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Research Techniques Made Simple: Mouse Bacterial Skin Infection Models for Immunity Research

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Abstract

Bacterial skin infections are a major societal health burden and are increasingly difficult to treat due to the emergence of antibiotic resistant strains such as community-acquired methicillin-resistant *Staphylococcus aureus*. Understanding the immunological mechanisms that provide durable protection against skin infections has the potential to guide the development of immunotherapies and vaccines to engage the host immune response to combat these antibiotic resistant strains. To this end, mouse skin infection models allow researchers to examine host immunity by investigating the timing, inoculum, route of infection and the causative bacterial species in different wildtype mouse backgrounds as well as in knockout, transgenic and other types of genetically engineered mouse strains. To recapitulate the various types of human skin infections, many different mouse models have been developed. For example, four models frequently used in dermatological research are based on route of infection, including: (i) subcutaneous infection models, (ii) intradermal infection models, (iii) wound infection models, and (iv) epicutaneous infection models. In this article, we will describe these skin infection models in detail along with their advantages and limitations. Additionally, we will discuss how humanized mouse models such as the human skin xenograft on immunocompromised mice might be used in bacterial skin infection research.

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AUTHOR CONTRIBUTIONS

CY and NKA wrote the paper and CY, NKA and LSM edited the final draft.

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CONFLICT OF INTEREST

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INTRODUCTION

The skin provides the first line of defense by providing a physical barrier with a low pH and temperature, an abundance of antimicrobial peptides and the normal healthy skin microbiome that protect against microbial invasion. However, when the protective skin barrier is damaged, breached, or develops a microbial dysbiosis, skin infections can arise. *Staphylococcus aureus* (*S. aureus*) is the leading cause of skin and soft tissue infections (SSTIs) in the U.S. (Dantes et al., 2013, Suaya et al., 2014). With the emergence of antibiotic-resistant bacterial clinical isolates such as community-acquired methicillin-resistant *S. aureus* (CA-MRSA), it is critical to understand the host immune responses that promote bacterial clearance in order to develop non-antibiotic immune-based therapies to prevent and/or treat skin infections. To investigate these immunological processes, mouse models that mimic various human skin infections have been developed and have been instrumental in identifying novel immunotherapeutic targets. This review will discuss different mouse skin infection models along with a human skin xenograft model, and the advantages and limitations of each model. Although we will focus on *S. aureus* and other bacterial pathogens to describe each mouse skin infection model, these models do not exclude or may not be representative of fungal, parasitic, or viral skin infections.

Mouse Models of Skin infection

Mouse skin infection models can be categorized into four groups based on the depth of infection: (i) subcutaneous infection in which the bacteria are inoculated below the dermis; (ii) intradermal infection in which the bacteria are inoculated into the dermis; (iii) wound infection in which the bacteria are inoculated into full-thickness incisional or excisional wounds; and (iv) epicutaneous infection in which the surface of the skin is exposed to the bacterial inoculum (Figure 1). These four models will be described in the context of *S. aureus* skin infections. Lastly, we will discuss the potential for translational studies with human skin xenografts. Understanding the strengths and weaknesses of each model will help provide key insights into which system is most appropriate to study specific immunologic responses as summarized in Table 1.

1. Subcutaneous Infection Models—The subcutaneous infection model mimics more invasive infections, such as subcutaneous abscesses and cellulitis (McCaig et al., 2006, Miller et al., 2005). Upon subcutaneous inoculation of *S. aureus* into the backs of mice, a deep abscess comprised of neutrophils forms around that bacteria. This abscess typically forms below the panniculus carnosus muscle in the deep dermis that primarily involves the subcutaneous fat above the deeper muscle layers (Liese et al., 2013, Tseng et al., 2011). Thus, this model has been widely used to elucidate immune mechanisms against deep soft tissue infections with various bacterial species such as *S. aureus* and *S. pyogenes* (Medina, 2010, Tseng et al., 2009). For instance, by subcutaneously inoculating different wild-type mouse strains with *S. aureus*, it was seen that resistance to the bacterial infection was associated with increasing number of infiltrating neutrophils at the site of infection (Nippe et al., 2011). The subcutaneous infection model has also been used to elucidate the role of antimicrobial peptides (AMPs) during *S. aureus* skin infections. The activities of hBD3 and LL-37 was shown to be essential for controlling subcutaneous skin infections by promoting

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the killing of *S. aureus* by either maintaining the anti-staphylococcal environment or permeabilizing the bacterial membrane, respectively (Cheung et al., 2018). Additionally, the subcutaneous model was used to discover an unexpected role for adipocyte-derived LL-37 in the control of *S. aureus* infection (Zhang et al., 2015). This model can also be used to investigate durable immune responses that protect the host from recurrent infections. For example, re-infected mice showed innate immune memory (*e.g.*, trained memory) of macrophages against a recurrent *S. aureus* subcutaneous infection (Chan et al., 2018). However, obtaining the muscle lesion size, which is a common readout for the subcutaneous infection model, involves a more invasive procedure that requires sacrificing the mice (Tseng et al., 2011).

2. Intradermal Skin Infection Models—The intradermal skin infection model also recapitulates the hallmarks of human *S. aureus* skin infections, including dermonecrotic lesions and neutrophilic skin abscesses, which corresponds to the progression and severity of the infection (Asai et al., 2010, Mölne et al., 2000). In addition, bioluminescent bacterial strains and *in vivo* optical imaging systems can be used in conjunction to noninvasively and longitudinally monitor the dynamics of the bacterial infection (Miller et al., 2006). Genetically engineered mouse strains are also useful to study components of the host response required for protection against skin infections. For example, the critical role of the inflammasome and IL-1β/IL-1R signaling in promoting neutrophil recruitment and host defense against *S. aureus* skin infections was uncovered using mice deficient in ASC (apoptosis-associated speck-like protein containing a C-terminal caspase recruitment domain), IL-1β or IL-1R as well as IL-1β-DsRed reporter mice (Cho et al., 2012, Miller et al., 2006, Miller et al., 2007). In addition, mice lacking γδ T cells exhibited significant host defense defects due to impaired IL-17 production (Cho et al., 2010). Transgenic reporter mouse strains, such as the IL-17A-tdTomato/IL-17F-GFP dual-color reporter mice, can provide insights into the expression kinetics and relevant expressing cell types of host-derived cytokines that are important for protection against intradermal *S. aureus* infections (Marchitto et al., 2019). The intradermal model can also be modified to investigate the mechanisms of immunological memory by re-infecting mice at a different skin site from the original intradermal infection (Gaidamakova et al., 2012, Montgomery et al., 2014, Sampedro et al., 2014). Remarkably, using a *S. aureus* intradermal skin re-infection model, a clonal population of γδ T cells was found to expand in the draining lymph nodes and traffic to the site of infection to confer protection against a secondary *S. aureus* intradermal infection (Dillen et al., 2018). Despite the widespread use of *S. aureus* intradermal models of infection, inherent biological differences between mice and humans need to be considered such as the activity of specific *S. aureus* toxins that are highly active against human but not mouse cells, especially superantigens such as toxic shock syndrome toxin-1 (TSST1) (Salgado-Pabón and Schlievert, 2014). To overcome this limitation, humanized mice that express the human receptors (*e.g.*, HLA-DR4 knock-in mice) targeted by these *S. aureus* toxins have been developed in which TSST1 has superantigen activity (Xu et al., 2014). Mouse immune cells are also less sensitive to the cytolytic activity of Panton-Valentine leukocidin (PVL) and α-hemolysin (Hongo et al., 2009, Spaan et al., 2013, Tseng et al., 2015). However, whereas α-hemolysin mainly has cytolytic activity against leukocytes and development of large purulent abscesses in humans, it induces keratinocyte cell death in

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mice that manifests as large dermonecrotic lesions (Kennedy et al., 2010). Additional interrogation of the pathophysiology and immunological responses can be done by histological, flow cytometric, or RNA/protein analyses to verify the relevance and validity phenotypic observations (Marchitto et al., 2019). Importantly, mice have an abundant population of γδ T cells called dendritic epidermal T cells (DETCs), which is not present in human epidermis (albeit 1–10% of resident T cells in the dermis of human skin are γδ T cells) (Nielsen et al., 2017). Mice also have more subsets of γδ T cells that reside at different layers of the skin with both conserved and distinct physiological functions as those in humans (Girardi, 2006, Suwanpradid et al., 2017). In addition to the differences in skin resident immune cells, there are other general immunological differences between the two species that could lead to discrepancies in infection outcomes between mouse and humans (McGovern et al., 2014). In humans, neutrophils make up the majority of circulating leukocytes whereas lymphocytes exist in higher percentages in mice (Mestas and Hughes, 2004). Furthermore, differences in hair follicles also contribute to differential protective mechanisms in mouse and human skin by influencing the accessibility, mobility, and communication of epithelial cells that initiate innate immune response against foreign pathogens (Al-Nuaimi et al., 2010, Bekeredjian-Ding et al., 2017, Oh et al., 2016). Therefore, it is important to consider a broad spectrum of differences between mouse and human when performing skin infection models.

3. Wound Infection Models—*S. aureus* is the most common pathogen isolated from infected skin wounds, with diabetic patients being particularly susceptible to the development of chronic, non-healing wounds (Dunyach-Remy et al., 2016, Giurato et al., 2017, Tong et al., 2015). *Pseudomonas aeruginosa* is another invasive bacterial species commonly found in wounds that causes severe tissue damage (Mutluoglu and Uzun, 2011, Sivanmaliappan and Sevanan, 2011). Mouse wound infection models replicate multiple features of infected human wounds such as purulent drainage, necrotic debris and delayed wound healing. The mouse wound infection model is performed by inoculating bacteria into full-thickness incisional cuts or excisional wounds (Dai et al., 2011). For example, incisional wounds can be inoculated with a bioluminescent *S. aureus* strain in Lysozyme M-EGFP (LysM-EGFP) reporter mice to longitudinally monitor both the bacterial burden and neutrophil recruitment dynamics during the course of infection and wound healing (Figure 2A–D) (Anderson et al., 2019, Kim et al., 2008). Furthermore, histological analysis of the infected wound skin can be used to analyze neutrophil abscess area, bacterial band width, and the presence of specific cells (Figure 2E) (Cho et al., 2011). The benefits of these different wound infection models include the ability to replicate polymicrobial infections that typically occur in human wounds (Dalton et al., 2011, Pastar et al., 2013). By infecting the wounds of diabetic mice with polymicrobial isolates from human diabetic foot ulcers, Kalan et al. were able to correlate strain-specific *S. aureus* phenotypes in mice with patient outcomes (Kalan et al., 2019). With the availability of a new strain of bioluminescent *S. aureus* expressing click beetle red luciferase and a *P. aeruginosa lux* strain, it is now possible to longitudinally and noninvasively monitor the dynamics of each bacterial strain in the context of wound infection (Miller et al., 2019). Additionally, various different strains of genetically-engineered diabetic mice exist that exhibit impaired host defense against *S. aureus* wound infections, similar to human diabetics (Guo et al., 2013, Ortines et al., 2018).

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It is important to consider the route and depth of infection in the skin as these can affect the immunological processes involved. For instance, both IL-1α and IL-1β were found to be involved in neutrophil recruitment and immunity against a *S. aureus* wound infection, while IL-1β played a more predominant role against an intradermal *S. aureus* infection (Cho et al., 2011, Yan et al., 2016). Different cellular composition between mouse and human skin may lead to challenges in translating findings in mouse wound infection models. Unlike human skin, mouse skin is highly populated with DETCs, which are responsible for sensing skin injury and producing IL-17A to promote wound healing and to strengthen skin barrier function (MacLeod et al., 2013). Another limitation to this model is that wound contraction is much more pronounced in mouse skin than human skin. Some groups have tried to overcome this limitation by covering the wound bed with a transparent breathable film (that also keeps the wound open longer) or suturing a splint to prevent wound contracture (Griffin et al., 2015).

4. Epicutaneous Infection Models—*S. aureus* commonly colonizes the lesional skin of human atopic dermatitis (AD) patients and the level of colonization correlates with disease severity (Byrd et al., 2017, Kong et al., 2012). Patients with hyper-immunoglobulin E syndrome, which is often due to a dominant negative mutation in STAT3 gene, have been characterized by atopic manifestations and higher susceptibility to *S. aureus* and/or *Candida* cutaneous infections as a result of impaired Th17 development (Horváth et al., 2011, Milner et al., 2008). These clinical observations have caused intense interest in understanding the role of *S. aureus* in the immune pathogenesis of AD skin inflammation. To model this, a *S. aureus*-soaked gauze pad is applied to the shaved and depilated dorsal skin of mice. The erythematous skin inflammation that mimic human AD conditions in mice can be measured by disease scoring, epidermal thickening, and elevated serum IgE, while the increased skin barrier defect can be measured through transepidermal water loss (TEWL) (Alexander et al., 2018, Nakamura et al., 2013). The use of mouse genetic cre/lox systems provide another important tool for researchers to identify the cells involved in immune responses by targeting gene deletion in a specific cell type. For example, a cre/lox mouse with T cell specific deletion of MyD88 was used to uncover a novel role for IL-36-mediated IL-17 T cell responses in epicutaneous *S. aureus*-driven skin inflammation (Liu et al., 2017). Tape stripping of the skin can be performed prior to epicutaneous skin infection to recapitulate the barrier defect seen in AD skin. In this model, *S. aureus* -derived proteases and phenol-soluble modulin alpha (PSMα), which are under the regulation of the bacteria's quorum sensing system, promoted skin inflammation by inducing epidermal proteolysis and skin barrier damage (Williams et al., 2019). Similarly, *S. aureus* was shown to exploit the barrier defect in filaggrin-deficient (ft/ft) mice to promote Th2 and Th22 cytokines that are associated with exacerbation of AD skin inflammation (Nakatsuji et al., 2016). Exploitation of skin barrier defects is not limited to *S. aureus*, but also vaccinia virus, which is the cause of a life-threatening condition called eczema vaccinatum in AD patients. Furthermore, cutaneous exposure to vaccinia virus in ft/ft mice through scarification, which recapitulates the route of exposure during smallpox vaccination in humans, showed IL-17A mediated dissemination of the virus in the skin (Oyoshi et al., 2015). Therefore, the epicutaneous infection model is useful in investigating the host and pathogen-derived factors that contribute to AD-like skin inflammation and AD-associated complications. Nonetheless,

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some of these models have used depilatory creams that result in baseline skin inflammation. Moreover, the models that wrap a pathogen-soaked gauze pad around the mouse to artificially expose the mouse skin to the pathogen of interest does not truly recapitulate the normal *S. aureus* colonization of uncovered skin in AD patients.

To investigate the cross-talk between the skin microbiome and host immune cells, an alternate epicutaneous infection model has been developed where a bacteria-soaked cotton swab is rubbed onto the shaved backs of mice (Belkaid and Segre, 2014, Kugelberg et al., 2005). This model was instrumental in understanding how skin discriminates between commensal and pathogenic skin microbes. In particular, the commensal *S. epidermidis* promoted T regulatory cell (Treg) expansion and skin immune tolerance in a crucial window in neonatal life (Scharschmidt et al., 2015). However, *S. aureus* manipulated IL-1β release to inhibit Treg expansion and induce skin inflammation (Leech et al., 2019). Furthermore, the model has been used to understand how the commensal bacterial strain *S. epidermis* promotes protection against pathogens as well as accelerate wound healing (Linehan et al., 2018). On the other hand, epicutaneous inoculation with *Corynebacterium accolens* promoted skin inflammation through activation of long-lasting skin T cells (Ridaura et al., 2018). Additionally, isolated *S. aureus* strains colonizing human AD induced more skin inflammation than laboratory strains isolated from other body sites (Byrd et al., 2017). Alternatively, *Candida albicans* was applied to the skin to interrogate a role for cutaneous sensory neurons in host defense (Kashem et al., 2015). Despite the usefulness of the swab epicutaneous model, it generally is done with multiple bacterial (or fungal) applications that might not fully replicate the normal colonization of commensal microbes on human skin.

Human Skin Xenograft Model

Given the inherent differences between human and mouse skin, human skin xenografts can be used to validate and translate the findings in mouse models to human skin (Parker, 2017). To prevent graft rejection, human skin biopsies are sutured onto immunodeficient mice that include NSG (NOD.Cg-Prkdc^{scid} IL2rg^{tm1Wjl}), NOG (NOD.cg-Prkdc^{scid} IL2rg^{tm1Sug}), and NRG (NOD.Cg-Rag1^{tm1Mom} IL2rg^{tm1Wj}) mice, all of which lack T, B and NK cells (Kenney et al., 2016). Moreover, it is possible to perform human skin xenografts in combination with engraftment of CD34^{+} stem cells (allowing the development of human immune cells in the same mice) to provide the new *in vivo* capability to study the human immune system in the context of a human skin infection (Brehm et al., 2012). There are numerous advantages for the use of human skin, including healthy samples that are readily available and engrafted skin tissue with epidermal and dermal layers and vascularized skin that closely resembles normal human skin. For example, Soong et al. demonstrated toxin-deficient, *agr* mutants of *S. aureus* are able to persist on the human skin by stimulating autophagy (Soong et al., 2015). In addition, epicutaneously swabbed *S. aureus* on human skin xenografts led to local production of IL-8, which induced neutrophil migration to the skin to promote bacterial clearance (Schulz et al., 2019). Studies involving human skin xenograft infections are not widely used, and thus represent an exciting opportunity in the dermatology field to translate the immunological findings from mouse skin infection models to human skin.

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CONCLUSION

Mouse models of skin infection remain the most commonly used model of skin infections due to their relatively inexpensive experimental costs as well as the opportunity to take advantage of genetically engineered mice and *in vivo* optical imaging techniques. Currently, a great variety of skin infection models and genetically engineered mice are readily available, which serve as extremely valuable tools for noninvasive and longitudinal monitoring of the underlying immune responses and host-pathogen interactions that occur during skin infections. Mouse skin infection models will continue to be essential for better understanding skin immunological responses in different contexts, including skin colonization, impetiginization, abscesses and wounds as well as in the setting of diseases such as atopic dermatitis and diabetes. Unfortunately, mouse models cannot completely replicate the pathogenesis of human disease. Therefore, these limitations need to be considered when translating the results to cutaneous immune responses in human skin (summarized in Table 1). Further advancements in humanized skin xenografts in immunocompromised mice are continually being developed to help validate and improve the discrepancies between the species.

MULTIPLE CHOICE QUESTIONS

1. Which of the following would be the most immunologically relevant purpose to re-infect mice in a skin infection model?

- **A.** To study primary T cell responses to skin infection.
- **B.** To examine memory T cell responses to skin infection.
- **C.** To study innate immune responses during initial skin infection.
- **D.** To study polymicrobial infections.

Answer: B. To examine memory T cell responses to skin infection

Detailed Answer: Memory T cells are involved in the secondary response to skin infection.

2. Which of the genetically engineered mouse strains can be used to monitor cytokine expression kinetics during skin infections?

- **A.** IL-17A/F KO mouse
- **B.** Mouse with specific IL-17A/F deletion in T cells
- **C.** IL-17A-tdTomato/IL-17F-GFP dual-color reporter mice
- **D.** All of the above

Answer: C. IL-17A-tdTomato/IL-17F-GFP dual-color reporter mice

Detailed Answer: The IL-17A-tdTomato/IL-17F-GFP dual-color reporter mouse allows for *in vivo* visualization of IL-17A and IL-17F with an In Vivo Imaging System.

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3. Which of the following skin infection models has the potential to be used with human skin xenografts?

A. Epicutaneous model

B. Intradermal model

C. Wound model

D. All of the above

Answer: D. All of the above

Detailed Answer: Human skin xenografts can be adapted to work with any of the skin infection models.

4. The epicutaneous skin infection model replicates which type of skin inflammation?

A. Atopic dermatitis

B. Psoriasis

C. Vitiligo

D. Alopecia areata

Answer: A. Atopic dermatitis

Detailed Answer: The epicutaneous model replicates *S. aureus* colonization and skin inflammation on atopic dermatitis skin.

5. Which bacteria is the leading cause of skin infections in humans?

A. Staphylococcus epidermidis

B. Pseudomonas aeruginosa

C. Staphylococcus aureus

D. Corynebacterium accolens

Answer: C. *Staphylococcus aureus*

Detailed Answer: *S. aureus* is the leading cause of skin and soft tissue infections in humans.

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SUMMARY

Advantages

- Mouse skin infection models are powerful tools to elucidate immune mechanisms of protection and identify therapeutic targets against skin infections.
- Human skin xenografts on immunocompromised mice provide the potential to validate findings from mouse infection models in human skin.

Limitations

- Immune responses can differ against the same infectious agent depending on the skin infection model used and should be verified in each model separately.
- There are inherent immunological and physiological differences between mouse and human skin.

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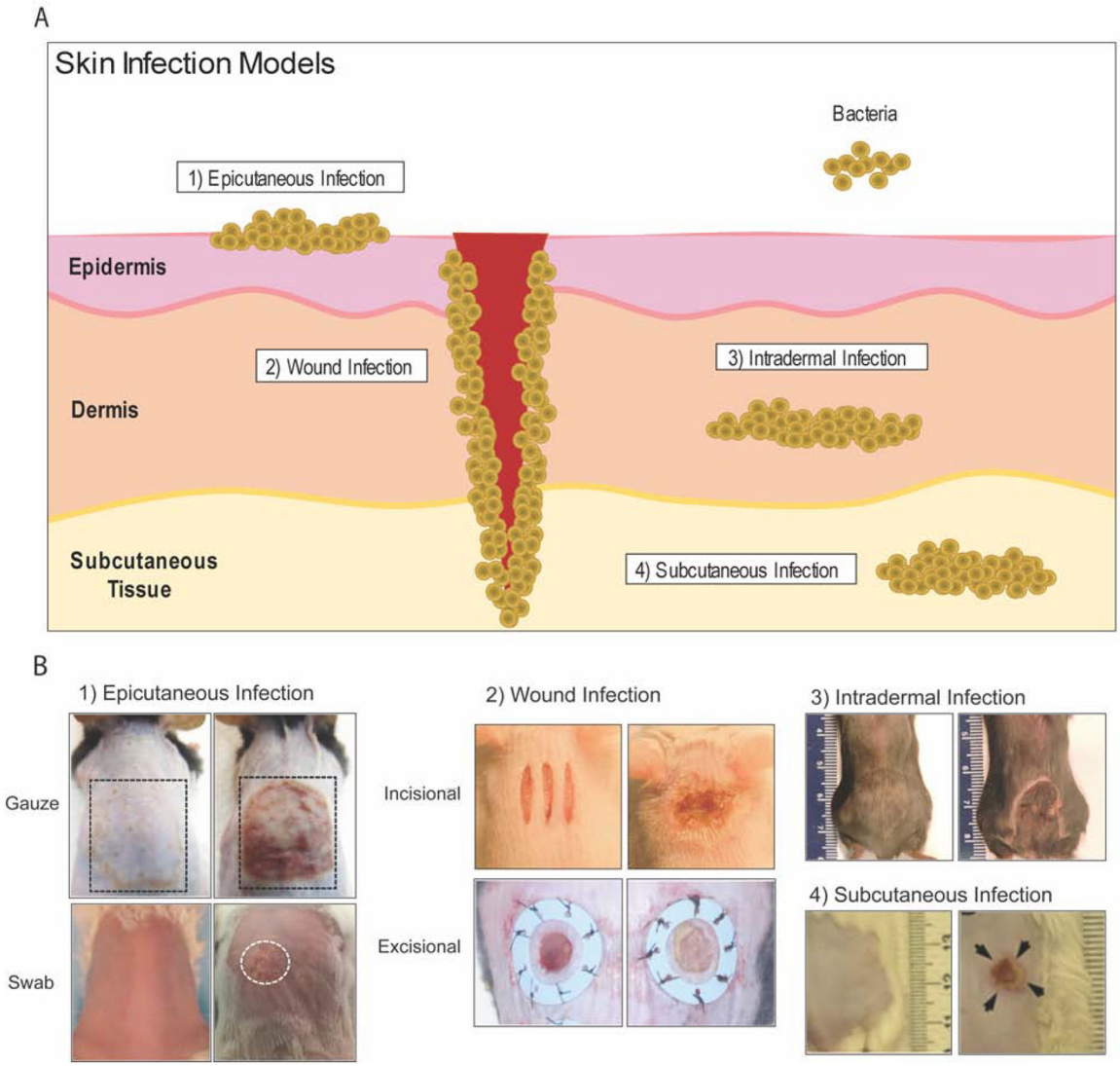

Figure 1. Graphical and photographic representations of bacterial skin infection models.

(**A**) Graphical representation of mouse skin infection models as defined by the depth of infection in the skin. (**B**) Representative clinical photographs of each of the following skin infection models (left panel: control; right panel: experimental): (1) epicutaneous infection where bacteria was inoculated on the surface of intact skin by applying a gauze soaked with bacteria or swabbing (Dai et al., 2011, Malhotra et al., 2016, Williams et al., 2019), (2) wound infection where *S. aureus* was inoculated on a full-thickness skin incisional or splint-sutured excisional wound (Archer et al., 2020, Morimoto et al., 2014), (3) intradermal infection model where *S. aureus* was inoculated into the dermis of the dorsal skin and developed dermonecrosis (Liu et al., 2017), (4) subcutaneous infection where *S. aureus* was inoculated into the subcutaneous tissue, which lead to dermonecrosis and muscle necrosis (Tseng et al., 2011).

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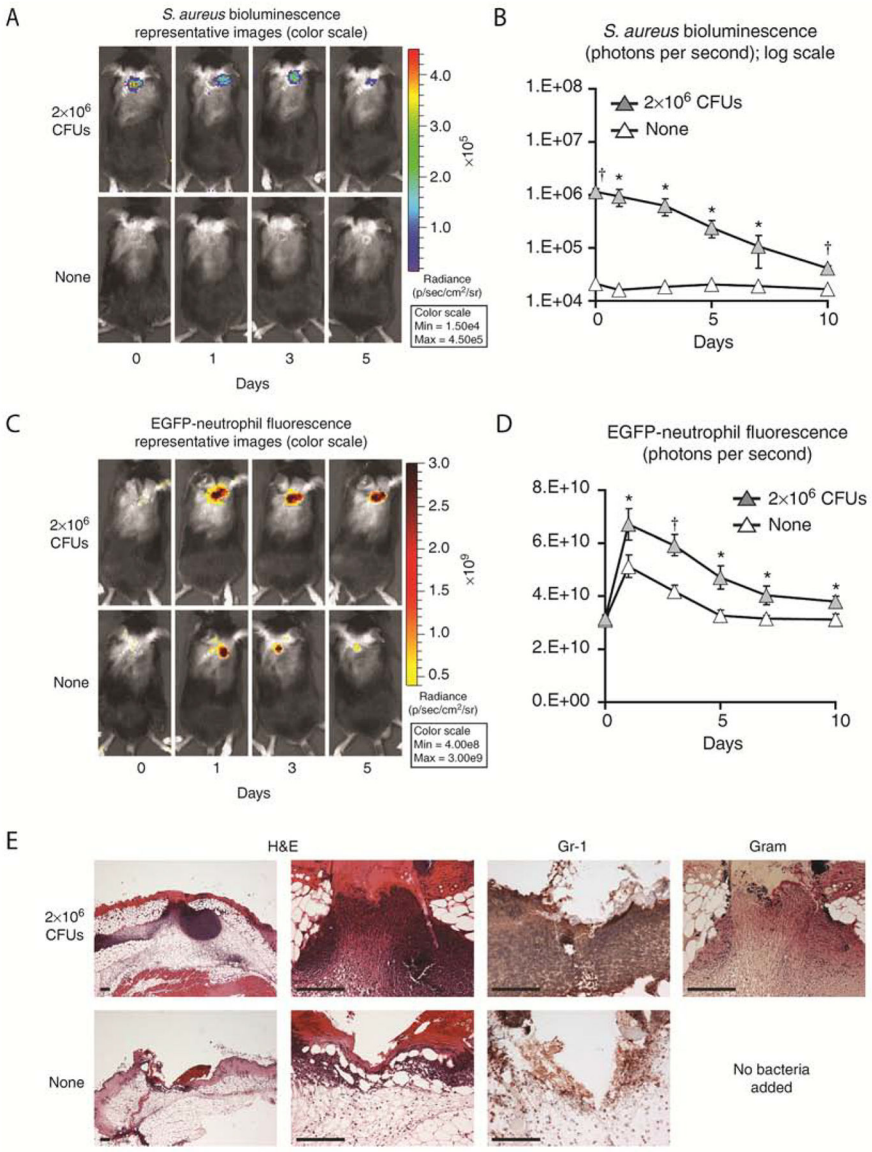

Figure 2. *S. aureus* skin infection *in vivo* imaging and histology.

Three 8-mm in length, parallel scalpel wounds on the backs of (**A-D**) LysM-EGFP mice or (**E**) C57BL/6 mice inoculated with 2 × 106 colony-forming units (CFUs) per 10 μl of *Staphylococcus aureus* or no bacteria (none). (**A**) Representative photographs of *in vivo S. aureus* bioluminescence. (**B**) *In vivo S. aureus* burden as measured by *in vivo* bioluminescence imaging (mean total flux (photons per second) ± SEM) (logarithmic scale). (**C**) Representative photographs of *in vivo* EGFP-neutrophil fluorescence. (**D**) *In vivo* fluorescence imaging of EGFP-neutrophil infiltration (mean total flux (photons per second) ± SEM). (**E**) Representative photomicrographs of sections from skin punch biopsies at 1 day after wounding ± *S. aureus* infection labeled with hematoxylin and eosin (H&E) stain, anti-Gr-1 mAb (neutrophil marker), and Gram stain. Scale bars = 150 μm. This figure was derived from (Cho et al., 2011).

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Table 1.

Summary of mouse skin infection models for immunity research

Type	Human Relevance	Model Description	Limitations	References
Subcutaneous model	• Cellulitis • Necrotizing fasciitis • Myositis	• Inoculation of bacteria into subcutaneous tissue • Used to study infection in the context of dermal, subcutaneous, and muscular tissues	• Some measurements require invasive sampling	(Berube et al., 2014, Jeong et al., 2019, Nippe et al., 2011, Tseng et al., 2011)
Intradermal model	• Folliculitis • Furuncle • Cellulitis • Erysipelas	• Injection of bacteria into dermis • Used to elucidate the epidermal and dermal contribution to protection against infection	• Immunological differences between humans and mice (*e.g.*, γδ T cells subsets, composition of circulating immune cells).	(Asai et al., 2010, Brown et al., 2009, Dillen et al., 2018)
Wound models				
• Incisional Wound	• Diabetic ulcerative skin infections • Surgery site infections • External wound infections • Polymicrobial infections	• Infection of full-thickness skin incisions • Examination of wound healing and immunity in response to bacterial infection	• Differences in wound healing mechanisms between mouse and humans	(Guo et al., 2013, Ortines et al., 2018, Zolfaghari et al., 2009)
• Excisional Wound	• Diabetic ulcerative skin infections • Surgery site infections • External wound infections • Polymicrobial infections	• Infection of full-thickness skin excisional wounds • With film or suturing, can better replicate re-epithelization wound closure of human skin	• Differences in wound healing mechanisms between mouse and humans	(Fila et al., 2016, Shi et al., 2007)
Epicutaneous models				
• Gauze Infection	• Atopic dermatitis skin inflammation	• Covered topical infection on intact or tape stripped skin • Used to investigate disease pathogenesis of human atopic dermatitis	• Unknown contribution of depilatory cream to skin inflammation • Contact via gauze does not replicate direct colonization of bacteria on patient skin	(Liu et al., 2017, Nakatsuji et al., 2016, Williams et al., 2019)

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Type	Human Relevance	Model Description	Limitations	References
• **Swab Infection**	• Noninvasive bacterial colonization • Atopic dermatitis skin inflammation • Impetigo	• Uncovered topical infection on intact or tape stripped skin • Used to investigate how the skin microbiome influences the local immune system	• Exposure to non-physiological inoculum	(Kugelberg et al., 2005, Linehan et al., 2018, Malhotra et al., 2016, Pastagia et al., 2011)
• **Human Skin Xenograft**	• Closely resembles normal human skin	• Transplantation of human skin onto immunocompromised mice • Potential to apply murine skin infection models in human skin to validate translational relevance of findings	• Limited to immunocompromised mice • Skin infection models are largely untested	(Schulz et al., 2019)