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Abstract of the dissertation

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The title of the doctoral dissertation

Study on the therapeutic strategies of psoriasis targeting novel regulatory pathways in γδT cells

（γδT 細胞の新規制御経路とこれを標的とした乾癬の治療戦略に関する研究）

< abstract >

Psoriasis is a chronic inflammatory skin disease characterized by epidermal hyperproliferation and cellular infiltration. Previous studies have shown that psoriasis development depends on proinflammatory cytokines, such as interleukin (IL)-23 and IL-17. IL-23 produced by innate immune cells, such as dendritic cells and macrophages, in psoriatic lesions activates a subset of helper T cells to release IL-17, promoting neutrophil recruitment and epidermal keratinocyte proliferation. However, recent studies have revealed that innate γδT cells are involved in psoriasis pathogenesis as the primary source of IL-17. The purpose of the present study was to unravel the regulatory mechanisms of IL-17-producing γδT (γδT17) cells and establish the basis of psoriasis therapies targeting γδT17 cells.

In Chapter 1, γδT17 cell regulation through nuclear receptors, REV-ERBs, and the therapeutic strategy of psoriasis targeting this regulatory pathway were shown. REV-ERBsare ligand-dependent transcription factors and generally known to regulate circadian rhythm. Although a recent study revealed that REV-ERBs suppress the function of IL-17-producing helper T cells, the role of REV-ERBs in γδT17 cells regulation had been unclear. γδT17 cells were significantly increased in the secondary lymphoid organs of REV-ERB-deficient mice. IL-17 production by γδT cells was suppressed by short-term treatment with a synthetic REV-ERB agonist, SR9009, both *in vitro* and *in vivo*. Furthermore, topical application of SR9009 to the skin reduced the inflammatory symptoms of imiquimod (IMQ)-induced psoriasiform dermatitis in mice. These results demonstrate

that γδT17 cells associated with psoriasis development are regulated by REV-ERBs and that modulation of REV-ERB activity in γδT17 cells using synthetic ligands may become a novel therapeutic approach for psoriasis.

Next in Chapter 2, the role of an inflammatory cytokine called tumor necrosis factor-like ligand 1A (TL1A) and its receptor, death receptor 3 (DR3), in γδT17 cell activation and its relevance with psoriasis pathogenesis were examined. Neutralization of TL1A by anti-TL1A antibody injection inhibited the cytokines production by γδT17 cells in IMQ-treated mouse skin. DR3 was constitutively expressed in splenic and dermal γδT17 cells. TL1A induced cytokine production by splenic γδT17 cells synergistically with IL-23. TL1A exacerbated the dermal symptoms of the murine psoriasis model generated by intradermal IL-23 injection in wild-type but not in γδT cell-deficient mice. These findings suggest a novel regulatory mechanism of γδT17 cells through TL1A and DR3 and its involvement in psoriasis pathogenesis as a possible therapeutic target.

In conclusion, the present study on the novel regulatory mechanism of γδT17 cells may provide insights into psoriasis pathogenesis and therapeutics.