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Advancing Infectious Disease Research: Development and Characterization of Human Skin and Immune System (hSIS) Humanized Mouse and Rat Models

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Advancing Infectious Disease Research: Development and Characterization of Human Skin and Immune System (hSIS) Humanized Mouse and Rat Models

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Abstract

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. 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.

Introduction

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 (Biradar, Lotze and Mailliard, 2020). 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 (Biradar *et al.*, 2022).

Several emerging pathogens, with community-associated methicillin-resistant Staphylococcus aureus (CA-MRSA) as a prominent example, specifically target the skin for infection and disease (Ghafoor, 2023). 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(Agarwal, Beatty, Ho, *et al.*, 2020).

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(Tahir and Khan, no date). 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(Angeleo, Antonio and Khan, no date). However, these models have predominantly focused on either human skin or immune components, lacking the co-engraftment of both critical elements(Agarwal, Beatty, Biradar, *et al.*, 2020).

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.(Johnson and Smith, no date)

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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.

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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]

Discussion

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.

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Conclusion

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.

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