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Research Techniques Made Simple: Murine Models of Human Psoriasis

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Abstract

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.

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

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CONFLICT OF INTEREST

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SUPPLEMENTARY MATERIAL

Supplementary material is linked to this paper. Teaching slides are available as supplementary material.

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 pathognomonic features and have significant overlapping clinical and histologic findings, such as psoriasis, systemic lupus erythematosus, and atopic dermatitis. As a result, the literature contains multiple examples wherein mouse models commonly used in preclinical psoriasis studies are simultaneously being used to support findings for human diseases with entirely different etiologies, such as the 12-*O*-tetradecanoylphorbol-13-acetate model for acute irritant dermatitis (Dai et al., 2017) and IMQ-induced skin inflammation for systemic lupus erythematosus (Yokogawa et al., 2014). Other limitations associated with the inducible models are related to the specific methods used to stimulate skin inflammation. There is a general lack of standardized protocols for the topical application or intradermal injection of proinflammatory chemicals. Common variations include treatment frequency, duration, product manufacturer, dosage or chemical concentration, animal housing conditions, genetic background of animals, and treated anatomical site. These differences make it difficult to interpret or compare studies and likely explain some of the challenges experienced when trying to reproduce specific research findings. Finally, the acute model systems are not amenable to long-term treatment and, therefore, do not fully recreate the prolonged inflammatory state observed in patients with chronic forms of psoriasis.

Genetically engineered (transgenic) models

Genetically engineered or transgenic models are mice with specific gene alterations resulting in the overexpression or loss/knockout (KO) of a particular protein. In contrast to the acute model systems, traditional transgenic mice have gene alterations that are present at birth and involve all cell types throughout the body (i.e., germline or whole-body KO). However, advanced laboratory techniques now allow for the creation of transgenic mice with genetic alterations restricted to a certain tissue type or cell population under the regulatory control of a specific gene promoter (e.g., keratin 5 or 14) and/or a modulator of gene expression such as tetracycline/doxycycline or tamoxifen (Gunschmann et al., 2014; Scharfenberger et al., 2014).

The principal advantage of whole-body KO mice is that the absence of a gene allows scientists to investigate the in vivo effects of gene-specific alterations. This technology represents an essential laboratory tool for investigating the genetic and molecular mechanisms contributing to particular clinical phenotypes and potentially provides insights into the etiology of human disease. Some common examples of whole-body KO mice used to study human psoriasis are the Il1rn$^{-/-}$ (Shepherd et al., 2004) and hypomorphic CD18-null mice (Bullard et al., 1996), which result in the spontaneous development of a psoriatic-like phenotype. The limitations of whole-body KO mice are that they are labor intensive, time consuming, expensive, and often result in embryonic or early prenatal death. Single gene perturbations are also not necessarily reflective of the genetic alterations found in human tissues and are not representative of complex, multigenic disease states like psoriasis. The alteration of a gene throughout the body also limits the investigator's ability to determine which cells populations or tissues are primarily responsible for an observed phenotype.

Tissue-specific and conditional transgenic mice offer many advantages over those with germline alterations. A gene perturbation in a specific cell population or tissue type often overcomes the lethality commonly seen with traditional germline alterations. The restriction of gene alterations to specific tissues or cell types, such as the epidermis, permits experiments that can determine an individual gene's contribution to a disease state or phenotype. Several examples of tissue-specific mice that overexpress a particular gene and exhibit a psoriasis-like skin phenotype have been described, including the K14-AREG, K14-VEGF, and K5-Stat3C mouse models (Cook et al., 1997; Detmar et al., 1998; Sano et al., 2005). Conversely, tissue specific-KO mice have been described, such as the K14-Cre-Ikk2$^{fl/fl}$ mouse model (Stratis et al., 2006). The tissue-specific model systems also allow further phenotype modifications by limiting gene perturbations to specific cell populations or tissue types that are under the control of inducers or repressors of gene expression. The K5-CreERT2 JunB$^{fl/fl}$ c-Jun$^{fl/fl}$ mouse model (Zenz et al., 2005) is a common example of a tissue-specific inducible KO mouse. In contrast, the K5-IL-17C (Johnston et al., 2013) and KC-Tie2 (Wolfram et al., 2009) mouse models represent tissue-specific overexpressors, in which the gene of interest can be repressed by administered doxycycline. The spatiotemporal control system of conditional mice enables scientists to customize gene expression and resultant disease manifestations to better mimic the disease state observed in humans. Some of the limitations of the tissue-specific and conditional transgenic mouse models are that they may still lead to embryonic or early prenatal death, affect the expression of more than one gene, or result in undesired ("leaky") expression of the gene of interest. Additionally, the requirement for the use of a gene modulator like doxycycline results in potential confounding and/or discrepancies in laboratory results as a result of variations in drug delivery and the feeding behaviors of mice.

The recent discovery of the clustered regularly interspaced palindromic repeats (i.e., CRISPR)-associated (Cas9) system in prokaryotes has transformed the laboratory science of genetic engineering. This gene editing technology is already being used in dermatology research (Guitart et al., 2016) and has been used to generate transgenic mice for preclinical psoriasis studies (Ippagunta et al., 2016). The primary advantages of this technology are the precision of its gene editing mechanisms, the ability to alter multiple genes simultaneously

via a single guide RNA, and the decreased amount of time required to generate a transgenic mouse compared with traditional technologies. Its main limitations are its off-target biological effects and the observed variations in single guide RNA efficiency. Although CRISPR/Cas9 technology represents an exciting, powerful gene editing technology with enormous potential, its introduction into dermatology research is relatively new. Therefore, the implications of this technology are not fully understood.

Xenograft (humanized) models

Xenotransplantation mouse models of psoriasis offer an alternative to transgenic mice. The xenograft or humanized models are created when mice are engrafted with human tissues or cells. In preclinical psoriasis studies, nonlesional or lesional psoriatic skin is transplanted on the backs of immunocompromised mice, such as severe combined immunodeficient or AGR129 mice. Both model systems allow engraftment without undergoing tissue rejection due to the absence of B and T lymphocytes, whereas AGR129 mice also lack type I(A) and II(G) IFN receptors and Rag-$2^{-/-}$, which results in impaired natural killer cell activity (Boyman et al., 2004). In this way, transplanted human tissues develop into psoriatic plaques because of the expansion of resident immune cell populations found in donor skin.

The main advantage of using the xenograft models of psoriasis is that they use human-derived tissues and, therefore, most closely mimic the immunologic and genetic basis of the human disease. The frequent use of xenograft mice is hampered by several limitations, including its extensive technical prerequisites and the requirement of large amounts of donor tissue. Significant phenotypic variations are also observed because of variations in the quality of the tissue graft, intrinsic immunologic and genetic differences between human donors, and the influence of murine host factors (e.g., absent transgenic expression of psoriasis-associated human cytokines).

TOWARD BETTER MOUSE MODELS IN PSORIASIS

Despite remarkable advances in the technologies that allow for the generation of advanced mouse models, no current system fully reproduces all features of human psoriasis. Although the prospect of perfectly modeling any human disease in mice may be unattainable, there is still a need for the improved use of existing models and the continued development of novel mice. Here, we briefly discuss several obstacles impeding the study of human psoriasis in mice and make several suggestions to aid scientists in their efforts to create better mouse models.

Innate anatomic, immunologic, and genetic variations

Mice have several obvious cellular and anatomic differences compared with humans (Figure 1), including thinner dermal and epidermal tissue layers with increased keratinocyte turnover, densely arranged hair follicles (fur), short segments of interfollicular epithelium with absent rete ridges, improved wound healing, and the presence of a striated muscle layer (panniculus carnosus) deep to the adipose tissue (Gudjonsson et al., 2007). The immune system of mice varies widely from that of humans, including major differences in innate immunity (e.g., increased expression of defensins and the absence of MHC II expression on

T lymphocytes), the presence of different immune cell populations (e.g., $CD8^+$ dendritic cells), modification mechanisms for the skewing of T helper type 1 and 2 lymphocytes, and the predominance of γδ T cells in murine epidermis (Mestas and Hughes, 2004). Mice also have a dramatically increased metabolic rate and shortened lifespan compared with humans. Finally, the genetic diversity of mice compared with humans is relatively limited because of inbreeding. These interspecies differences need to be carefully considered when interpreting preclinical laboratory findings because a disease phenotype or anti-psoriatic treatment response observed in mice may not represent a viable mechanism of human disease.

Need for standardized procedures, assessments, and validation studies

The variations in laboratory treatment protocols, diet and housing environments, scoring systems used to characterize joint and skin findings (e.g., modified Psoriasis Area Severity Index scoring system), and biologic assessment used to evaluate mouse tissues represents a serious impediment to the in vivo study of psoriatic disease. These variations undermine our field's ability to reliably compare studies and meaning-fully interpret published findings. Laboratory procedures and immunohistologic assessments in need of standardization or definition include the adoption of objective methods for assessing histologic features of disease (e.g., measurements of epidermal thickness vs. qualitative comparisons), scoring systems that define disease phenotypes, methods for properly orienting and processing mouse tissues (e.g., fixation method), and use of a set of histologic and biological markers to help define true psoriasis phenotypes (e.g., keratin 6/16, Ki67, antimicrobial peptides like S100 proteins, and markers of TNF/IL-23/IL-17 signaling). The generalizability of results or findings produced in a single mouse model of psoriasis are likely to be of less significance than those that are validated in other model types. Furthermore, the formal testing of highly effective human psoriasis therapies (e.g., cyclosporine, TNF inhibitors, or antagonists of IL-23/T17 signaling) in mouse models of psoriasis can also serve as a sieve to help determine the clinical significance of reported results.

Recognition of potential confounding variables

Many factors have been reported as potential confounding variables or unintended consequences of treatment in preclinical psoriasis studies. First, intrinsic differences in the immune system of various genetic strains of mice commonly used in psoriasis research (e.g., C57Bl/6 and BALB/c) have been reported (Watanabe et al., 2004). The additional influence of sex on the psoriatic phenotypes elicited in mice has not been systematically evaluated and should be considered. These dissimilarities have the potential to significantly alter study results and should be deliberately considered when choosing a specific breed of mice to study. Second, the unintended consequences of potential intralesional or topical treatments have also been described and are often over-looked. This concept is best illustrated by the IMQ-induced model of psoriasis wherein topically applied IMQ results in a variable skin phenotype due to differences in the product vehicle used by different manufacturers (Walter et al., 2013). Additionally, the oral ingestion of IMQ has been shown to induce a robust systemic inflammatory response in mice (Grine et al., 2016). Both examples emphasize the absolute necessity of proper experimental and treatment controls when studying psoriasis-like phenotypes in mice. Other potential confounding variables that need to be contemplated include differences in the ages of the mice, comparative response of intralesional versus

topical interventions, anatomic-specific disease responses (e.g., truncal skin vs. body appendages such as the ears or tail), and the impact of intentional or unintentional alterations in the mouse microbiome.

CONCLUSION

The complexity of human psoriasis combined with the intricacies of mouse biology creates a formidable challenge for laboratory scientists. There is a growing need for improved murine models of psoriasis and the standardization of laboratory procedures used to study the phenotype and treatment response observed in these models. Although no single psoriasis-like mouse model is likely to embody the totality of human psoriasis, in vivo systems are indispensable tools for advancing our understanding of this inflammatory disease and elucidating the molecular basis of this inflammatory condition and its associated comorbidities.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

IMQ	imiquimod
KO	knockout

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Planning Committee/Speaker Disclosure:

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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.

CME Accreditation and Credit Designation:

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education through the joint providership of Beaumont Health and the Society for Investigative Dermatology. Beaumont Health is accredited by the ACCME to provide continuing medical education for physicians. Beaumont Health designates this enduring material for a maximum of 1.0 *AMA PRA Category 1 Credit(s)*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

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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.

MULTIPLE CHOICE QUESTIONS

1. The imiquimod (IMQ) model used to study human psoriasis is what type of murine model?

- **A.** Acute (inducible) model
- **B.** Whole-body transgenic model
- **C.** Tissue-specific knockout
- **D.** Xenograft model

2. Which is a primary limitation of the IMQ-induced model used to study human psoriasis?

- **A.** The need for long-term topical application to induce an inflammatory skin phenotype
- **B.** The significant technical expertise required to use this model system
- **C.** The nonspecific nature of the skin inflammation induced by topical IMQ
- **D.** The ability of IMQ to induce skin inflammation in a single genetic strain of mice

3. Compared with whole-body transgenic mice, what is one advantage of a tissue-specific transgenic mouse model?

- **A.** Tissue-specific transgenic models are not associated with embryonic or early prenatal death.
- **B.** Tissue-specific transgenic models are less inexpensive and are not labor intensive.
- **C.** Tissue-specific transgenic models overcome the potential for undesirable/leaky gene expression.
- **D.** Tissue-specific transgenic models enable scientists to isolate the molecular mechanisms directly contributing to an observed phenotype.

4. Which type of mouse model is believed to most closely mimic the cellular, phenotypic, and genetic characteristics of human disease?

- **A.** Acute (inducible) model
- **B.** Whole-body transgenic model
- **C.** Tissue-specific knockout
- **D.** Xenograft model

5. Which of the following factors are potential confounding variables that may affect the interpretation of an inflammatory phenotype in a psoriasis-like mouse model?

A. Gestational age or sex of the mice

B. The vehicle of topical applications

C. Alterations in the murine microbiome

D. All of the above

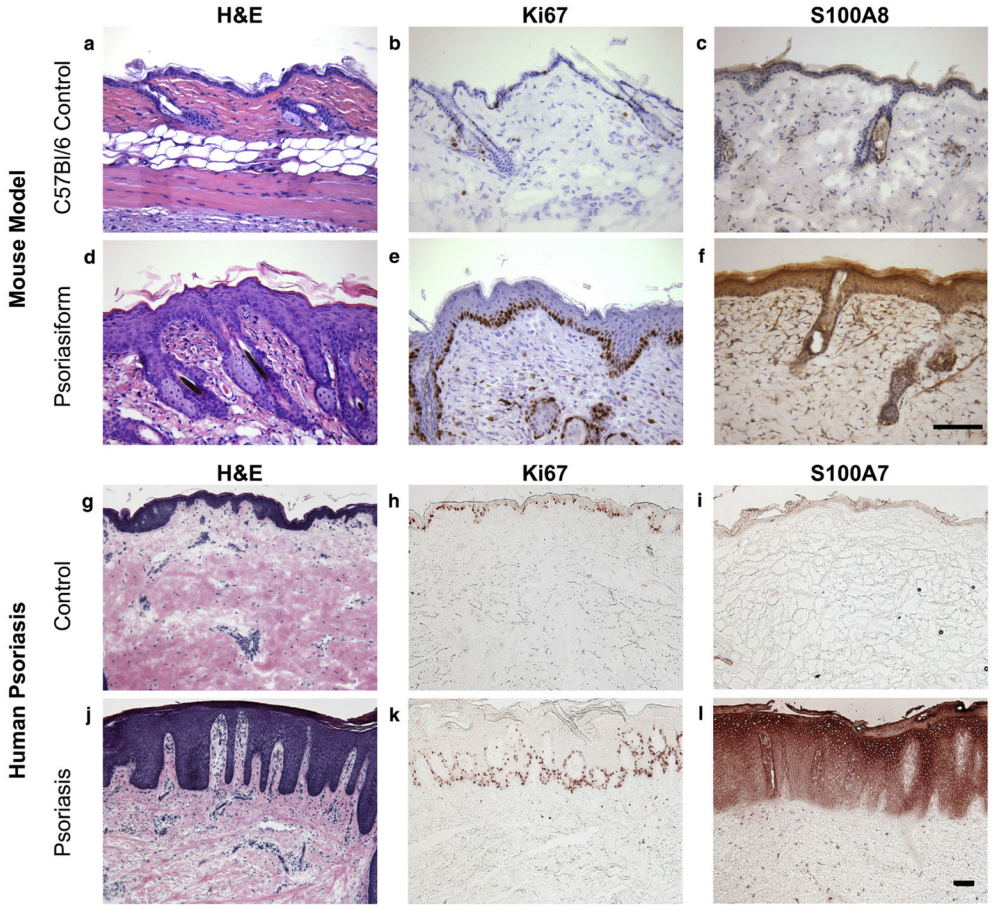

Figure 1. Representative cellular, histologic, and immunohistochemical differences between control and inflamed skin from C57BL/6 mice versus human.

Murine skin displays several cellular, histologic, and immunohistologic differences compared with human skin, including thinner skin tissue layers, increased keratinocyte turnover, densely arranged hair follicles, short interfollicular epithelial segments with absent rete ridges, and the presence of a striated muscle layer (panniculus carnosus) deep to the adipose tissue. Composite of images showing the H&E staining of (**a**) untreated wild-type C57BL/6 mouse skin with correlating immunohistochemistry staining for (**b**) Ki67 and (**c**) S100A8 compared with the (**d**) H&E, (**e**) Ki67, and (**f**) S100A8 staining in a psoriasiform mouse model. Similar H&E staining of (**g**) control human skin with correlating immunohistochemistry staining for (**h**) Ki67 and (**i**) S100A7 compared with the (**j**) H&E, (**k**) Ki67, and (**l**) S100A7 staining in lesional psoriatic skin. Scale bars in **f** and **l** = 100 μm. H&E, hematoxylin and eosin.

Table 1.

Summary of the major types of preclinical mouse models currently being used to study psoriatic disease

Model Type	Model Description	Common Examples	Advantages	Limitations	References
Acute (inducible)	Induction of psoriasis-like phenotype after the topical application of a chemical, intradermal injection, or physical disruption of the skin	• IMQ-induced dermatitis • TPA application • Cytokine injection (e.g., IL-23) • Epidermal tape-stripping model • Delayed-type hypersensitivity (e.g., oxazolone and DNFB)	• Convenient, easy to use, inexpensive • Limited requirements for specific genetic background of mouse strain • Limited technical training before use • Inducible disease at desired age or specific time point	• Unintended consequences of topical agent, chemical, or vehicle • Inappropriate use due to model advantages • Nonstandardized protocols/ treatment • Models not suitable for chronic use • Influenced by genetic background of mice	Asherson and Zembala (1970), Kopp et al. (2003), Rose et al. (2012), Sano et al. (2005), Stanley et al. (1991), van der Fits et al., (2009)
Genetically engineered (transgenic)	KO: development of psoriasis-like features resulting from the absence of specific gene(s) Tissue-specific and conditional systems: further phenotype modification by limiting the perturbed gene(s) to specific cell populations or tissue types under the regulation of specific gene promoters and/or modulators of gene expression (e.g., tamoxifen or tetracycline/ doxycycline)	KO • $CD18^{-/-}$ (hypomorphic CD18) • $Il1rne^{-/-}$	• Whole-body gene alterations: KO or overexpression mouse model • Powerful mouse model system that allows for the testing and investigation of gene-specific effects in vivo	• Often results in embryonic/ prenatal death • Gene perturbation may not reflect the actual gene altered in human disease • Whole-body alterations limit ability to isolate cellular or tissue-specific gene effects • Single gene alterations do not recapitulate complex, multigenic diseases like psoriasis	Bullard et al. (1996), Shepherd et al. (2004)
		Tissue-specific overexpressor • K14-AREG • K14-VEGF • K5-Stat3C Tissue-specific KO • K14-Cre-$Ikk2^{fl/fl}$	• Limits gene expression to specific cell populations or tissue types • Overexpression or KO constructs • Design may overcome lethality associated with whole-body gene KO	• Labor-intensive model system • Conditional gene expression may still result in embryonic or early prenatal death • Potential undesirable expression of gene of interest (“leaky” system) • Gene perturbation	Cook et al. (1997), Detmar et al. (1998), Sano et al., (2005), Stratis et al. (2006)

Model Type	Model Description	Common Examples	Advantages	Limitations	References
				may not reflect the actual gene altered in human disease	
		Inducible KO • K5-CreERT2 $JunB^{fl/fl}$ c-$Jun^{fl/fl}$ Repressible overexpressor • K5-IL-17C • KC-Tie2	• Gene controlled by tamoxifen or tetracycline/doxycycline (on/off) • Gene alterations restricted to specific tissues or cell types within a desired time-frame (spatiotemporal control) • Circumvents lethality issues • Ability to control disease enables study of acute or early phenotype changes	• Labor-intensive model system • Transgene may affect more than target gene • Potential undesirable expression of gene of interest (“leaky” system) • Confounding effects due to short- and long-term treatment with the inducer • Gene expression or deletion influenced by drug application, dose, and feeding behavior	Johnston et al. (2013), Wolfram et al. (2009), Zenz et al., (2005)
Xenograft (humanized)	Transplantation of psoriatic human skin or immune cells into severely immunocompromised mice	• Lesional psoriatic skin on AGR129 ($IFN\alpha/\beta/\gamma R^{-/-}$) • $CD4^{+}CD45RB^{hi}$ cells into C.B-17/$Prkdc^{scid}$	• Most closely mimics the cellular, phenotypic, and genetic characteristics of human disease in mice	• Technically difficult and labor intensive • Graft phenotype dependent on immune populations already present in skin • Phenotypic variation observed with different donor tissues and graft quality • Human tissues influenced by host factors	Boyman et al., (2004); Ma et al. (2008)

Abbreviations: IMQ, imiquimod; KO, knockout; TPA, 12-*O*-tetradecanoylphorbol-13-acetate.