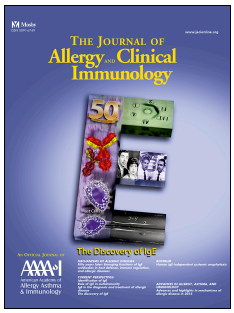
Accepted Manuscript



Interplay Between the Skin Barrier and Immune Cells in Patients with Atopic Dermatitis Unraveled by Means of Mathematical Modeling

David Bending, PhD, Masahiro Ono, MD, PhD

PII: S0091-6749(17)30565-1

DOI: 10.1016/j.jaci.2017.03.015

Reference: YMAI 12727

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

Received Date: 23 January 2017

Revised Date: 7 March 2017

Accepted Date: 27 March 2017

Please cite this article as: Bending D, Ono M, Interplay Between the Skin Barrier and Immune Cells in Patients with Atopic Dermatitis Unraveled by Means of Mathematical Modeling, *Journal of Allergy and Clinical Immunology* (2017), doi: 10.1016/j.jaci.2017.03.015.

Editorial, JACI

Interplay between skin barrier and immune cells in atopic dermatitis unravelled by mathematical modelling

David Bending, PhD[1] & Masahiro Ono, MD PhD[1§]

Department of Life Sciences, Faculty of Natural Sciences, Imperial College London, Sir Alexander Fleming Building, Imperial College Road, London, SW7 2AZ, United Kingdom

§ Corresponding author: Masahiro Ono, MD PhD, Department of Life Sciences, Sir Alexander Fleming Building, Imperial College Road, South Kensington, London, SW7 2AZ, United Kingdom. E-mail address: m.ono@imperial.ac.uk

Atopic dermatitis (AD) is a chronic inflammatory skin disease, involving skin barrier impairment [1] and immune system dysregulation[2]. The skin barrier is integral for the protection from microbe and allergen infiltration. It is physically in the outermost layer of the epidermis, and comprises terminally differentiated, denucleated keratinocytes, which structure is dependent on keratin and filaggrins (FLG), and extracellular matrix containing lipids, structural proteins, and serine proteases kallikreins (KLKs)[1]. Dysfunctions of these components can result in barrier defects[1], as typically found in loss-of-function mutations of the *FLG* gene[2]. In addition, the barrier function is regulated by the microbiota. For example, *Staphylococcus aureus* activates KLKs, which degrade FLG proteins[3]. Barrier disruption increases skin permeability to allergens, leading to innate immune cell activation (e.g. dendritic cells (DCs) and Langerhans cells), and subsequent priming of T-cells. T-cells play central roles, differentiating into T-helper type 2 (Th2) cells, which further disrupt barrier function[4]. Barrier disruption also directly activates keratinocytes through KLKs, which activate protease-activated receptor (PAR) 2 on keratinocytes[1], leading to the secretion of the cytokines IL-25, IL-33, and thymic stromal lymphopoietin (TSLP)[2], which promote Th2 differentiation[2].

AD represents a challenging disease to study mechanistically, given that the interplay of different cellular systems, environmental stressors and genetic variability is highly dynamic and complex. In the study by Domínguez-Hüttinger *et al.*[5], the multidisciplinary group took a new approach to generate and analyse a novel mathematical model of AD, and they investigated the systems mechanisms behind disease pathogenesis. Here we discuss their findings, critically analyse the paper, and investigate its biological and medical significance.

It is a critical issue in systems studies to determine the key components to be included in the model, which depends heavily on the aims of the study[6]. Here the authors investigated a minimal "skeletal" structure of the whole skin system, including barrier, keratinocytes, DCs and T-cells, aiming to understand how the activities of these different players are regulated in normal conditions, and dysregulated in AD. Based on a literature review, the authors chose barrier dysfunction, keratinocyte activation, and Th2 differentiation as the critical players to be analysed in their model, while also considering several mechanisms such as microbial invasion and antimicrobial peptides. Since microbiota were not investigated, the study is essentially about the interplay between two cellular systems: keratinocytes and immune cells.

Here we give an overview of the new mathematical model of AD by Domínguez-Hüttinger *et al.*[5]. Skin barrier defects, which can be induced by environmental stressors, may result in increased microbial invasion (designated as "*infiltrated pathogens*" by the authors, although these presumably also include commensal bacteria) of the epidermal layer, further damaging the barrier integrity. Meanwhile, invading microbes convey barrier invasion through activation of keratinocytes via pattern-recognition receptors (PRRs) and indirectly PAR2 as well through KLKs. Microbes must be cleared by the activity of keratinocytes and immune cells, in order to return keratinocytes to the normal state. This mechanism is designated as a *reversible switch* (the authors call it *innate immune receptor activity*, however the mechanism is principally focused on *PRR activity in keratinocytes*). Meanwhile, stimulated keratinocytes activate DCs presumably by cytokines, while DCs act as a gatekeeper for the T-cell system: they retain and integrate the signals from keratinocytes, and only when the signals reach a certain threshold, DCs are able to activate T-cells, which the authors model as an irreversible differentiation of T-cells into allergy-causing Th2 cells. This is defined as an *irreversible switch* (**Fig. 1**). The two key switches in the keratinocyte system and the immune system were thus assumed to produce simple binary response (i.e. either ON or OFF) in their model.