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

Broad Section I

Title of Project： Understanding the mechanism of the cutaneous immune-diversity and its relationship with other organs

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Research Project Number: 20H05697 Researcher Number：00362484
Keyword：Dermatology, Immunology, Allergy

【Purpose and Background of the Research】

Elucidation of the mechanism of skin immune response to external invasion leads not only to the understanding of the pathogenic mechanism of skin diseases such as atopic dermatitis, but also to the understanding of the immune response in other organs. The applicant found that lymphoid tissue construction (SALT) was induced in the skin in response to external invasion, and named it iSALT. Currently, elucidation of the physiological role of iSALT in the skin and systemic immune response is expected.

The aim of our study is: (1) Elucidate the induction mechanism of iSALT and the role of iSALT in inducing diversity of skin immune responses. (2) Understand the effect of iSALT on systemic immunity. (3) Figure out the pathophysiology of inflammatory skin diseases and the role of skin as the starting point of systemic immune control by applying the findings obtained in mice to human research.

【Research Methods】

So far, the applicant has found iSALT in the Th1 type immune response (contact dermatitis model), and its formation requires perivascular macrophages and CXCL2 produced from them, and it occurs in the posterior capillary vein region. We have already elucidated a part of the mechanism of iSALT formation, such as the induction of high endothelial venules (HEV) in the posterior capillary vein region. However, there are still many unclear points such as which subset of perivascular macrophages are involved, their activation mechanism, the involvement of forming factors other than CXCL2, and the induction mechanism of HEV. In particular, HEV is a structure that is not found in steady-state skin, and may be a tissue infiltration pathway for naive T cells, central memory T cells, etc., similar to its function in lymph nodes.

Therefore, first, we separate perivascular macrophages and vascular endothelial cells from the steady state and contact dermatitis and analyze the expression profile using the single-cell RNA sequencing method. Then we elucidate the subsets and functions of these cell types in the process of iSALT formation. Based on the results obtained there, we will identify the factors for perivascular macrophage activation, iSALT formation, and HEV formation. Then, we will try to identify new iSALT and HEV-forming factors by using specific inhibitors and conditional knockout mice of those factors. Furthermore, cells producing various morphogenetic factors will be identified using candidate cell-deficient mice to elucidate the whole picture of the iSALT formation mechanism.

【Expected Research Achievements and Scientific Significance】

In this study, we will take advantage of iSALT, which is a new secondary lymphoid construct that we have independently discovered, as a starting point to elucidate the mechanism of diversity of acquired skin immune responses and to cut into the systemic allergy progression mechanism from the skin, such as allergic march. Furthermore, we will elucidate the spatiotemporal dynamism of cell dynamics and the mechanism of inducing various immune responses by organically combining cutting-edge technologies such as skin bioimaging technology, single-cell RNA sequencing method, and mass cytometry analysis method.

If the skin immunity and systemic immune control mechanism from the skin is clarified by this study, it is expected that skin immune control will lead to control of not only skin diseases but also immune diseases in other organs.

【Publications Relevant to the Project】

- Kabashima K Honda T, Ginhoux F, Egawa G. 2019. The immunological anatomy of the skin. ***Nat Rev Immunol*** 19: 19-30
- Dainichi T, Kitoh A, Otsuka A, Nakajima S, Nomura T, Kaplan DH, Kabashima K. 2018. The epithelial immune microenvironment (EIME) in atopic dermatitis and psoriasis. ***Nat Immunol*** 19: 1286-98

【Term of Project】

FY2020-2024

【Budget Allocation】

151,000 Thousand Yen

【Homepage Address and Other Contact Information】

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