Research Techniques Made Simple: Murine Models of Human Psoriasis

Jason E. Hawkes[1,2], Jonas A. Adalsteinsson[2], Johann E. Gudjonsson[3,5] and Nicole L. Ward[4,5]

Psoriasis vulgaris is a common, inflammatory skin disease affecting approximately 3% of the population in the United States. The etiology of psoriasis and its associated comorbidities are complex and the result of complicated interactions between the skin, immune system, disease-associated susceptibility loci, and multiple environmental triggers. The modeling of human disease in vivo through the use of murine models represents a powerful, indispensable tool for investigating the immune and genetic mechanisms contributing to a clinical disease phenotype. Nevertheless, modeling a complex, multigenic disease like psoriasis in mice has proven to be extremely challenging and is associated with significant limitations. Over the last four decades, more than 40 unique mouse models for psoriasis have been described. These models can be categorized into three major types: acute (inducible), genetically engineered (transgenic), and xenograft (humanized). The purpose of this Research Techniques Made Simple article is to provide an overview of the common types of psoriasis-like mouse models currently in use and their inherent advantages and limitations. We also highlight the need for improved psoriasis mouse model systems and several key factors to be considered as this field of laboratory science advances.

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Description: This article, designed for dermatologists, residents, fellows, and related healthcare providers, seeks to reduce the growing divide between dermatology clinical practice and the basic science/current research methodologies on which many diagnostic and therapeutic advances are built.

Objectives: At the conclusion of this activity, learners should be better able to:

- Recognize the newest techniques in biomedical research.
- Describe how these techniques can be utilized and their limitations.
- Describe the potential impact of these techniques.

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[1]*Laboratory for Investigative Dermatology, Rockefeller University, New York, New York, USA;* [2]*Department of Dermatology, Icahn School of Medicine at Mount Sinai, New York, New York, USA;* [3]*Department of Dermatology, University of Michigan, Ann Arbor, Michigan, USA; and* [4]*Department of Dermatology, Case Western Reserve University, Cleveland, Ohio, USA*

[5] *These authors contributed equally to this work.*

Correspondence: Nicole L. Ward, Department of Dermatology, Case Western Reserve University, Cleveland, Ohio 44106, USA. E-mail: nlw4@case.edu or Johann E. Gudjonsson, Department of Dermatology, University of Michigan, 1500 East Medical Center Drive, Ann Arbor, MI 48109, USA. E-mail: johanng@med.umich.edu

Abbreviations: IMQ, imiquimod; KO, knockout

ADVANTAGES

- The ability to model human disease in animals is a powerful in vivo laboratory tool that permits scientists to elucidate genetic and immune mechanisms contributing to psoriasis.
- Acute mouse models of psoriasis represent a relatively inexpensive, easy-to-use system that results in the rapid induction of skin inflammation.
- Advanced mouse models permit gene alterations to be restricted to specific tissues or cell types and allow control of expression within a desired time-frame (spatiotemporal control).

LIMITATIONS

- Transgenic models of psoriasis are expensive and labor intensive, and they may result in death or the potential undesirable expression of a transgene (i.e., a "leaky" system).
- Xenotransplantation models of psoriasis are technically difficult, labor intensive, and highly dependent on inherent donor characteristics, and they require substantial amounts of tissues.
- All mouse models of psoriasis have intrinsic disadvantages, and no current model fully recapitulates all features of human psoriasis.

INTRODUCTION

Psoriasis vulgaris is a chronic T-cell–mediated skin disease typified by thickened, scaly, erythematous plaques on the scalp, trunk, and extremities. The development of psoriasis is the result of a complex interaction between skin, the immune response, psoriasis-associated genes, and multiple environmental exposures (Hawkes et al., 2017). Patients with psoriasis also exhibit signs and symptoms of systemic inflammation, resulting in an increased risk for multiple comorbid conditions, including polyarthritis, cardiovascular disease, and metabolic syndrome (Takeshita et al., 2017). However, the precise molecular mechanisms driving the development of psoriasis and its associated comorbid conditions have not been fully elucidated.

The ability to model human disease in animals represents a powerful in vivo laboratory tool that permits scientists to systematically study the genetic and immune mechanisms contributing to psoriatic disease. The purpose of this article is to provide an overview of the common types of mouse models currently being used to study psoriasis. The laboratory techniques used to generate theses various types of mouse models can be reviewed in previously published Research Techniques Made Simple articles (Griffin et al., 2015; Gunschmann et al., 2014; Scharfenberger et al., 2014; Tellkamp et al., 2014). Finally, we will discuss the importance of these mouse models in helping further advance our understanding of psoriasis and our ability to manage this multifaceted skin disease.

CURRENT MOUSE MODELS OF PSORIASIS

Over the last four decades, more than 40 unique mouse models for psoriasis have been described. Each of these murine models recapitulates various aspects of human psoriasis. The extent to which a certain mouse model mirrors human psoriasis can be explained, in part, by the genetic and/or biological basis of that specific model system. The current models being used to study psoriasis can be divided into three major types: acute (inducible), genetically engineered (transgenic), and xenograft (humanized). An overview of these three model types is summarized in Table 1. The advantages and limitations associated with each model type underscores the complexity of modeling multigenic human diseases such as psoriasis.

Acute (inducible) models

Since the initial description of the imiquimod (IMQ)-induced psoriasiform dermatitis model (van der Fits et al., 2009), acute or inducible mouse models have rapidly become one of the most widely used systems for studying human psoriasis. Acute models of psoriasis involve the induction of a psoriasiform-like skin phenotype (e.g., erythema, scale formation, epidermal thickening, immune cell infiltration, and/or joint disease) following the topical application, intradermal injection, or disruption of the epidermal skin barrier via mechanical forces. Common examples of this model include the repeated application of immune-activating chemicals to the skin of mice, including IMQ, 12-*O*-tetradecanoylphorbol-13-acetate, oxazolone, and 2,4-dinitrofluorobenzene (DNFB). Inflammation in the skin can also be induced by the intradermal injection of proinflammatory cytokines (e.g., IL-23) or antigens (e.g., mannan from *Saccharomyces cerevisiae*). Finally, cutaneous inflammation can be provoked in mice by the repeated application and removal of tape, which results in disruption of the epidermal barrier by stripping off layers of the stratum corneum (Sano et al., 2005).

The advantages of these acute models are primarily due to their low cost, rapid induction of skin inflammation, and relative ease of use compared with other, more labor intensive model types that will be described. The capability of these chemical agents to stimulate skin inflammation in multiple genetic strains of mice enables scientists to study inflammatory reactions and to test the effects of potential psoriasis treatments in innumerable combinations. The convenience of the acute model systems has had a directing influence on preclinical psoriasis studies as illustrated by the dramatic increase in publications using the IMQ-induced model and its application to more than 85 unique transgenic models (Hawkes et al., 2017). Finally, the ability to induce a skin disease phenotype at a specific time point in mice of a certain age may be beneficial, depending on the specific research question being studied.

However, the acute model systems have significant limitations. One of the primary limitations of these model systems are due in large part to the relatively nonspecific nature of the induced skin inflammation. This issue is particularly problematic when studying human skin diseases that lack