【Grant-in-Aid for Scientific Research (S)】

Biological Sciences (Medicine, Dentistry, and Pharmacy)

Title of Project : Understanding the Mechanism How the Skin Responses to External Stimuli

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Research Project Number : 15H05790 Researcher Number : 00362484
Research Area : Clinical Medicine, Dermatology
Keyword : Dermatology, Immunology, Allergy

【Purpose and Background of the Research】

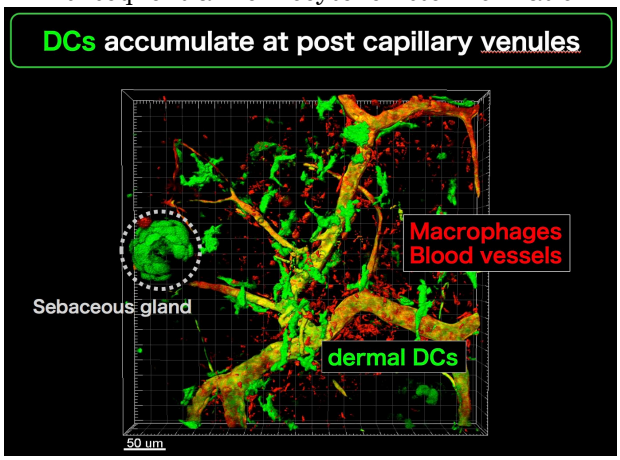
In the 1980s, Streilein et al. introduced the term "skin-associated lymphoid tissue (SALT)" based on observations that revealed the existence of T cells and dendritic cells (DCs) in the skin and that T cells are activated in the skin draining lymph nodes. However, it remains unclear whether and how T cells are activated in the skin in the viewpoint of SALT. Therefore, SALT has remained conceptual.

Through the detailed examination of a skin specimen obtained from a patient with contact dermatitis, we discovered that dermal DCs (dDCs) form clusters with T cells just beneath the epidermal spongiosis. This observation suggests that dDC clustering plays a role in the elicitation phase of contact dermatitis.

In this context, we hypothesized that dDC clustering in contact dermatitis might be essential for memory T cell activation in the skin to elicit their acquired immune functions in the perspective of SALT.

Using two-photon microscopy, we discovered that dDCs are attracted by perivascular macrophages at the post-capillary venules in the elicitation phase of contact hypersensitivity (CHS), a murine model of contact dermatitis (**Figure**).

This sequential leukocyte cluster formation is essential for efficient activation of memory T cells; now it can be assumed as a lymphoid tissue. The structure does not exist in the steady state, but emerges in response to local inflammatory conditions. Herein, we propose this structure to be termed as "inducible SALT (iSALT)". However, the role of iSALT remains to be clarified.



【Research Methods】

Firstly, we will examine whether iSALT enables naïve T cell priming or B cell class switching and antibody production in situ. Secondly, the functional and pathological differences between iSALT and other skin lymphoid structures will be determined. Thirdly, we will investigate whether iSALT or iSALT-like structures are established in other settings, such as atopic dermatitis and psoriasis.

【Expected Research Achievements and Scientific Significance】

To understand the role of iSALT will reveal the mechanism how the skin responds to the external stimuli, which will lead to the understanding of skin immune diseases. In addition, controlling the functions of iSALT will improve the efficacy of cancer vaccination via the skin.

【Publications Relevant to the Project】

・Natsuaki Y, Egawa G, Nakamizo S, Ono S, Hanakawa S, Okada T, *et al.* Perivascular leukocyte clusters are essential for efficient activation of effector T cells in the skin. *Nature Immunology* 2014, **15**(11): 1064-1069.
・Otsuka A, Nakajima S, Kubo M, Egawa G, Honda T, Kitoh A, *et al.* Basophils are required for the induction of Th2 immunity to haptens and peptide antigens. *Nature Communications* 2013, **4**: 1739.

【Term of Project】 FY2015-2019

【Budget Allocation】 147,000 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.kuhp.kyoto-u.ac.jp/~skin/index.html