



Revolutionizing Dermatological Research: Humanized Rodent Models and Cutting-Edge Strategies for Skin Disease Modeling

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March 12, 2024

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Abstract

This research delves into the creation and characterization of humanized mouse and rat models, incorporating full-thickness human skin grafts with the goal of closely replicating human physiology for applications in dermatological research, drug development, and transplantation studies. The paper meticulously outlines the methodology employed for generating these models, evaluates their viability, and explores the potential implications for advancing our comprehension of skin biology and pathology. Emphasizing the successful integration of full-thickness human skin into rodent hosts, the study points toward promising avenues for translational research within the field of dermatology. The subsequent section of the paper conducts a comprehensive review of immune-competent human skin disease models, highlighting their pivotal role in drug discovery. This review addresses current model limitations, explores innovative in vitro alternatives, scrutinizes diseases such as fibrosis, autoimmune disorders, psoriasis, cancer, and contact allergy, and underscores the necessity for superior non-animal, human immune-competent, and scalable skin disease models equipped with comprehensive biomarkers. Throughout, the paper underscores the urgent need for accurate drug discovery methodologies in line with ethical guidelines, notably the principles of the 3Rs (reduction, refinement, and replacement of animals in experiments).

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].

Methodology

Full-thickness human skin samples, obtained with the informed consent of donors undergoing elective surgeries, were acquired in strict adherence to ethical guidelines and institutional regulations. To foster graft acceptance, immunocompromised mice and rats, specifically NOD-SCID or nude mice and athymic rats, were selected as hosts, minimizing the risk of host rejection. The transplantation process involved grafting full-thickness human skin onto the dorsum of the rodent hosts, with continuous monitoring of graft viability, integration, and vascularization throughout the study duration.

To comprehensively evaluate the success of graft integration, various techniques were employed. Histological analysis provided detailed insights into the structural integration of human skin grafts, while immunohistochemistry techniques enabled the examination of key markers indicative of graft viability, including keratinocyte proliferation and neovascularization. Molecular profiling was conducted to further characterize the molecular aspects of the graft-host interaction, providing a nuanced understanding of the integration process. These methodological approaches collectively aimed to illuminate the intricate dynamics of full-thickness human skin grafts on

immunocompromised rodent hosts, contributing valuable insights to the field of dermatological research.

Results and Discussions

The implementation of full-thickness human skin grafts onto immunocompromised mice and rats showcased notable success in the integration of human skin into the rodent hosts. Continuous monitoring of graft viability, integration, and vascularization revealed robust outcomes, laying the foundation for promising avenues in translational dermatological research. Histological analysis unveiled well-integrated human skin structures within the rodent hosts, signifying a successful transplantation process. Immunohistochemistry techniques provided a closer look at key markers, particularly highlighting the proliferation of keratinocytes and the development of neovascularization, affirming the vitality of the integrated human skin grafts.

Molecular profiling further enriched our understanding of the molecular dynamics involved in the graft-host interaction. The comprehensive evaluation of these humanized models demonstrated their potential to closely replicate aspects of human skin biology. The success in integrating full-thickness human skin grafts into immunocompromised rodents holds significant promise for advancing dermatological research, offering a more accurate and representative platform for studying skin physiology, pathology, and potential interventions.

The positive outcomes of this study lay the groundwork for transformative breakthroughs in translational dermatology, emphasizing the potential of humanized rodent models as invaluable tools for drug development and transplantation studies. As we navigate through the intricacies of these humanized models, it becomes evident that the integration of full-thickness human skin grafts into rodent hosts has the potential to revolutionize our understanding of skin biology and reshape the landscape of therapeutic interventions for dermatological conditions.

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.

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