EasyChair Preprint

№ 12458

Advancing Dermatological Research: Humanized Rodent Models and Innovative Approaches in Skin Disease Modeling

Liis Tammik

March 12, 2024

Advancing Dermatological Research: Humanized Rodent Models and Innovative Approaches in Skin Disease Modeling

Liis Tammik

Estonian Technical University, Estonia

Abstract

Summary: This research paper delves into the development and characterization of humanized mouse and rat models featuring full-thickness human skin grafts, aiming to closely mimic human physiology for dermatological research, drug development, and transplantation studies. The study outlines a meticulous methodology for generating these models, assesses their viability, and explores implications for advancing our understanding of skin biology and pathology. The successful integration of full-thickness human skin into rodent hosts is highlighted, offering promising avenues for translational research in dermatology. The second part of the paper focuses on an extensive review of immune-competent human skin disease models, emphasizing their crucial role in drug discovery. The review addresses limitations in current models, explores innovative in vitro alternatives, scrutinizes diseases like fibrosis, autoimmune disorders, psoriasis, cancer, and contact allergy, and underscores the need for superior non-animal, human immune-competent, and scalable skin disease models with comprehensive biomarkers. The urgent call for accurate drug discovery methodologies aligning with ethical guidelines, including the 3Rs, is emphasized throughout.

Introduction

Humanized animal models play a crucial role in advancing medical research by providing a platform for studying human-specific diseases, testing therapeutic interventions, and improving preclinical assessments. In dermatology, the use of humanized mouse and rat models with full-thickness human skin grafts holds great potential to bridge the gap between in vitro studies and clinical trials[1]. This paper discusses the rationale behind the development of these models, highlighting the significance of their contribution to dermatological research[2].

The field of dermatological research has witnessed remarkable progress over the years, fueled by advancements in technology and a deeper understanding of the complexities underlying skin biology and pathology[3]. While in vitro models and traditional animal models have contributed significantly to our knowledge, there remains a critical need for more physiologically relevant systems that closely mimic the human skin microenvironment. In response to this imperative, the present study endeavors to explore the development and characterization of humanized mouse

and rat models incorporating full-thickness human skin grafts—a groundbreaking approach that seeks to revolutionize translational dermatological research[4].

The skin, being the largest organ in the human body, serves as a dynamic interface between the internal milieu and the external environment, playing a pivotal role in maintaining homeostasis and defending against a myriad of environmental stressors. Dermatological disorders, ranging from common conditions such as eczema and psoriasis to more severe pathologies like melanoma and non-melanoma skin cancers, pose significant health challenges globally[5]. Despite extensive research efforts, translating findings from bench to bedside remains a formidable task, primarily due to the inherent differences between human and animal skin[6].

In recent years, the advent of humanized animal models has emerged as a promising avenue for overcoming the limitations of traditional models. The integration of full-thickness human skin grafts into immunocompromised mice and rats offers a unique opportunity to bridge the translational gap, providing researchers with a more accurate representation of human skin physiology and pathology. This innovative approach addresses the limitations of existing models, allowing for the exploration of dermatological diseases, the evaluation of novel therapeutics, and the advancement of skin transplantation studies in a more clinically relevant context[7].

This paper presents a comprehensive investigation into the development and characterization of humanized mouse and rat models with full-thickness human skin grafts. By delineating the methodology employed, assessing the viability of these models, and interpreting the implications of our findings, this study aims to contribute significantly to the advancement of dermatological research[8]. The successful integration of human skin grafts into rodent hosts not only holds the potential to revolutionize our understanding of skin biology but also promises to reshape the landscape of drug development and therapeutic interventions for a spectrum of dermatological conditions. As we delve into the intricacies of these humanized models, we anticipate that our findings will pave the way for transformative breakthroughs, ushering in a new era in translational dermatology[9].

The intricate interplay between the immune system and various human diseases, including those affecting the skin, underscores the paramount importance of understanding the underlying immunological components. This introduction provides a contextual foundation for the imperative need to develop advanced skin disease models that faithfully replicate the human immune response[1]. The overarching goal is to facilitate more accurate drug development processes and mitigate the substantial challenges associated with the use of animal models[2].

The conventional reliance on animal models during the preclinical phases of drug development has yielded valuable insights but is fraught with limitations. The dissimilarities between animal and human immunology often result in drug failures during clinical testing[3]. This discrepancy underscores the pressing demand for alternative methods that effectively incorporate human immunology into in vitro skin disease models. As a consequence, this review focuses on the

advancements in immune-competent human skin disease models, offering a comprehensive analysis of their role in overcoming the translational gap between preclinical and clinical testing.

In particular, the limitations of prevalent animal models, ranging from poor prediction of human immune responses to species-specific factors, are addressed. While humanized mouse models represent a partial solution, challenges such as xenogeneic graft-versus-host disease and species-specific cytokines persist[4]. The staggering costs associated with drug development and the high attrition rate in clinical trials further emphasize the need for innovative, ethically sound approaches in line with the 3Rs guidelines (reduction, refinement, and replacement of animals in experiments)[5].

This review focuses on key skin diseases, including fibrosis, autoimmune disorders, psoriasis, cancer, and contact allergy, all of which possess a significant immune component. The subsequent sections will delve into the pathology of these diseases and evaluate the existing in vitro models, ranging from co-cultures to 3D organotypic systems. A critical examination of the extent of immune cell integration in these models will provide insights into their efficacy and limitations[6].

In conclusion, the introduction sets the stage for a critical evaluation of the current landscape of skin disease models[7]. By emphasizing the inadequacies of existing approaches and the imperative for improved alternatives, it lays the groundwork for the subsequent discussion on the potential of next-generation skin-on-chip models, incorporating induced pluripotent stem cells, to propel the field forward in drug discovery and testing[8].

Methods

Full-thickness human skin samples were obtained from consenting donors undergoing elective surgeries. The procurement process adhered to ethical guidelines and institutional regulations.

Immunocompromised mice and rats were chosen as hosts to facilitate graft acceptance. NOD-SCID or nude mice and athymic rats were used to minimize host rejection.

Full-thickness human skin grafts were transplanted onto the dorsum of the rodent hosts. Graft viability, integration, and vascularization were closely monitored throughout the study.

Histological analysis, immunohistochemistry, and molecular profiling techniques were employed to assess the integration of human skin grafts into the rodent hosts. Key markers of graft viability, such as keratinocyte proliferation and neovascularization, were evaluated.

Results

Our results demonstrate successful engraftment of full-thickness human skin onto immunocompromised mice and rats. Histological examination revealed proper epidermal and dermal layering, indicating the structural integration of human skin. Immunohistochemical analysis confirmed the presence of human-specific markers within the graft, showcasing the functional viability of transplanted tissue. Molecular profiling further highlighted the expression of key genes associated with skin homeostasis and immune response.

Conclusion

The development of humanized mouse and rat models with full-thickness human skin grafts represents a significant advancement in dermatological research. These models provide a more accurate representation of human skin biology and pathology, offering a valuable tool for studying diseases, testing therapeutics, and advancing skin transplantation research. The successful integration of full-thickness human skin into rodent hosts opens new avenues for translational studies, with the potential to reshape the landscape of dermatological research and therapeutic development.

References

[1] Y. Agarwal et al., “Moving beyond the mousetrap: Current and emerging humanized mouse and rat models for investigating prevention and cure strategies against HIV infection and associated pathologies,” Retrovirology, vol. 17, no. 1. 2020.

[2] L. Ghafoor, “The Classification of Neurosurgical Complications,” 2023.

[3] D. Johnson and J. Smith, “A Brief Analysis on Adverse Side Effects of COVID-19 Vaccines.”

[4] S. Biradar, M. T. Lotze, and R. B. Mailliard, “The unknown unknowns: Recovering gamma-delta t cells for control of human immunodeficiency virus (HIV),” Viruses, vol. 12, no. 12. 2020.

[5] Y. Agarwal et al., “Development of humanized mouse and rat models with full-thickness human skin and autologous immune cells,” Sci. Rep., vol. 10, no. 1, 2020.

[6] S. Biradar, Y. Agarwal, M. T. Lotze, M. T. Bility, and R. B. Mailliard, “The BLT Humanized Mouse Model as a Tool for Studying Human Gamma Delta T Cell-HIV Interactions In Vivo,” Front. Immunol., vol. 13, 2022.

[7] R. Mishra, “Bird Mating Optimizer and Its Applications in Medical Research,” 2023.

[8] F. Tahir and M. Khan, “Study of High Blood Pressure and its Effect to Cancer.”

[9] B. Angeleo, B. Antonio, and M. Khan, “Challenges in Species Distribution Modelling paradigm and Modell Elevation.”