

Journal Pre-proof

New insights of human atopic dermatitis provided by mouse models

Kenji Matsumoto, MD, PhD, Hideaki Morita, MD, PhD, Susumu Nakae, PhD

PII: S0091-6749(21)01136-2

DOI: <https://doi.org/10.1016/j.jaci.2021.07.016>

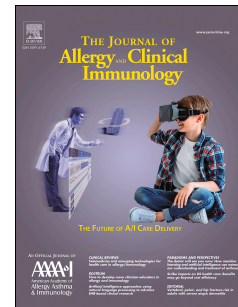
Reference: YMAI 15205

To appear in: *Journal of Allergy and Clinical Immunology*

Received Date: 19 May 2021

Revised Date: 11 July 2021

Accepted Date: 20 July 2021



Please cite this article as: Matsumoto K, Morita H, Nakae S, New insights of human atopic dermatitis provided by mouse models, *Journal of Allergy and Clinical Immunology* (2021), doi: <https://doi.org/10.1016/j.jaci.2021.07.016>.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2021 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology.

New insights of human atopic dermatitis provided by mouse models

Kenji Matsumoto, MD, PhD,^a Hideaki Morita, MD, PhD,^a Susumu Nakae, PhD^{b,c}

From the ^aDepartment of Allergy and Clinical Immunology, National Research Institute for Child Health and Development, Tokyo; ^bGraduate School of Integrated Sciences for Life, Hiroshima University, Hiroshima; and ^cPrecursory Research for Embryonic Science and Technology, Japan Science and Technology Agency, Saitama, Japan

Disclosure of potential conflicts of interest: The authors declare that they have no relevant conflicts of interest.

This work was supported in part by a grant from the National Center for Child Health and Development of Japan (grant no. 2020B-4 to K.M.).

Corresponding author: Kenji Matsumoto, MD, PhD
Department of Allergy and Clinical Immunology,
National Research Institute for Child Health and Development,
2-10-1 Okura, Setagaya-ku, Tokyo 157-8535, Japan.
Phone: +81-3-3416-0181 (ext. 4950) FAX: +81-3-5494-7173
E-mail: matsumoto-k@ncchd.go.jp

Key words: atopic dermatitis, mouse model, inducible model, recovery, Vitamin D analogue

Atopic dermatitis (AD) is the most common chronic inflammatory disorder of the skin. It is characterized by skin–barrier dysfunction, immune dysregulation and itch–scratch behavior. Patients with AD exhibit a wide spectrum of signs and symptoms, and AD phenotypes reportedly differ depending on age, region, ethnicity, etc.¹ Comprehensive gene expression (transcriptome) analyses revealed that the pathogenesis of AD involves both adoptive and innate immune responses through complex interactions among various tissue–resident cells and inflammatory cells, and that AD endotypes also differ depending on age, region, ethnicity, etc.² Therefore, the efficacy of anti–AD remedies, especially recently authorized ones, should be optimized to those endotypes.

Mouse models are indispensable for studying and optimizing the efficacy of drugs for diseases with multiple phenotypes and endotypes. To date, more than 20 mouse models of AD have been reported. These models can be divided into two groups based on spontaneous/inducible onset of AD. Several genetically–defined mice spontaneously exhibited AD symptoms, as summarized in a recent review article in the *Journal*.³ On the other hand, various inducible models have been reported that use a special diet or topical application of haptens, antigens, a cytokine, chemicals and others (Table I). Some of the stimulants, such as haptens, antigens and staphylococcal enterotoxin B, activate mainly adoptive immune responses, whereas others activate mainly innate immune responses. A major advantage of such inducible models is that we can investigate the precise mechanisms of not only the exacerbation but also the resolution of the skin lesions.

During the natural course of AD, most patients experience recurrent exacerbation and resolution of their skin lesions over time. As a result, patients exhibit multiple different manifestations of the skin lesions, ranging from erythema to xerosis, acanthosis and lichenification. However, the mechanisms behind resolution of AD have been poorly understood, simply because there is no way to assess the molecular kinetics deep under the skin without using an invasive technique.

But now, in this issue of the *Journal*, Pellefigues et al.⁴ provide novel information about the molecular mechanisms behind AD resolution by using an MC903–induced AD model mouse. They report that epithelial–derived thymic stromal lymphopoietin (TSLP) directly activated basophils, while basophil–derived IL-4 and macrophage colony–stimulating factor (M-CSF) regulated both keratinocyte proliferation/differentiation and macrophage differentiation toward the M2 type. During skin lesion resolution, IL-4 was associated with restoration of barrier function through induction of two barrier proteins, filaggrin and desmoglein. Moreover, M2 macrophages played important roles in efferocytosis, tissue repair and remodeling. Thus, basophil–derived IL-4 likely plays pivotal roles in both exacerbation and resolution of AD.

However, that study had some limitations. First, none of the mouse models of AD fully recapitulate human AD: several recent transcriptome–profiling studies demonstrated that

well-known AD models share only 4–37% homology with human AD.⁵⁻⁹ That is presumably because mouse skin and human skin are anatomically different: the mouse keratinocyte layer is very thin, and its barrier function is weak compared with human skin. Some such mouse models do not manifest itch-scratch behavior. In addition, to sufficiently induce chronic type 2 responses in the skin, repeated exposure is indispensable for switching from an initial type 1 response to a type 2 response especially in hapten-induced models, and for switching from an innate immune response-triggered type 2 inflammation without itchiness to those with significant itch-scratching behavior accompanied by pathological changes in the dorsal root ganglia in the MC903 (calcipotriol)-induced model.¹⁰

We are very curious whether a resolution mechanism exists in other AD models and also in human AD. In addition, if IL-4/IL-13 is indispensable for induction of M2 macrophages, does the resolution process differ between AD patients treated, or not treated, with dupilumab, a monoclonal antibody against the IL-4 receptor α chain? We believe that future studies in AD models that take into account the time-axis of AD will help us understand and modulate the resolution of atopic dermatitis over time, which is one of the poorly understood aspects of human atopic dermatitis.

References

1. Yew YW, Thyssen JP, Silverberg JI. A systematic review and meta-analysis of the regional and age-related differences in atopic dermatitis clinical characteristics. *J Am Acad Dermatol* 2019;80:390-401.
2. Brunner PM, Guttman-Yassky E, Leung DY. The immunology of atopic dermatitis and its reversibility with broad-spectrum and targeted therapies. *J Allergy Clin Immunol* 2017;139:S65-S76.
3. Nakajima S, Nomura T, Common J, Kabashima K. Insights into atopic dermatitis gained from genetically defined mouse models. *J Allergy Clin Immunol* 2019;143:13-25.
4. Pellefigues C, Naidoo K, Mehta P, Schmidt AJ, Jagot F, Roussel E, et al. Basophils promote barrier dysfunction and resolution in the atopic skin. *J Allergy Clin Immunol* 2021 Mar 2:S0091-6749(21)00281-5. doi: 10.1016/j.jaci.2021.02.018. Epub ahead of print. PMID: 33662369.
5. Ewald DA, Noda S, Oliva M, Litman T, Nakajima S, Li X, et al. Major differences between human atopic dermatitis and murine models, as determined by using global transcriptomic profiling. *J Allergy Clin Immunol* 2017;139:562-71.
6. Kim YW, Ko EA, Jung SC, Lee D, Seo Y, Kim S, et al. Transcriptomic insight into the translational value of two murine models in human atopic dermatitis. *Sci Rep*

- 104 2021;11:6616.
- 105 7. Xu Y, Chen S, Chen J. Profiling transcriptomic changes and signaling pathways in
- 106 atopic dermatitis by integrative analyses on multiple databases. *Mol Genet Genomics*
- 107 2021;296:341-53.
- 108 8. Ando T, Xiao W, Gao P, Namiranian S, Matsumoto K, Tomimori Y, et al. Critical role
- 109 for mast cell Stat5 activity in skin inflammation. *Cell Rep* 2014;6:366-76.
- 110 9. Choi J, Sutaria N, Roh YS, Bordeaux Z, Alphonse MP, Kwatra SG, et al. Translational
- 111 Relevance of Mouse Models of Atopic Dermatitis. *J Clin Med* 2021;10:613.
- 112 10. Oetjen LK, Mack MR, Feng J, Whelan TM, Niu H, Guo CJ, et al. Sensory neurons
- 113 co-opt classical immune signaling pathways to mediate chronic itch. *Cell* 2017;171:217-
- 114 28.

TABLE I. Inducible mouse models of atopic dermatitis

Treatments	Mouse strain	AD induction mechanism	Clinical/pathological features	Findings of transcriptome analysis*	References†
Diet					
Elimination of unsaturated fatty acids from diet	Hairless mice (hr/hr)	Marked scratching behavior due to induction of allopregnanolone	Epidermal thickening; Type 2 inflammation; itch		Fujii M, Exp Dermatol 2005
Topical Applications					
Haptens					
Oxazolone, repeated exposure	Hairless mice (hr/hr)	Following initial type 1 response, repeated exposure induces hapten-specific type 2 response	Epidermal hyperplasia; Type 2 inflammation; itch	17% homology to human AD	Man MQ, J Invest Dermatol 2008
DNCB, repeated exposure	CBA/J	Following initial type 1 response, repeated exposure induces hapten-specific type 2 response	Epidermal hyperplasia; Type 2 inflammation; itch	Share common pathway dysregulation	Kim YW, Sci Rep 2021
DNFB, 2X, 14 days apart	BALB/c	Hapten-specific type 1, 17 and type 2 responses	Epidermal hyperplasia; Type 1, 17 and type 2 inflammation; itch		Kitamura A, Sci Rep 2018
TNCB, repeated exposure (8W)	NC/Nga	Following initial type 1 response, repeated exposure induces hapten-specific type 2 response	Type 2 inflammation with high IgE production; itch		Kim YH, J Vet Sci 2020
CMIT/MIT with	BALB/c	Repeated exposure induces barrier	Type 2/type 17 inflammation		Go HN, Sci Rep

OVA		dysfunction with type 2/type 17 responses			2020
Antigens					
OVA with mechanical barrier disruption	BALB/c	OVA-specific type 2 responses to TSLP; T-cell activation is indispensable	Epidermal hyperplasia; Type 2 inflammation; itch	11% homology to human AD	Wang G, Clin Exp Allergy 2007
HDM extract	NC/Nga	Barrier dysfunction, antigen-specific and non-specific type 2 responses	Epidermal thickening; Type 2 inflammation; itch		Matsuoka H, Allergy 2003
HDM + SEB	C57BL/6	Activation of T cells with SEB-specific repertoire; mast cell activation is indispensable	Epidermal thickening; Type 1, type 17/22, type 2 inflammation	Some overlap in global gene expression profile changes	Kawakami Y, Allergol Int 2007
Cytokine					
IL-23 injection	CCR2 ^{-/-}	Induction of IL-22, TSLP and IL-4	Acanthosis; hyperkeratosis; epidermal thickening; Type 1, type 17/22, type 2 inflammation	37% homology to human AD	Bromley SK, PLoS One 2013
Chemicals and others					
Vitamin D or its analog, MC903 (calcipotriol)	C57BL/6J	TSLP induction and basophil activation	Epidermal hyperplasia; Type 2 inflammation; itch		Li M, Proc Natl Acad Sci USA 2006
Particulate matter (PM 2.5)	Hairless mice (hr/hr)	PAHs, major components of PM2.5, induce TNF- α production via activation of AHRs, leading to barrier	Th1/Th2 inflammation; itch		Kim BE, JCI Insight 2021

dysfunction

AD, atopic dermatitis; DNCB, dinitrochlorobenzene; DNFB, dinitrofluorobenzene; TNCB, trinitrochlorobenzene; CMIT/MIT, chloromethylisothiazolinone/methylisothiazolinone; OVA, ovalbumin; HDM, house dust mite; SEB, staphylococcal enterotoxin B; CCR2, C-C chemokine receptor 2; PAHs, polycyclic aromatic hydrocarbons; AHRs, aryl hydrocarbon receptors; TSLP, thymic stromal lymphopoietin.

*Transcriptome analyses were performed in References 5-9.