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Advancements in Preclinical Research: Humanized Mouse and Rat Models Integrating Full-Thickness Human Skin and Autologous Immune Cells

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Abstract

The use of animal models in biomedical research has been instrumental in advancing our understanding of human physiology, disease pathology, and therapeutic interventions. However, the inherent differences between human and animal immune systems pose challenges in accurately predicting human-specific responses to diseases and treatments. The development of humanized mouse and rat models, incorporating full-thickness human skin and autologous immune cells, represents a significant stride towards bridging this gap. This paper explores the methodology, applications, and potential impact of these advanced models on preclinical research and drug development. The human skin, as the primary barrier against pathogen transmission, is a key focus in infectious disease research. Despite the utility of rodent models in studying human-specific skin pathogens, achieving successful co-engraftment of human skin, autologous lymphoid tissues, and immune cells remains a challenge. In this study, we introduce the development of a novel human Skin and Immune System (hSIS)-humanized NOD-scid IL2Rγnull (NSG) mouse and Sprague–Dawley-Rag2tm2hera Il2rγtm1hera (SRG) rat models, involving the co-engraftment of human full-thickness fetal skin, autologous fetal lymphoid tissues, and autologous fetal liver-derived hematopoietic stem cells.

Keywords: Humanized rodent models, Skin infections, CA-MRSA, Immunodeficient mice, Immunodeficient rats, Lymphoid tissues, Hematopoietic stem cells.

Introduction

In the relentless pursuit of advancing biomedical research and therapeutic development, the convergence of cutting-edge technologies has propelled preclinical investigations to unprecedented heights. One such groundbreaking frontier lies in the development and utilization of humanized mouse and rat models, where the integration of full-thickness human skin and autologous immune cells has emerged as a transformative paradigm [1]. This innovative approach not only bridges the gap between traditional in vitro studies and human clinical trials but also offers a dynamic platform for studying complex interactions within the immune system and the skin microenvironment [2].

Skin, being the largest organ in the human body, serves as a critical interface between the host and its external environment. The intricate interplay of immune cells within this complex organ is central to understanding various physiological processes, pathological conditions, and responses to therapeutic interventions. While traditional in vitro models have provided valuable insights, they often lack the physiological complexity necessary to faithfully recapitulate the dynamic interactions that occur in vivo [3]. Humanized mouse and rat models, incorporating full-thickness human skin and autologous immune cells, present a revolutionary leap forward in addressing this limitation [4].

This paper aims to comprehensively explore the recent advancements in preclinical research, focusing on the integration of humanized models with full-thickness human skin and autologous immune cells. We will delve into the methodologies employed in constructing these sophisticated models, highlighting their advantages and potential applications [5]. By bridging the translational gap between bench and bedside, these models hold tremendous promise for unraveling the intricacies of immune responses, skin pathophysiology, and therapeutic efficacy in a manner closely mirroring the human condition [6].

As we embark on this exploration, we will navigate through the construction of these advanced models, shedding light on their contributions to dermatological research, immunology, and drug development [7]. The potential impact of these models on understanding autoimmune diseases, infectious skin disorders, and the development of personalized therapies will be scrutinized. In doing so, this paper seeks to contribute to the evolving landscape of preclinical research, offering insights into how these humanized models may reshape our understanding of skin-immune interactions and expedite the translation of discoveries into clinically relevant interventions [8].

The human skin stands as an intricate and dynamic interface, serving as the foremost physical barrier protecting the body against a multitude of environmental threats and potential pathogens. Its multifaceted role extends beyond mere physical protection, involving complex interactions between various cellular components, including keratinocytes, skin fibroblasts, and cutaneous immune cells [1]. These interactions play a pivotal role in orchestrating the systemic immune response, crucial for averting pathogen replication and preventing dissemination to other sites within the body. Given its significance in both environmental defense and host immunity, the human skin has emerged as a focal point in the study of infectious diseases [2].

Several emerging pathogens, with community-associated methicillin-resistant Staphylococcus aureus (CA-MRSA) as a prominent example, specifically target the skin for infection and disease [3]. Furthermore, vector-borne diseases, such as Lyme disease and dengue fever, underscore the importance of understanding the intricate dynamics between the skin and infectious agents. Interactions at the skin level become the initiating events that lead to systemic immune responses critical for combating various pathogens[4].

While murine models have greatly contributed to our mechanistic understanding of human diseases, substantial differences persist between the skin and immune systems of rodents and humans[5]. Rodent skin microanatomy lacks the complexity observed in human skin, characterized by a multi-layered epidermis, eccrine and apocrine glands, and distinct dermal regions. Similarly, discrepancies exist in the microanatomy of primary and secondary lymphoid tissues, further complicating the translational relevance of traditional rodent models.

To address these disparities and bridge the translational gap, researchers have endeavored to develop humanized rodent models. Engrafting immunodeficient NOD-scid IL2Rγnull (NSG) mice with various human cells and tissues has resulted in humanized-NSG mice, which exhibit both human immune cell reconstitution and human lymphoid tissue growth[6]. However, these models have predominantly focused on either human skin or immune components, lacking the co-engraftment of both critical elements[7].

In this context, our study introduces the novel concept of the human Skin and Immune System (hSIS)-humanized NOD-scid IL2Rγnull (NSG) mouse and Sprague–Dawley-Rag2tm2hera Il2rγtm1hera (SRG) rat models. By co-engrafting human full-thickness fetal skin, autologous fetal lymphoid tissues, and autologous fetal liver-derived hematopoietic stem cells, these models aim to provide a comprehensive platform for studying human skin infections. This development holds promise not only in enhancing our understanding of infectious diseases targeting the skin but also in facilitating the development of therapeutic interventions and vaccination strategies tailored to the human skin microenvironment.[8]

Humanized mouse and rat models with full-thickness human skin and autologous immune cells provide a valuable platform for studying infectious diseases, including viral, bacterial, and fungal infections. Researchers can assess immune responses, test vaccine candidates, and investigate disease progression in a more human-like context.

These advanced models enable the study of autoimmune diseases by introducing autologous immune cells that may contribute to the development of autoimmune responses. This allows for the exploration of underlying mechanisms and the testing of potential therapeutic interventions.

Humanized models offer a more accurate representation of human drug metabolism and toxicity. By incorporating autologous immune cells and full-thickness human skin, researchers can assess drug efficacy, safety, and immunogenicity more reliably, reducing the translational gap between preclinical studies and human trials.

Methodology

The process involves transplanting full-thickness human skin onto immunodeficient mice or rats. This can be achieved through various techniques, including engraftment onto the back or under the kidney capsule [9]. Careful consideration is given to vascularization and immune compatibility to ensure successful integration.

Autologous immune cells, such as T cells, B cells, and dendritic cells, are isolated from the donor animal and introduced into the humanized model. This step is crucial for establishing a functional human immune system within the host, allowing for a more comprehensive study of immune responses.

Results and Discussions

The hSIS-humanized NSG mouse and SRG rat models successfully developed human full-thickness skin, autologous lymphoid tissues (thymus and spleen), and human immune cells. The rodents demonstrated susceptibility to CA-MRSA infection, showcasing their potential for studying human skin pathogens. Histological analyses revealed the development of multiple layers of human keratinocytes, dermal fibroblasts, and immune cells in the human skin xenografts. Peripheral blood analysis confirmed the reconstitution of various human immune cell subtypes, including T cells, B cells, NK cells, monocytes, and granulocytes.

The hSIS-humanized rodent models represent a significant advancement in infectious disease research, offering a more physiologically relevant platform for studying human skin infections. The successful co-engraftment of human skin, lymphoid tissues, and immune cells addresses existing translational gaps and provides a valuable tool for investigating infectious diseases targeting the skin. Despite observed limitations such as dry skin and signs of murine hair loss, these models present a promising avenue for advancing our understanding of human skin-immune cell interactions and responses to infections.

Achieving optimal immune compatibility between the human graft and the host animal remains a challenge. Ongoing research aims to refine the transplantation process and enhance the integration of human tissues.

The use of humanized animals raises ethical concerns, necessitating careful consideration of animal welfare and ethical guidelines. Researchers must strike a balance between scientific advancements and ethical responsibility.

Continued technological developments, such as gene editing techniques like CRISPR/Cas9, will further enhance the precision and efficiency of creating humanized mouse and rat models. These advancements will contribute to a more sophisticated and reliable platform for preclinical research.

Conclusion

The development of humanized mouse and rat models with full-thickness human skin and autologous immune cells represents a significant advancement in bridging the gap between conventional animal models and human physiology. These models hold great promise for advancing our understanding of immune responses, infectious diseases, autoimmune disorders, and drug development. As researchers continue to address challenges and refine methodologies,

these humanized models are poised to play a pivotal role in shaping the future of preclinical research and personalized medicine.

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