Elucidation and Application of Local Immune Regulation Based on Inducible Skin-Associated Lymphoid Tissue (iSALT)

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Purpose and Background of the Research

● Outline of the Research

The skin is a frontline barrier organ that is most exposed to environmental influences. However, the detailed mechanisms underlying these immune responses remain largely unexplored. Recently, the research team discovered that exposure to external antigens induces the formation of inducible Skin-Associated Lymphoid Tissue (iSALT), demonstrating that the skin can locally initiate adaptive immune responses. This research aims to elucidate the mechanisms of iSALT formation, its structural characteristics, immune cell dynamics, and functional significance, thereby establishing a foundational technology for immune modulation.
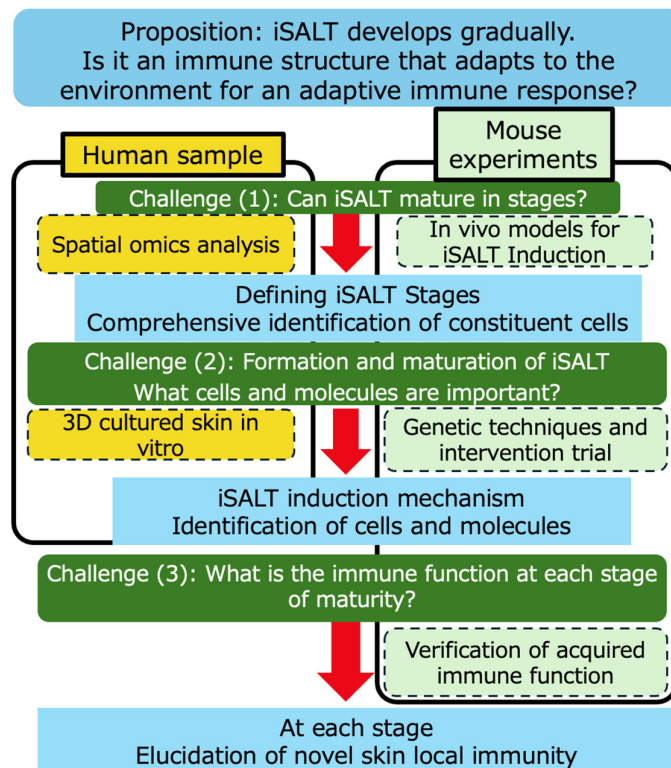
● Significance and Importance of This Research
- Establishing a novel paradigm for immune regulation within the skin.
- Potential for systemic immune modulation through skin-targeted immune control.

● Overall Research Concept Diagram

● Research Methods
- Induction and analysis of iSALT using 3D bioprinting and human skin organoids.
- Real-time visualization of iSALT dynamics through skin intravital imaging technology.
- Single-cell RNA sequencing and spatial transcriptomics to elucidate cellular and molecular mechanisms.
- Functional manipulation of iSALT-mediated immune responses to understand their roles in disease pathogenesis.
- Comparative studies between human and mouse skin samples to identify species-specific characteristics of iSALT.

Proposition: iSALT develops gradually. Is it an immune structure that adapts to the environment for an adaptive immune response?

Human sample / Mouse experiments

Challenge (1): Can iSALT mature in stages?

Spatial omics analysis / In vivo models for iSALT Induction

Defining iSALT Stages Comprehensive identification of constituent cells

Challenge (2): Formation and maturation of iSALT What cells and molecules are important?

3D cultured skin in vitro / Genetic techniques and intervention trial

iSALT induction mechanism Identification of cells and molecules

Challenge (3): What is the immune function at each stage of maturity?

Verification of acquired immune function

At each stage Elucidation of novel skin local immunity

● Expected Research Achievements

This research aims to clarify the mechanisms of iSALT formation and define the full scope of local immune regulation within the skin. The focus is on understanding how iSALT functions as a site for adaptive immune induction and identifying key immune cells involved in this process.
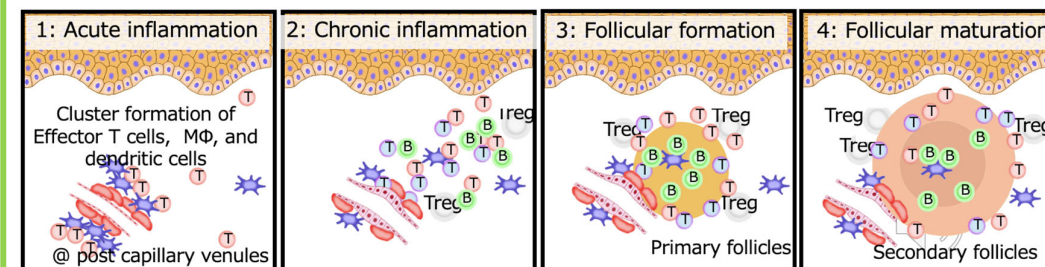
● Major Research Objectives
1. Establish a staging classification system for iSALT based on its developmental phases (figure below).
2. Identify the cellular and molecular mechanisms involved in iSALT formation and maturation.
3. Investigate the immune-inducing functions of iSALT and its potential applications in inflammatory skin diseases and cancer immunotherapy.
4. Develop a foundation for novel therapeutic strategies to suppress inflammation and allergic reactions through local immune regulation.
5. Conduct human skin sample analyses to determine the involvement of iSALT in actual diseases.
6. Establish a foundation for drug development targeting iSALT and explore its therapeutic applications.
7. Investigate the potential for applying iSALT-based immune regulation to other barrier organs (e.g., gut, respiratory tract).
8. Analyze how environmental factors (UV radiation, air pollution, microbiota) influence iSALT formation and function.

● Social Significance and Applications
- Development of novel treatment strategies for immune-mediated and inflammatory skin diseases.
- Application of skin-targeted immune regulation for vaccine development and cancer immunotherapy.
- Exploration of systemic immune modulation via skin-targeted interventions.
- Identification of new therapeutic targets for inflammatory and autoimmune diseases through the study of local immunity.
- Elucidation of iSALT abnormalities in disease pathogenesis (e.g., atopic dermatitis, psoriasis, autoimmune diseases, skin cancer).
- Contribution to precision medicine through advancements in skin immunology.

Verification of the maturation process of iSALT and proposal of a new stage classification

1: Acute inflammation — Cluster formation of Effector T cells, MΦ, and dendritic cells @ post capillary venules

2: Chronic inflammation

3: Follicular formation — Primary follicles

4: Follicular maturation — Secondary follicles