

Journal Pre-proof

Uncovering non-canonical autophagy in dermal dendritic cells in contact hypersensitivity: A key mechanism of immune tolerance

Kazunari Sugita, MD, PhD

PII: S0091-6749(20)30412-7

DOI: <https://doi.org/10.1016/j.jaci.2020.03.009>

Reference: YMAI 14464

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

Received Date: 12 February 2020

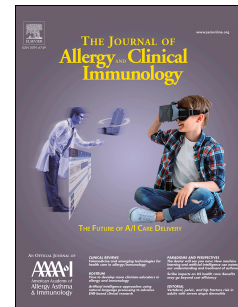
Revised Date: 16 March 2020

Accepted Date: 19 March 2020

Please cite this article as: Sugita K, Uncovering non-canonical autophagy in dermal dendritic cells in contact hypersensitivity: A key mechanism of immune tolerance, *Journal of Allergy and Clinical Immunology* (2020), doi: <https://doi.org/10.1016/j.jaci.2020.03.009>.

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.

© 2020 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology.



**Uncovering non-canonical autophagy in dermal dendritic cells in contact
hypersensitivity: A key mechanism of immune tolerance**

Kazunari Sugita, MD, PhD

Division of Dermatology, Department of Medicine of Sensory and Motor Organs, Tottori
University Faculty of Medicine, Yonago, Japan

Corresponding author: Kazunari Sugita, MD, PhD

Division of Dermatology, Department of Medicine of Sensory and Motor Organs, Tottori
University Faculty of Medicine, Yonago 683-8504, Japan

Phone: +81 (0) 859 38 6597

Fax: + 81 (0) 859 38 6599

E-mail: sugita@tottori-u.ac.jp

Competing interests

The authors declare no competing financial interests.

Key words: immune tolerance, UVB, autophagy, contact hypersensitivity, dendritic cells,
Rubicon

Chronic inflammatory diseases are a public health problem worldwide and include infectious diseases, allergies, metabolic diseases, cardiovascular diseases, and autoimmune disorders. Inflammation is a normal immune response for protection against environmental agents and tissue damage. Activation of immune responses due to the presence of allergens, microbes, or damaged cells leads to the attraction of immune cells to the affected area and triggers the release of cytokines and the formation of complex immune networks. The mechanisms of immune tolerance underlying allergic diseases have been investigated and have been found to be tightly regulated. The functions of regulatory T cells and regulatory B cells are widely accepted as an important mechanism of immune regulation. Failure to eliminate the causative agents or to suppress inflammation can lead to chronicity of diseases, and this is true not only for atopic diseases but also for autoimmune diseases, resulting in tissue dysfunction. In addition, dysregulation of tissue repair promotes the development of pathological fibrosis and ultimately leads to organ failure and death.¹ Therefore, resolution of inflammation is necessary for the recovery phase of tissue damage that contributes to the clearance of dying cells as well as activated inflammatory cells. Better understanding of the control of inappropriate inflammatory responses will help the identification of potential therapeutic targets.

Autophagy is a conserved, self-degradative process in the lysosome that serves a fundamental role in maintaining cellular homeostasis. Under starvation conditions, wherein there is a shortage of nutrient supply, recycling of cellular components is essential for protein synthesis and obtaining an energy source. In addition, autophagy plays a role in the elimination of harmful or excessive proteins.² The study of autophagy has provided us with great advances over the past decade through the understanding of cellular and organellar metabolism. We now know that autophagy, controlled by autophagy-related (ATG) genes, plays a significant role not only in cellular homeostasis but also in human diseases, including neurodegeneration, cancer, and immune diseases. In contrast to canonical autophagy, the pathways involved in

non-canonical autophagy have been recently characterized and require only some of the core ATG proteins that result in the formation of functional autophagosomes.³ LC3-associated phagocytosis (LAP), a type of non-canonical autophagy, is a critical regulator of immunotolerance and suggests a link between the clearance of dying cells and inflammation. In this issue of JACI, Sil and colleagues explore whether LAP, which requires the activity of Rubicon (RUBCN), is distinct from the canonical pathway and mediates the immunosuppressive effect of dying cells by demonstrating UVB-induced immunosuppression in a murine model of contact hypersensitivity (CHS).⁴ They generated *Rubcn*^{-/-} mice as a model of LAP-deficiency and explored the molecular and cellular mechanisms that regulate the immunosuppressive response to dying cells. They found that RUBCN is an important mediator of UVB-induced immune tolerance of CHS. In addition, untreated *Rubcn*^{-/-} mice exhibited decreased expression of inflammatory genes in the basal level compared to control mice, indicating that RUBCN is a negative regulator of autophagy.

Ultraviolet (UV) radiation is an environmental factor that affects human health and plays a pathological role in allergy and autoimmunity. UV exposure can induce immunosuppression leading to skin cancer. UV radiation also influences the immunomodulation of CHS by affecting the skin immune system, which comprises complex immune cells, physical barriers, and various factors. Therefore, the mechanism underlying UV-induced immunotolerance machinery was attributed to Rubicon, a non-canonical autophagy-associated protein, is a fundamental connection between homeostasis and inflammation. The investigators found that *Rubcn*^{-/-} mice exhibited impaired UV-induced immunotolerance in CHS compared to *Rubcn*^{+/+} mice.⁴

For the induction of CHS, antigen presentation and recognition in both skin and draining lymph nodes are necessary for adequate immune responses. Dendritic cells (DCs) prime antigen-specific effector T cells, including cytotoxic CD8⁺ T cells and Th1 cells, and activate T

cells to produce cytokines or chemokines. Dermal DCs (dDCs) are classified into at least two subsets, including CD103⁺ dDCs (conventional DC1) and CD11b⁺ dDCs (conventional DC2).⁵ Importantly, dermal DC2s and IFN- γ producing CD8⁺ T cells abundantly infiltrated target sites in *Rubcn*^{-/-} mice model of CHS pretreated with UV. Additionally, there was a significant increase in the migration of *Rubcn*^{-/-} dermal DC2s with higher antigen presenting capacity in the draining lymph nodes.⁴ However, pre-exposure to UV did not increase the percentage of DC1s in *Rubcn*^{-/-} mice. In this context, enhanced activity of autophagy brought about by Rubicon deficiency in DC2s might contribute to immune cell activation and proliferation and antigen presentation. Impressively, these data are supported by observations made on conditional *Cd11c-Cre*⁺ *Rubcn*^{fllox/fllox} mice to clearly define how DC2-specific non-canonical autophagy is involved in the suppression of skin inflammation. Since DC2s are required for the generation of Th2 immune responses and can induce Th1 and Tc1 responses in CHS in the absence of DC1 and Langerhans cells, there may be other factors that regulate Th1 and Tc1 cells, and dDCs play redundant roles in cutaneous immune responses.⁶

In their original article, Sil et al. explore whether their findings from animal models are similar to those from healthy human subjects. They found that RUBCN was preferentially expressed in the human dDCs and LCs. In another experiment using a murine model of CHS, an adoptive transfer of DCs from the UV-irradiated mice into naïve recipients reduced the CHS response.⁷ In humans, a lack of sufficient UV exposure may contribute to an increased incidence of atopic diseases.⁸ However, UV irradiation can also have detrimental effects on human health with increased risks of skin cancers, including malignant melanoma and non-melanoma skin cancer.⁹ Collectively, despite both the beneficial and harmful biological implications on human skin, as well as the fact that not all results obtained from murine models can be translated to complex human diseases, it is likely that dDCs in non-canonical autophagy play a role in CHS. A recent study showed that IL-25 induces dDCs to produce IL-1 β , thereby

contributing to CHS.¹⁰ The non-canonical function of autophagy, as well as the ability of dDCs for immune activation and T cell differentiation, support the idea that changes in the autophagy-related protein RUBCN can influence skin pathologies that depend on non-canonical autophagic pathways.

As summarized above, the rapidly developing field of non-canonical autophagy is now being recognized, with interest growing toward immune tolerance. Understanding the role of non-canonical autophagy and the proteins involved in this process may reveal crucial information about the potential use of non-canonical autophagy as a therapeutic target, as well as about disease pathology.

References

1. Eming SA, Wynn TA, Martin P. Inflammation and metabolism in tissue repair and regeneration. *Science* 2017; 356:1026-30.
2. Ohsumi Y. Historical landmarks of autophagy research. *Cell Res* 2014; 24:9-23.
3. Scarlatti F, Maffei R, Beau I, Ghidoni R, Codogno P. Non-canonical autophagy: an exception or an underestimated form of autophagy? *Autophagy* 2008; 4:1083-5.
4. Sil P, Suwanpradid J, Muse G, Gruzdev A, Liu L, Corcoran DL, et al. Non-canonical autophagy in dermal dendritic cells mediates immunosuppressive effects of UV exposure. *J Allergy Clin Immunol* 2019.
5. Kabashima K, Honda T, Ginhoux F, Egawa G. The immunological anatomy of the skin. *Nat Rev Immunol* 2019; 19:19-30.
6. Kumamoto Y, Linehan M, Weinstein JS, Laidlaw BJ, Craft JE, Iwasaki A. CD301b(+) dermal dendritic cells drive T helper 2 cell-mediated immunity. *Immunity* 2013; 39:733-43.
7. Ng RL, Scott NM, Strickland DH, Gorman S, Grimbaldston MA, Norval M, et al. Altered immunity and dendritic cell activity in the periphery of mice after long-term engraftment with bone marrow from ultraviolet-irradiated mice. *J Immunol* 2013; 190:5471-84.
8. Thyssen JP, Zirwas MJ, Elias PM. Potential role of reduced environmental UV exposure as a driver of the current epidemic of atopic dermatitis. *J Allergy Clin Immunol* 2015; 136:1163-9.
9. Kim Y, He YY. Ultraviolet radiation-induced non-melanoma skin cancer: Regulation of DNA damage repair and inflammation. *Genes Dis* 2014; 1:188-98.
10. Suto H, Nambu A, Morita H, Yamaguchi S, Numata T, Yoshizaki T, et al. IL-25 enhances TH17 cell-mediated contact dermatitis by promoting IL-1 β production by dermal dendritic cells. *J Allergy Clin Immunol* 2018; 142:1500-9 e10.

139 **Figure legends**

140 **FIG 1. Rubicon is involved in UVB-irradiated cutaneous immune tolerance.** Rubicon
141 mediates LC3-associated phagocytosis (LAP), and Rubicon deficiency increases the
142 infiltration of CD8⁺ T cells and dermal dendritic cells (dDC2), which have antigen-presenting
143 capabilities.

144

