatic) stem cells (ASCs), induced pluripotent stem cells (iPSCs), and embryonic stem cells (ESCs). These cells mainly differ in their potency and ability to differentiate into specific types of cells [17].

ASCs are derived from fully matured tissue and are either unipotent (can only form one cell type) or multipotent (can generally only differentiate into cell types from one tissue lineage). Regarding the skin, mesenchymal stem cells (bone marrow-derived) and epidermal stem cells (epidermis-derived) are the most common ASCs used for skin tissue engineering.

iPSCs are ASCs that have been genetically induced or "reprogrammed" into an embryonic/pluripotent state, allowing them to differentiate into more than one type of tissue cell lineage. ESCs are considered the top choice of stem cells in medicine due to their totipotency (they can differentiate into all cell types); many ethical concerns surround using ESCs, however, because they are derived from embryos in the early stages of development [17].[1]

Stem Cells and Biomaterials

Stem cells, by themselves, are insufficient for regenerating skin tissue. They require scaffolds or other biomaterials to provide the necessary structure for growth. These structures must be biocompatible with the body and provide adequate support for successful cell growth and differentiation [18]. While a new and rapidly advancing field, scientists are currently focused on: 1) the types of biomaterials used (natural vs. synthetic polymers); and 2) how to create scaffold structures that help anchor and support the growth of the stem cells.



[1] **FIGURE:** example of ASC differentiation, iPSC differentiation, ESC differentiation. Created with BioRender.com

Figure 1. Example of ASC differentiation, iPSC differentiation, ESC differentiation. Created with BioRender.com

Biomaterials/polymers generally fall into two main categories: natural and synthetic. Examples of common natural biomaterials used for skin substitution are collagen, chitosan, and fibrin, or a multitude of stem cell types, many of which are already found within the layers of the skin. These biomaterials are biologically more similar to the native composition of skin and may be more compatible with the body's immune system. On the other hand, synthetic polymers include polyethylene glycol (PEG) and poly lactic-co-glycolic acid (PLGA). These molecules often provide greater structural integrity and are often easier to manufacture [18,19,20].

Both types of biomaterials are often used simultaneously; using different types of polymers, scientists can manipulate the behavior of the biomaterial skin scaffold, including but not limited to degradation rate, cell attachment, and porosity [21]. These factors are crucial to skin reconstruction because the scaffold should mimic the native area enough to encourage cell migration/proliferation.

Different methods can be used for creating scaffolds and diverse structures for the stem cells to adhere to, including electrospinning, patterning/molding, and 3D-bioprinting. Electrospinning utilizes an electrostatic field to form fine polymer fibers to create a random or fixed alignment pattern. This method allows the doctor to create fibers that mimic the natural direction of tissue growth. Patterning/molding, on the other hand, involves molding and etching polymers into a specific shape. This method can be used to create more complicated structures. Lastly, 3D bioprinting can create specific scaffolds layer by layer through the use of bioinks, polymers used to create artificial tissue substitutes [21].

Clinical Trials

Clinical trials of stem cell scaffolding have had promising degrees of success. One study used collagen and fibroblast graft hosting epidermal stem cells to treat full-thickness wounds on mice with full skin loss. The experiment saw a significantly greater improvement in healing time and scar formation than control mice without grafting [22]. Another study seeded epidermal stem cells and fibroblasts into porcine-derived acellular dermal substrates to treat full-thickness skin defects in mice. The results showed healing with no significant complications and a complete restructuring of the dermis besides skin appendages and epidermis with proliferation of keratinocytes found to be derived from the seeded graft [23]. Furthermore, adult human bone marrow stem cells grafted on a polypropylene, N-isopropyl acrylamide, and gelatin crosslinked hydrogel were used to treat skin-defected mice. This study showed a significantly quicker healing process than mice treated with a control scaffold, and the transplanted cells could restructure and connect parts of the epithelium [24].

The results of these studies are just the beginning to creating a functional stem cell scaffold for human skin tissue regeneration. Essential factors to consider are cell adhesion abilities, rates of cell proliferation, and environmental influences (such as temperature) that could potentially compromise the scaffold's effectiveness.

Conclusion and Discussion

The revolutionizing advances in skin tissue engineering and bioengineering show promising results for the future of skin tissue regeneration. Transplants for extensive skin wounds are becoming increasingly less desirable due to many downsides, including a high risk of rejection and poor replication of native skin structure. Fortunately, research surrounding the combination of stem cells – cells with considerable regeneration potential – and biomaterials have discovered alternatives that do not involve the major risks presented by traditional

transplants. Although clinical trials to develop stem cell scaffolds are still in progress and need to be tested & approved for use, further research and progress in bioengineering should allow us to do so in the near future.

References

[1] Lopez-Ojeda, Wilfredo, et al. "Anatomy, Skin (Integument)." *PubMed*, StatPearls Publishing, 2020, www.ncbi.nlm.nih.gov/books/NBK441980/.

[2] ---. "Skin: Layers, Structure and Function." Cleveland Clinic, 13 Oct. 2021, my.clevelandclinic.org/health/body/10978-skin.

[3] Yousef, Hani, et al. "Anatomy, Skin (Integument), Epidermis." *PubMed*, StatPearls Publishing, 14 Nov. 2020, www.ncbi.nlm.nih.gov/books/NBK470464/.

[4] Cleveland Clinic. "Hypodermis (Subcutaneous Tissue): Function & Structure." Cleveland Clinic, 19 Oct. 2021, my.clevelandclinic.org/health/body/21902-hypodermis-subcutaneous-tissue.

[5] Information, National Center for Biotechnology, et al. *The Innate and Adaptive Immune Systems*. Institute for Quality and Efficiency in Health Care (IQWiG), 30 July 2020, www.ncbi.nlm.nih.gov/books/NBK279396/#:~:text=in%20our%20methods.-.

[6] Immune Deficiency Foundation. "The Immune System and Primary Immunodeficiency | Immune Deficiency Foundation." *Primaryimmune.org*, 2016, primaryimmune.org/immune-system-and-primary-immunodeficiency.

[7] "Immune Response: MedlinePlus Medical Encyclopedia." *Medlineplus.gov*, 2022, medlineplus.gov/ency/article/000821.htm#:~:text=Innate%2C%20or%20nonspecific%2C%20immunity%20is.

[8] ---. *What Are the Organs of the Immune System? Www.ncbi.nlm.nih.gov*, Institute for Quality and Efficiency in Health Care (IQWiG), 30 July 2020, www.ncbi.nlm.nih.gov/books/NBK279395/#:~:text=Primary%20lymphoid%20organs%3A%20These%20organs.

[9] Prohaska, Joseph, and Christopher Cook. "Skin Grafting." *Nih.gov*, StatPearls Publishing, 4 Apr. 2019, www.ncbi.nlm.nih.gov/books/NBK532874/.

[10] "Skin Grafts for Burn Treatment | Regions Hospital." *Www.healthpartners.com*, www.healthpartners.com/care/hospitals/regions/specialties/burn-center/skin-grafting/.

[11] "Tissue Donation Statistics ." *Www.utsouthwestern.edu*, www.utsouthwestern.edu/education/medical-school/departments/transplant-services-center/faqs/statistics.html.

[12] Ngan, Vanessa. "Flaps | DermNet NZ." Dermnetnz.org, 2007, dermnetnz.org/topics/flaps.

[13] "Skin Flap Surgery." *Reconstructive Plastic Surgery Melbourne*,

rpsmelbourne.com.au/services/melanoma-skin-cancer/skin-flaps/.

[14] Zhou, Junyi, et al. "Fundamental Immunology of Skin Transplantation and Key Strategies for Tolerance Induction." *Archivum Immunologiae et Therapiae Experimentalis*, vol. 61, no. 5, 18 May 2013, pp. 397–405, https://doi.org/10.1007/s00005-013-0233-2.

[15] Justiz Vaillant, Angel A., and Michael Mohseni. "Chronic Transplantation Rejection." *PubMed*, StatPearls Publishing, 2023, www.ncbi.nlm.nih.gov/books/NBK535435/#:~:text=Acute%20rejection%20occurs%20days%20or.

[16] Hussain, Yaseen, and Haroon Khan. "Immunosuppressive Drugs." *Encyclopedia of Infection and Immunity*, 2022, pp. 726–740, https://doi.org/10.1016/b978-0-12-818731-9.00068-9.

[17] Chen, Ming, et al. "Stem Cells for Skin Tissue Engineering and Wound Healing." *Critical Reviews in Biomedical Engineering*, vol. 37, no. 4-5, 2009, pp. 399–421, https://doi.org/10.1615/critrevbiomedeng.v37.i4-5.50.

[18] Hilmi, Abu Bakar Mohd. "Vital Roles of Stem Cells and Biomaterials in Skin Tissue Engineering." *World Journal of Stem Cells*, vol. 7, no. 2, 2015, p. 428, https://doi.org/10.4252/wjsc.v7.i2.428.

[19] Dash, Biraja C., et al. "Stem Cells and Engineered Scaffolds for Regenerative Wound Healing." *Bioengineering*, vol. 5, no. 1, 9 Mar. 2018, p. 23, https://doi.org/10.3390/bioengineering5010023.

[20] Przekora, Agata. "A Concise Review on Tissue Engineered Artificial Skin Grafts for Chronic Wound Treatment: Can We Reconstruct Functional Skin Tissue in Vitro?" *Cells*, vol. 9, no. 7, 6 July 2020, p. 1622, https://doi.org/10.3390/cells9071622.

[21] Nicholas, Mathew N., et al. "Methodologies in Creating Skin Substitutes." *Cellular and Molecular Life Sciences*, vol. 73, no. 18, 6 May 2016, pp. 3453–3472, https://doi.org/10.1007/s00018-016-2252-8.

[22] Hu, Kuikui, et al. "An Experimental Study on the Repair of Full Skin Loss of Nude Mice with Composite Graft of Epidermal Stem Cells." *Burns*, vol. 32, no. 4, 1 June 2006, pp. 416–422, https://doi.org/10.1016/j.burns.2005.10.014.

[23] Ju Lin Xie, et al. "A Study of Using Tissue-Engineered Skin Reconstructed by Candidate Epidermal Stem Cells to Cover the Nude Mice with Full-Thickness Skin Defect." *Journal of Plastic Reconstructive and Aesthetic Surgery*, vol. 60, no. 9, 1 Sept. 2007, pp. 983–990, https://doi.org/10.1016/j.bjps.2005.12.062.

[24] Cherng Kang Perng, et al. "Culturing Adult Human Bone Marrow Stem Cells on Gelatin Scaffold with PNIPAAm as Transplanted Grafts for Skin Regeneration." *Journal of Biomedical Materials Research Part A*, vol. 84A, no. 3, 1 Jan. 2008, pp. 622–630, https://doi.org/10.1002/jbm.a.31291.