"Animal Models for Atopic Dermatitis: Bridging Bench to Bedside"

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ABSTRACT

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by intense itching, eczematous lesions, and impaired skin barrier function. Its pathogenesis involves a complex interplay of genetic predisposition, immune dysregulation, and environmental factors. Animal models have become indispensable tools for studying AD mechanisms and testing potential therapies. AD models are typically categorized into spontaneous, induced, and genetically modified types. Spontaneous models, such as NC/Nga mice, develop AD-like lesions under conventional conditions and are valuable for examining disease progression in response to environmental triggers. Induced models use allergens (e.g., house dust mites) or irritants (e.g., dinitrochlorobenzene) to provoke AD-like inflammation, allowing researchers to study immune responses and treatment efficacy in a controlled environment. Genetically modified models replicate specific molecular features of AD. For instance, filaggrin-deficient mice model epidermal barrier defects, while immune-altered models highlight the role of Th2-dominant inflammation in AD. These models have deepened understanding of AD by illustrating how genetic and environmental factors interact with immune signaling pathways. They have also been instrumental in evaluating therapies, from conventional treatments like corticosteroids and calcineurin inhibitors to newer biologics such as dupilumab. Additionally, animal models are being used to explore emerging therapies targeting the JAK-STAT pathway and skin microbiome modulation. Despite their utility, current models have limitations in fully replicating human AD. Future research should aim to improve their translational relevance through the development of refined and humanized models, complemented by advanced in vitro systems, to better bridge the gap between preclinical research and clinical application.

Keywords: Atopic Dermatitis (AD), Immune dysregulation, Barrier dysfunction, genetically modified mice, Therapeutic evaluation

INTRODUCTION

Atopic dermatitis (AD), also known as eczema, is a chronic, relapsing, inflammatory skin condition that affects both children and adults. It is characterized by itchy, red, and inflamed skin, often accompanied by dry, scaly patches. The disease primarily affects the skin but is associated with a systemic immune dysfunction. AD is considered a part of the "atopic triad," which includes asthma and allergic rhinitis, reflecting a strong link to allergic disorders(1). The exact cause of atopic dermatitis is not fully understood, but it is believed to result from a combination of genetic, immunological, and environmental factors. Individuals with a family history of atopy (allergies, asthma, or eczema) are at a higher risk of developing AD(2). Mutations in the filaggrin (FLG) gene, which plays a critical role in skin barrier function, have also been identified as a key factor contributing to the disease's pathogenesis. AD affects approximately 15-20% of children and 1-3% of adults worldwide, making it one of the most common chronic skin conditions. The prevalence of AD has been increasing, particularly in developed countries, which may be related to urbanization and lifestyle factors(3).

EPIDEMIOLOGY

Approximately one in five people may experience atopic dermatitis at some point in their lives, however the disease's incidence varies widely across the globe(4). Very little has been written about the global epidemiology of atopic dermatitis (AD) during the 2009–2019 timeframe. Since comprehensive prevalence and incidence data can show the disease's impact in the population of adults, adolescents, and children in various geographic locations, epidemiological studies are crucial in presenting the risk factors of AD. Dietary changes, environmental changes and skin barrier deficiencies brought on by FLG mutations were the risk variables that were shown to cause and promote AD. By altering the pH and skin moisture, FLG mutation may compromise the function of the skin barrier(5).

PATHOPHYSIOLOGY

For understanding the inflammatory lesions in atopic dermatitis, two primary hypotheses have been put proposed. An imbalance in the adaptive immune system is the subject of the first theory, while a compromised skin barrier is the subject of the second. These two theories might support one another even if they are not believed to be mutually exclusive.

1. Immunological Hypothesis: According to the notion of immunological imbalance, atopic dermatitis is caused by an imbalance of T cells, namely regulatory T cells and T helper cell types 1, 2, 17, and 22. The predominant Th2 differentiation of naive CD4+ T cells occurs in the allergic (atopic dermatitis) condition, especially in acute eczema. Th1 differentiation is prevented as a result of the increased synthesis of interleukins, mainly IL 4, IL-5, and IL-13, which raises IgE levels thereafter.

2. The Skin Barrier Hypothesis: The fact that people with mutations in the filaggrin gene are more likely to develop atopic dermatitis6 is the basis for the more current idea of skin barrier abnormalities(6). The structural proteins in the stratum corneum and stratum granulosum that aid in holding the keratinocytes together are encoded by the filaggrin gene. This keeps the stratum corneum moist and the skin barrier maintained. Reduced production of filaggrin due to gene abnormalities results in Trans epidermal water loss and failure of the skin barrier, which in turn causes eczema. There is evidence that the compromised skin barrier, which causes dry skin, increases the amount of allergens that penetrate the skin, causing hay fever, asthma, and allergic sensitization(7). The major goal of preventing the progression of eczema into allergic airway disease may be to prevent dry skin and active eczema in early life by applying emollients. As shown in Fig. 1

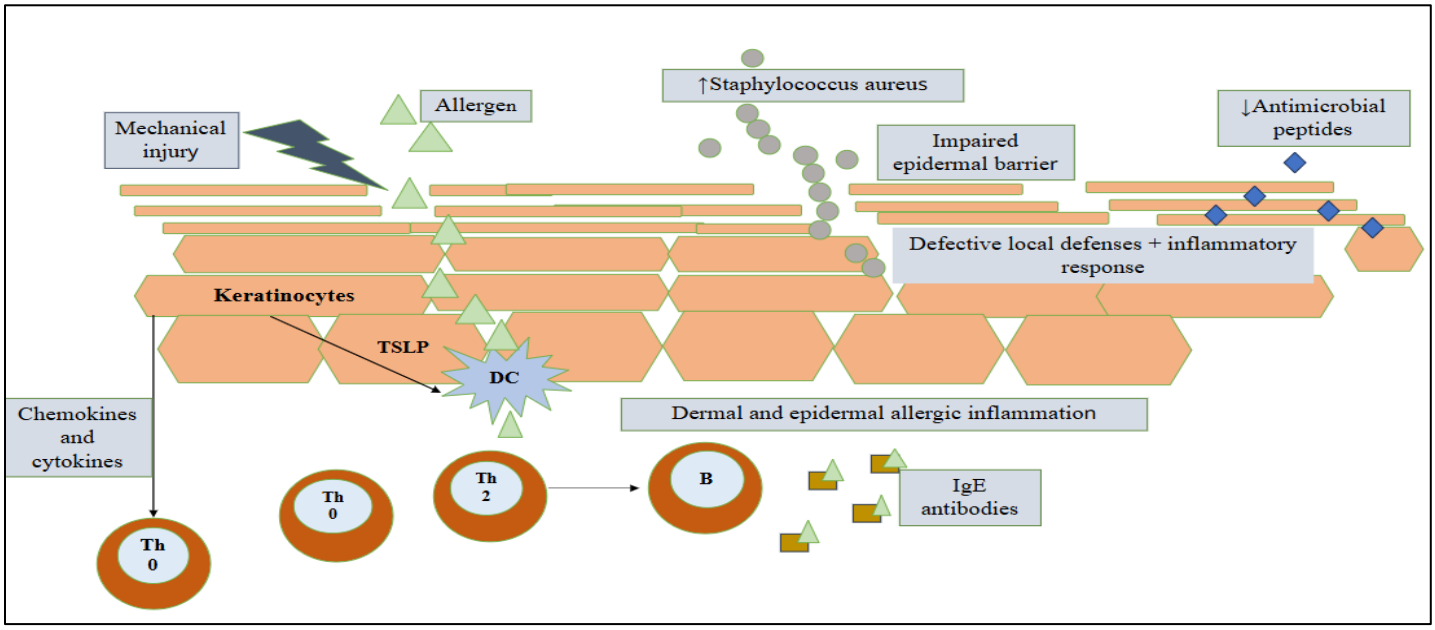

Figure 1 Pathophysiology f AD

IN VITRO MODELS:

1. Two-Dimensional Culture Systems: These models consist of immune cells or keratinocytes cultured in a two-dimensional environment(8). They include keratinocyte Culture Models and co-culture systems.

- **Keratinocyte culture model** include further two types Primary Keratinocytes and Immortalized Keratinocyte Cell Lines as shown in Table No. 1

TABLE NO. 1: Two-Dimensional Culture Systems

Model Type	keratinocyte Culture Models	Immortalized Keratinocyte Cell Lines
Origin	human skin biopsies	Originated from primary keratinocytes or other sources, they have undergone genetic modification to enable endless multiplication. For example, N/TERT-1 and HaCaT are the most frequent
Life Span	Limited, can be cultured for few passages before senescence	Unlimited can undergo many can be cultured for several passages without undergoing senescence
Genetic Stability	Preserving the genetic and epigenetic characteristics of the donor tissue to create a more physiologically realistic replica.	Can experience alterations in genetics and epigenetics throughout time as a result of the immortalization process and ongoing proliferation.

Relevance to AD	Highlight each AD patient's distinct illness characteristics and natural diversity.	Although it might not be able to accurately capture the complicated phenotype of AD, it produces a reliable and repeatable model.
Advantages	They are therefore perfect for researching disease causes and even patient-specific responses because they more closely resemble the in vivo conditions of human skin. Useful for patient specific study and understanding the heterogeneity of AD.	➢ High genetic homogeneity leads to high reproducibility and consistency. ➢ It is widely accessible and can be grown in huge quantities. ➢ Simpler to culture and maintain compared to primary cells.
Disadvantages	High donor variability therefore poses a challenge to reproducibility. Restricted Availability because large-scale research cannot be conducted without a steady supply of new tissue samples, which is impractical. Isolation and culture can be technically difficult and time-consuming.	The simulation may not completely replicate the in vivo environment of human skin, thus resulting in a less precise portrayal of disease mechanisms. The potential for mutations to accumulate over time poses a risk, leading to possible changes in the behavior and response of cells to various treatments. Absence of diversity among individual patients, which may pose a challenge in researching the heterogeneity of AD.
Applications	Ideal for personalized questions, comprehension of illness mechanisms unique to each patient, and evaluation of unique responses to treatment. Used to analyze the innate genetic and epigenetic properties of keratinocytes in patients with atopic dermatitis.	Ideal for conducting mechanistic inquiries, conducting high-throughput screening of potential medicinal compounds, and carrying out assays that require a high number of cells. Used in initial stages of research to identify potential targets and various pathways involved in AD.

- **Co culture system include two types of cultures** Keratinocytes and Fibroblasts and Keratinocytes and Immune Cells as shown in Table No. 2

TABLE NO. 2: Co Culture System-Keratinocytes And Fibroblasts And Keratinocytes And Immune Cells

Model Type	Keratinocytes and Fibroblasts	Keratinocytes and Immune Cells
Cell type Present	**Keratinocytes:** forms the protective barrier of the skin. Role in AD: Barrier dysfunction, inflammatory response and altered differentiation.	**Keratinocytes:** forms the protective barrier of the skin. **Role in AD:** Barrier dysfunction, inflammatory response and altered differentiation.
	Fibroblasts: Primary dermis cell produce extra cellular matrix components and responsible for maintaining skin structure **Role in AD:** Contribute to skin remodeling, fibrosis, and production of growth factors and cytokines.	**Immune Cells:** T cells, dendritic cells, macrophages, mast cells, etc Role in AD: Mediate inflammation, contribute to immune responses, and interact with keratinocytes to perpetuate the inflammatory cycle.
Co-culture Characteristics:		
Interactions	Focuses on epithelial-mesenchymal interactions communicate via soluble factors and direct cell-cell contact, influencing each other's functions.	Focuses on immune-epithelial interactions. Interact through cytokines, chemokine's, and direct contact, modulating inflammatory responses
Advantage	1. Mimics in vivo environment of skin more closely than monocultures. 2. Allows study of interactions between epidermal and dermal components.	1. Captures the immune component of AD, allowing for detailed study of inflammatory processes and immune cell behavior. 2. Directly relevant to the inflammatory and immune aspect pathogenesis.

Disadvantage	Limited Immune Component	Less Focus on Structure
Applications	Research on skin barrier restoration, fibrosis, and effects of treatments on both epidermal and dermal layers.	Investigating inflammatory pathways, testing immunomodulatory treatments, and understanding immune cell infiltration and activation.

2. Three-Dimensional Skin or Epidermal Equivalents: These models reconstitute more complex stratified tissues exhibiting barrier properties. They can be challenged with interleukin cocktails or silenced expression of pivotal genes encoding epidermal barrier proteins to mimic AD features(8). As shown in Table No. 3

TABLE NO. 3: Three-Dimensional Skin or Epidermal Equivalents

Model	**Reconstructed Human Epidermis (RHE)**	**Full-Thickness Skin Models**	**Organotypic Skin Models**
Structure	Consists of a stratified layer of keratinocytes, mimicking the human epidermis	Includes both epidermal (keratinocytes) and dermal (fibroblasts) layers, providing a more comprehensive representation of human skin.	Created by culturing keratinocytes on a dermal equivalent, which can be made from fibroblasts embedded in a collagen matrix or other scaffold materials.
Production	Keratinocytes are cultured at the air-liquid interface, allowing them to differentiate and form a multilayered epidermal structure	Dermal layer is typically composed of fibroblasts embedded in a collagen matrix, with keratinocytes cultured on top to form the epidermis.	**Dynamic Environment:** Some models incorporate a dynamic environment, such as perfusion or mechanical stress, to better replicate in vivo conditions.
Advantages	High Relevance Closely mimics the structure and function of epidermis. Reproducibility	More accurately mimics the structure and interactions of skin. Versatility Suitable for a wide range of studies, including barrier, inflammation, function and tissue remodeling.	High Physiological Relevance Closely mimics, including interactions between different cell types and the extracellular matrix. Can be tailored to include specific cell types or conditions relevant to AD.
Disadvantage	**Limited Complexity**: Lacks the dermal component and immune cells, limiting the ability to study interactions beyond the epidermis.	**Increased Complexity and Cost**: More complex to produce and maintain, which can increase costs and technical demands.	**1. Technical Complexity**: More challenging to create and maintain than simpler models. **2. Cost**: Higher production costs due to increased complexity and requirements for specialized materials and equipment.
Applications	**1. Skin Barrier Studies**: Investigating integrity and function of skin barrier, including permeability and responses to barrier-disrupting agents. **2. Inflammatory Responses**: Studying the effects of pro-inflammatory cytokines (e.g., IL-4, IL-13) on keratinocyte behavior and barrier function. **Drug Testing**: Evaluating the efficacy and safety of topical treatments.	**1. Skin Architecture Studies**: Examining the interactions between epidermal and dermal layers, crucial for understanding skin remodeling and fibrosis in AD. **2. Complex Interactions**: Studying effects of treatments on both layers and their interactions. **Barrier and Inflammation Studies**: Investigating dermal components influencing epidermal barrier function and inflammatory responses.	**1. Pathogenesis Studies**: Investigating the mechanisms of skin barrier dysfunction, inflammation, and immune cell infiltration in AD. **2. Immune Interactions**: Incorporating immune cells (e.g., T cells, dendritic cells) to study their interactions with skin cells. **3. Treatment Evaluation**: Assessing the effects of novel therapies on a more physiologically relevant model.

3. Tissue Equivalents Co-cultured with Lymphocytes or Containing AD Patient Cells: These models involve the use of tissue equivalents cocultured with lymphocytes or containing AD patient cells. They can help study the interactions between immune cells and keratinocytes in AD(8).

ANIMAL MODELS: There are following models- As shown in Table No. 4

1. NC/Nga Mouse Model: This model is widely used to study AD. It exhibits skin lesions, inflammation, and immune cell activation similar to human AD.

2. Hapten-Induced Mouse Model: This model involves the application of a hapten, such as 2,4- dinitrochlorobenzene (DNCB), to induce skin lesions and inflammation.
3. Dermatophagoides Farina (DF) Model: This model involves the repeated application of DF to induce chronic skin inflammation and immune cell activation.
4. Dermatophagoides Pteronyssinus (DP) Model: This model involves the repeated application of DP to induce chronic skin inflammation and immune cell activation(9).

TABLE NO.4: Tissue Equivalents Co-Cultured With Lymphocytes Or Containing Ad Patient Cells

Model Type	NC/Nga Mouse Model:	Hapten-Induced Mouse Model:	Dermatophagoides Farina (Df) Model:	Dermatophagoides Pteronyssinus (DP) Model:
Origin	Bred in Japan at Nagoya University in 1957	The use of haptens in murine models dates back to the early 20th century. Haptens like oxazolone and 2,4-dinitrofluorobenzene (DNFB) are commonly employed to induce allergic contact dermatitis (ACD) and chronic Th2-like hypersensitivity reactions in mice(10).	D. farinae is nearly cosmopolitan in distribution, being found in association with house dust and bird nests worldwide. It likely originated in the Americas, hence the name **"American house dust mite"**(11)	Dermatophagoides pteronyssinus belongs to the family **Pyroglyphidae** and is cosmopolitan, thriving particularly in humid environments. This species, along with Dermatophagoides farinae **(the American house dust mite)**, is one of the most studied due to association with allergic diseases(12).
Life Spam	Typically around 2-3 years under optimal conditions. However, this can vary somewhat depending on environmental factors and the specific research protocol.	Generally limited to the duration of the experimental conditions, typically lasting a few weeks to months, depending on the frequency of hapten challenges and the specific aims of the study.	The life cycle of D. farinae includes egg, larva, protonymph, tritonymph, and adult stages. It takes 19-30 days to complete a life cycle. Mated females live about 2 months and lay about 1 egg per day over a 30-day period(13), (14).	The life cycle of D. pteronyssinus consists of several stages: egg, larva, protonymph, tritonymph, and adult. The entire cycle can be completed in approximately 30 days, with adults living an additional 1 to 3 months after reaching maturity(14) (12)(15). Average lifespan of a mated female is 70 days(16).
Genetic Stability	Genetically, the NC/Nga mice possess a quantitative trait locus (QTL) named derm1 located on chromosome 9, which is associated with the development of AD-like skin lesions(11)(17).	Genetic stability is crucial for reproducibility in these models, and strains like NC/Nga mice are often used due to their close resemblance to human AD in terms of skin pathology and immune response(18).	There is limited information on the genetic stability of D. farinae. As a species, it appears to be genetically adapted to the indoor environment of human dwellings.	D. pteronyssinus exhibits genetic stability, which is essential for its adaptability and survival in various environments. This stability allows for consistent allergenic profiles, which are critical for developing allergy tests and treatments. (14).
Relevance To AD	NC/Nga mice are particularly relevant because resemble human AD when housed in normal laboratory conditions. Key characteristics include: **1. Skin Lesions**: (11).	Hapten-induced models are particularly relevant for studying AD because they replicate key features of the disease, including Th2-dominant inflammation, elevated	D. farinae is a major trigger of allergic symptoms in atopic dermatitis (AD). Exposure to D. farinae allergens can exacerbate AD symptoms in sensitized individuals. Reducing	D. pteronyssinus is highly relevant to atopic dermatitis, as its allergens can trigger and exacerbate symptoms in sensitized individuals. The presence of dust mite allergens is strongly correlated with the severity of asthma and allergic

	2. Histological Features: (11)(19)(17). **3. Immune Response**: There is a notable Th2 polarization in the immune response of these mice, characterized by elevated levels of cytokines such as IL-4 and IL-5, which are critical in the pathogenesis of allergic diseases(11)(17).	serum IgE levels, and impaired skin barrier function. These models allow researchers to investigate the underlying mechanisms of AD and evaluate potential therapeutic interventions(16)(10).	exposure to house dust mites is an important part of managing AD.	rhinitis, and they are also implicated in skin conditions like AD. It disrupt epithelial barrier function, leading to increased permeability and inflammation in the skin, which is a hallmark of AD(14)(12).
Advantages	**1. Spontaneous Development of AD**: (19) [,14]. **2. Genetic Stability**: (19)(19). **3. Environmental Influence**: (19) [12]. **4. Immunological Relevance**: (19).	**1. Convenience and Cost-Effectiveness**: (10). **2. Reproducibility**: (10). **3. Rapid Induction of Disease**: (10). **4. Mimicking Human Disease Features**: (10).	**1. Effective Allergen Sources**(20)(21). **2. Immunotherapy Applications**: (21). **3. Research Utility**: **4. Diversity of Allergens**: (20).	**1. Well-defined life cycle and genetic stability**: **2. Relevance to allergic diseases**:. **3. Availability of extracts for diagnosis and research**: (22)(23).
Disadvantages	**1. Limited Lifespan**:. **2. Environmental Sensitivity**: (19). **3. Lack of Complete Human Relevance**: (19).	**1.Limited Characterization**:. **2. Species Differences**: (24).	**1. Potential for Adverse Reactions**: (21). **2. Limited Genetic Stability**: (20). **3. Environmental Control Challenges**:	**1. Variability in extract composition**: (23). **2. Complexity of allergic responses**:
Application	**1. Pathophysiological Studies**. (25)(19). **2. Therapeutic Testing** (25). **3. Genetic Research**: (19). **4. Environmental Impact Studies**.(19).	**1. Understanding Allergic Reactions** (26). **2. Therapeutic Testing**:(10). **3. Investigating Environmental Factors**.(10) .	**1. Allergy Testing** (20)(21). **2. Immunotherapy** (21). **3. Animal Models**. **4. Research on Allergens** (20).	**1. Allergy diagnosis**: (22)(23). **2. Immunotherapy**: (27). **3. Research on allergen structure and function**: (23). **4. Development of new diagnostic and therapeutic approaches**: (23).

COMPARISON OF IN VITRO AND ANIMAL MODELS:

In vitro models are advantageous for studying specific aspects of AD, like the interactions between immune cells and keratinocytes. Though, they may not fully summarize the complexity of human skin. On the other hand, animal model can provide a more comprehensive understanding of the ailment, mechanisms and can also be used to test therapeutic strategies. The NC/Nga mouse model is widely used due to its similarity to human AD. However, other models, such as the hapten-induced mouse model, can also be used to study specific aspects of AD.

FUTURE DIRECTIONS:

Future research should focus on developing more accurate and complex in vitro and animal models that better recapitulate the pathophysiology of AD. Additionally, the use of tissue engineering approaches can help develop personalized medicine for AD. The development of new therapeutic strategies, such as the use of flavonoids and other natural compounds, should also be explored. In conclusion, in vitro and animal models are essential tools for investigating the pathophysiology of atopic dermatitis and testing potential therapeutic strategies. The choice of model depends on the specific research question and the desired level of complexity. Future research should focus on developing more accurate and complex models that better recapitulate the pathophysiology of AD.

CONCLUSION:

Advanced in vitro models, such as tissue equivalents co-cultured with lymphocytes or incorporating cells from AD patients, provide a highly relevant platform for studying atopic dermatitis (AD). These models replicate the disease environment by integrating immune cells like T cells, dendritic cells, and macrophages with keratinocytes, enabling the investigation of immune-epithelial interactions in AD pathogenesis. Utilizing patient-derived cells enhances their physiological relevance, capturing the genetic and epigenetic diversity of AD and allowing for the study of disease heterogeneity, immune dysregulation, and personalized treatment responses. Additionally, these models facilitate the testing of novel immunomodulatory therapies, bridging the gap between fundamental research and clinical applications. While in vitro models enable detailed examination of immune cell and keratinocyte interactions, they cannot fully replicate the complexity of human skin. Animal models, such as the NC/Nga mouse and hapten-induced models, provide crucial insights into disease mechanisms and therapeutic responses, closely mirroring human AD. Future research should prioritize the development of more advanced models that better reflect human AD, including tissue engineering approaches for personalized medicine. Exploring new therapeutic strategies, such as flavonoids and other natural compounds, may further expand treatment options. The choice of an appropriate model depends on the specific research focus and required complexity, underscoring the importance of continuous advancements in AD modeling.

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