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学位論文題目	Skin resident memory CD8 T cells with a potential of producing IL-17A are accumulated in disease-naïve non-lesional sites of psoriasis (乾癬非病変部に IL-17A 産生皮膚 resident memory CD8 T 細胞が蓄積される)
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論文の内容の要旨
Abstract of thesis

In this doctoral dissertation, VO DUONG NGUYEN SA describes the role of skin resident memory CD8 T cells producing IL17 in the disease naïve skin lesions of psoriasis patients.　The summary is as follows:

(**Purpose**)

Despite a variety of descriptions regarding the role of IL-17A-producing CD4 T cells in the pathogenesis of psoriasis, many studies have shown the existence of CD8 T cells especially in epidermis of psoriasis skin. Infiltration of IL-17A-producing CD8 T cells has also been demonstrated both in lesional and resolved sites of psoriasis. From clinical aspects, psoriatic lesion is well-demarcated and recurs in the same sites. These phenomena lead to the hypothesis that disease formation is mediated by skin-sessile cells. Recent reports confirmed that human skin is populated by non-recirculating resident memory T cells (T_{RM}). However, the role of T_{RM} in psoriasis is not fully understood yet. Therefore, this study aimed to elucidate profiles of T_{RM} from lesional and disease-naïve non-lesional (DN) sites of psoriasis and investigate the involvement of T_{RM} in psoriatic disease development.

(**Material and method**)

Skin specimens were collected from lesional and DN sites of mild plaque-type psoriasis patients (n=17) with < 10 psoriasis area and severity index (PASI) score. Normal skin specimens were also taken from surgical discards (n=15). Then, T cells were isolated from these specimens by two weeks of explant culture. Profiles of T_{RM} were analyzed and compared by flow cytometry among three groups. Skin specimens were also processed for immunohistological evaluation.

(**Results**)

Psoriatic lesional and DN sites showed a slight tendency of CD8 T-cell enrichment compared to normal skin though the difference did not reach significance. Interestingly, among the CD8 T cell population, $CD103^+$ T_{RM} were prevalent in both lesional and DN sites while the percentage of CD103+ T_{RM} in CD4 fraction was lower in lesional sites of psoriatic patients compared to normal. $CD103^+$ CD8 T_{RM} were mainly confined in epidermis of both lesional and DN sites by immunofluorescence analysis, suggesting that these T cells reflect epidermal T_{RM}. CD8 T cells in psoriatic skin included more IL-17A-producing cells compared to those in normal skin. In CD4 fraction, IL-17A production was comparable among three groups. It was of note that CD4 T cells from normal skin also produced a considerable amount of IL-17A, in contrast to CD8 T cells from normal skin. Among CD8 T cells, $CD103^+$CD8 T_{RM} not only in lesional but also in DN sites showed stronger potential of producing IL-17A compared to those from normal skin. Although $CD103^-$CD8 T cells in psoriatic skin showed increased IL-17A production profiles, $CD103^+$CD8 T_{RM} population was a significantly bigger source of IL-17A. In these mild psoriasis patients, the ratio of IL-17A-producing cells in CD8 T cells from psoriatic lesional skin did not correlate with clinical indexes such as disease duration, PASI score or the existence of articular symptom. However, relative production levels of IL-17A, which is the ratio of % IL-17A-producing cells to % IFNγ-producing cells, in CD8 T cells from DN sites correlated with disease duration ($p < 0.005$). Among CD8 T cells, this relative IL-17A production levels in $CD103^+$CD8 T_{RM}, not in $CD103^-$CD8 T cells, correlated with disease duration.

(**Discussion**)

In this study, the authorfound a dominance of $CD103^+$CD8 T_{RM} cells both in lesional and DN sites, which have never experienced disease formation, of psoriatic patients. Thus, normal-looking sites in psoriasis patients already have skewed distribution of T cells before disease manifestation. Previous reports showed both active and resolved psoriatic lesions contain CD4 and CD8 T cells with a potential of producing IL-17A. Keratinocytes of DN sites were also reported to upregulate CCL20 expression, which recruit $CCR6^+$ IL-17A-producing T cells. The author also demonstrates the IL-17A-generating phenotype of CD8 T cells in psoriatic DN sites. Meanwhile, in CD4 fraction, IL-17A-producing potential was comparable among lesion, DN and normal skin. It is assumed that CD8 T cells are more strongly involved in preparation and initiation of disease formation. In comparison with $CD103^-$ CD8 T cells, $CD103^+$ CD8 T_{RM} demonstrated a significantly stronger ability of IL-17A production in both lesional and DN sites. These results may implicate a contribution of $CD103^+$ CD8 T_{RM} to the pathogenesis of lesion formation in DN sites. Furthermore, positive relation between the production ratio of IL-17A to IFNγ in $CD103^+$ CD8 T_{RM} fraction in DN with disease duration implies the accumulation of IL-17-generating T_{RM} in DN according to chronic disease activity.

(**Conclusion**)

The author demonstrates that IL-17A-producing CD8 T_{RM} are accumulated in epidermis of psoriatic DN sites according to disease course. Her results implicate that IL-17A-producing $CD103^+$ CD8 T_{RM} may be considered not

only as an index for baseline disease activity but also as a predictor of suited treatment intensity. In addition, IL-17A-producing CD8 T_{RM} may also be an attractive treatment target for preventing disease progress. On the other hand, since these DN sites do not immediately develop psoriatic lesions even in the presence of IL-17A-producing CD8 T_{RM}, finding other factors eliciting disease formation cascade will be of great importance in the treatment strategy of psoriasis.

審査の結果の要旨
Abstract of assessment result

（批評　General Comments）

This thesis claims that in the disease process of psoriasis, the resident memory CD8 T cells producing IL17 responsible for the pathology are already located in the disease naïve skin lesion. This novel finding will contribute to understanding of psoriasis pathology, its early diagnosis and future new therapeutics.

（最終試験の結果　Assessment）

The final examination committee conducted a meeting as a final examination on July 4, 2019. The applicant provided an overview of dissertation, addressed questions and comments raised during Q&A session. All of the committee members reached a final decision that the applicant has passed the final examination.

（結論　Conclusion）

The final examination committee approved that the applicant is qualified to be awarded Doctor of Philosophy in Medical Sciences.