Literature Review on Bioprinted Skin Equivalents

A Pirayesh, A Mosahebi, D Kalaskar
Department of Plastic Surgery & Surgical Biotechnology
University College London

The field of bioprinting has emerged as a revolutionary approach in tissue engineering, particularly in the development of skin equivalents.

Bioprinted skin models aim to replicate the complex architecture and functionality of native skin, which consists of multiple layers, including the epidermis, dermis, and hypodermis.
This literature review synthesizes current research on bioprinted skin equivalents, focusing on the complexity of each model and the cellular composition involved.

Overview of Bioprinted Skin Equivalents

Bioprinted skin equivalents are designed to mimic the structural and functional characteristics of human skin. These constructs are crucial for applications in regenerative medicine, particularly for treating severe wounds, burns, and chronic skin conditions. The complexity of these models varies significantly, depending on the types of cells used, the layering of tissues, and the incorporation of vascular structures. Recent advancements have highlighted the importance of including multiple cell types to achieve a more physiologically relevant model, which can enhance the healing process and improve the integration of the graft with host tissues (Cavallo, 2023; Mateo et al., 2016; Kang, 2024).

Cellular Composition of Bioprinted Skin Models

The cellular composition of bioprinted skin equivalents typically includes fibroblasts, keratinocytes, and, in more advanced models, endothelial cells and pericytes. Fibroblasts play a critical role in the dermal layer, providing structural support and producing extracellular matrix components, while keratinocytes are essential for forming the epidermis and contributing to barrier function. The inclusion of endothelial cells and pericytes is vital for creating vascularized skin models that can support nutrient and oxygen transport, which is crucial for the survival of the avascular epidermis (Mateo et al., 2016; Kang, 2024; Ansaf et al., 2023; Albanna et al., 2019).

Complexity of Bioprinted Skin Models

The complexity of bioprinted skin models can be categorized into several levels based on the number of cell types and the structural organization of the tissues.

Simple Models: These typically consist of a single layer of keratinocytes or fibroblasts embedded in a hydrogel matrix. While they can provide basic insights into cellular behavior, they lack the structural complexity of native skin (Cavallo, 2023; Cavallo et al., 2023).

Bilayered Models: These models incorporate both fibroblasts and keratinocytes, allowing for the development of a more realistic dermal-epidermal interface. Studies have shown that bilayered constructs can exhibit improved cell proliferation and differentiation compared to simpler models (Ansaf et al., 2023; Albanna et al., 2019; Derr et al., 2019).

Vascularized Models: Advanced bioprinted skin equivalents include vascular structures formed by endothelial cells and pericytes. These models are crucial for studying wound healing and skin diseases, as they closely mimic the physiological conditions of native skin (Kang, 2024; Kang et al., 2022; Augustine, 2018). - Multicellular Models: The most complex models integrate multiple cell types, including fibroblasts, keratinocytes, endothelial cells, and immune cells. These constructs can replicate the intricate interactions within the skin, providing a platform for drug testing and disease modeling (Jorgensen, 2023; Li et al., 2020; Kim et al., 2018).
Bioprinted Skin Models
Model Type | Cell Types Included
Complexity Level
Key Features

Simple Models | Keratinocytes or Fibroblasts | Low | Basic cellular behavior; lacks structural complexity

Bilayered Models | Fibroblasts, Keratinocytes | Medium | Improved dermal-epidermal interface; enhanced cell proliferation

Vascularized Models | Fibroblasts, Keratinocytes, Endothelial Cells | High Incorporates vascular structures; supports nutrient transport

Multicellular Models | Fibroblasts, Keratinocytes, Endothelial Cells, melanocytes | Very High | Mimics native skin interactions; suitable for drug testing and disease modeling

Advances in Bioprinting Technologies Recent advancements in bioprinting technologies have enabled the development of more sophisticated skin equivalents. Techniques such as inkjet printing, extrusion-based printing, and laser-assisted bioprinting allow for precise control over cell placement and tissue architecture. These technologies facilitate the creation of complex structures that can better replicate the native skin environment (Augustine, 2018; Millás et al., 2019; Yang et al., 2022).

Challenges and Future Directions Despite the progress made in bioprinting skin equivalents, several challenges remain. Achieving the appropriate mechanical properties, ensuring long-term cell viability, and replicating the dynamic nature of skin are ongoing areas of research. Future studies should focus on optimizing bioink formulations, enhancing vascularization strategies, and integrating additional skin appendages such as hair follicles and sweat glands to create fully functional skin models (Sörgel, 2023; Thépot et al., 2019; Bebiano, 2024; Fakhruddin, 2023).

Conclusion

The development of bioprinted skin equivalents represents a significant advancement in tissue engineering, with the potential to transform the treatment of skin injuries and diseases. The complexity of these models is crucial for their functionality, and ongoing research is essential to overcome existing challenges and enhance the applicability of bioprinted skin in clinical settings. As the field continues to evolve, the integration of innovative materials and technologies will likely lead to even more sophisticated and effective skin constructs.

Albanna, M., Binder, K., Murphy, S., Kim, J., Qasem, S., Zhao, W., … & Yoo, J. (2019). In situ bioprinting of autologous skin cells accelerates wound healing of extensive excisional full-thickness wounds. Scientific Reports, 9(1). https://doi.org/10.1038/s41598-018-38366-w

Ansaf, R., Ziebart, R., Gudapati, H., Torigoe, R., Victorelli, S., Passos, J., … & Wyles, S. (2023). 3d bioprinting—a model for skin aging. Regenerative Biomaterials, 10. https://doi.org/10.1093/rb/rbad060

Augustine, R. (2018). Skin bioprinting: a novel approach for creating artificial skin from synthetic and natural building blocks. Progress in Biomaterials, 7(2), 77-92. https://doi.org/10.1007/s40204-018-0087-0

Bebiano, L. (2024). Bioinspired and photo-clickable thiol-ene bioinks for the extrusion bioprinting of mechanically tunable 3d skin models. Biomimetics, 9(4), 228. https://doi.org/10.3390/biomimetics9040228

Cavallo, A. (2023). Fibrinogen-based bioink for application in skin equivalent 3d bioprinting. Journal of Functional Biomaterials, 14(9), 459. https://doi.org/10.3390/jfb14090459

Cavallo, A., Kayal, T., Mero, A., Mezzetta, A., Pisani, A., Foffa, I., … & Losi, P. (2023). Marine collagen-based bioink for 3d bioprinting of a bilayered skin model. Pharmaceutics, 15(5), 1331. https://doi.org/10.3390/pharmaceutics15051331

Derr, K., Zou, J., Luo, K., Song, M., Sittampalam, G., Zhou, C., … & Derr, P. (2019) Fully three-dimensional bioprinted skin equivalent constructs with validated morphology and barrier function. Tissue Engineering Part C Methods, 25(6), 334-343. https://doi.org/10.1089/ten.tec.2018.0318

Fakhruddin, K. (2023). Bioprinting of skin tissues: from concept to clinical applications. Journal of Medical Device Technology, 2(2), 86-90. https://doi.org/10.11113/jmeditec.v2n2.40

Jorgensen, A. (2023). Multicellular bioprinted skin facilitates human-like skin architecture in vivo. Science Translational Medicine, 15(716). https://doi.org/10.1126/scitranslmed.adf7547

Kang, M. (2024). Evaluation of anti-inflammatory activity of garlic extracts in 3d bioprinted skin equivalents. Advanced Nanobiomed Research, 4(7). https://doi.org/10.1002/anbr.202400007

Kang, M., Jang, J., Jo, H., Kim, W., Kim, B., Chun, H., … & Han, D. (2022). Advances and innovations of 3d bioprinting skin. Biomolecules, 13(1), 55. https://doi.org/10.3390/biom13010055

Kim, B., Gao, G., Kim, J., & Cho, D. (2018). 3d cell printing of perfusable vascularized human skin equivalent composed of epidermis, dermis, and hypodermis for better structural recapitulation of native skin. Advanced Healthcare Materials, 8(7). https://doi.org/10.1002/adhm.201801019

Li, X., Michael, S., Bharti, K., Ferrer, M., & Song, M. (2020). A biofabricated vascularized skin model of atopic dermatitis for preclinical studies. Biofabrication, 12(3), 035002. https://doi.org/10.1088/1758-5090/ab76a1

Mateo, N., García, M., Cañizo, J., Velasco, D., & Jorcano, J. (2016). 3d bioprinting of functional human skin: production and in vivo analysis. Biofabrication, 9(1), 015006. https://doi.org/10.1088/1758-5090/9/1/015006

Millás, A., Lago, J., Vasquez-Pinto, L., Massaguer, P., & Maria-Engler, S. (2019). Approaches to the development of 3d bioprinted skin models: the case of natura cosmetics. International Journal of Advances in Medical Biotechnology - Ijamb, 2(1), 03-13. https://doi.org/10.25061/2595-3931/ijamb/2019.v2i1.24

Sörgel, C. (2023). Perspectives on the current state of bioprinted skin substitutes for wound healing. Biomedicines, 11(10), 2678. https://doi.org/10.3390/biomedicines11102678

Thépot, A., Marquette, C., Courtial, E., Albouy, M., Dussoyer, M., & Santos, M. (2019). Mechanical properties of 3d bioprinted dermis: characterization and improvement.. https://doi.org/10.31487/j.rgm.2019.01.001

Yang, Y., Xu, R., Wang, C., Guo, Y., Sun, W., & Ouyang, L. (2022). Recombinant human collagen-based bioinks for the 3d bioprinting of full-thickness human skin equivalent. International Journal of Bioprinting, 8(4), 611. https://doi.org/10.18063/ijb.v8i4.611