PD-1 expression defines epidermal CD8+CD103+ T cells preferentially producing IL-17A and using skewed TCR repertoire in psoriasis

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論文題目
PD-1 expression defines epidermal $CD8^+CD103^+$ T cells preferentially producing IL-17A and using skewed TCR repertoire in psoriasis
(PD-1の発現は、乾癬においてIL-17Aを優先的に産生し、偏ったTCRレパートリーを使用する表皮の $CD8^+CD103^+$ T細胞を規定する)

論文の内容の要旨
[Introduction]
In psoriasis, $CD8^+CD103^+$ memory T cells residing in the epidermis represent an effector population capable of maintaining the condition and driving a recurrence of the disease. Tissue-infiltrating $CD8^+$ T cells expressing PD-1 are regarded as antigen-primed effector cells in others chronic inflammatory diseases. However, the expression and significance of PD-1 on skin-infiltrating $CD8^+$ T cells in human psoriasis is not known.

[Patients and Methods]
Skin samples were obtained from 8 patients with moderate to severe psoriasis vulgaris. Patients with plaque psoriasis were treated with Secukinumab at 300 mg once a week from baseline to week 4 and then every 4 weeks thereafter. Punch skin biopsies were obtained from active lesions, non-lesional skin and resolved skin (the same lesion at week 4 and 24 after treatment). Skin T cells were isolated and expanded ex-vivo. Flow cytometry and multicolor immunofluorescence were used for analyzing skin samples. (Clinical Research Review Board of Hamamatsu University School of Medicine Approval number: 18-215)

[Results]
By analyzing skin-infiltrating T cells from human psoriasis, we found that active psoriatic epidermis contained PD-1 expressing $CD8^+CD103^+$ T cells that correlated with the disease severity and histopathology. $PD\text{-}1^+CD8^+CD103^+$ T cells possessed a canonical psoriasis-specific resident memory phenotype with IL-23R expression and produced IL-17A, whereas $PD\text{-}1^-CD8^+CD103^+$ T cells preferentially produced IFN-γ. The diversity of skin-infiltrating T cells was dominated by $CD4^+$ T cells, while $CD8^+$ T cells, especially $CD8^+CD103^+$T cells, represented an oligoclonal population in active psoriasis. In addition, $PD\text{-}1^+CD8^+CD103^+$T cells used different TCR Vβs from $PD\text{-}1^-CD8^+CD103^+$T cells counterpart. In the early resolved lesion, the composition and functional status of $PD\text{-}1^+CD8^+CD103^+$T cells were markedly altered, while $PD\text{-}1^-CD8^+CD103^+$ T cells population was minimally changed.

[Discussion]

A currently important issue to be elucidated on the pathogenesis of psoriasis is related to skin resident memory T cells (T_{RM}). According to our results, PD-1 expression possibly delineates the phenotypic and functional status of epidermal $CD8^+$ T_{RM} cells that respond to IL-23 and produce IL-17A, while PD-1^- T_{RM} cells are negative for IL-23R and preferentially produce IFN-γ This functional dichotomy of T_{RM} cells is relevant to the enrichment of PD-1^+ epidermal T_{RM} cells, which correlated with the disease activity of psoriasis. Similarly, PD-1^+CD8^+ T_{RM} cells were regarded as major drivers in chronicity and severity of eczema in a murine model of acute contact dermatitis. Upon encounter with the cognate antigen, $CD8^+$ T_{RM} cells become activated and upregulate co-inhibitory molecule PD-1. The results indicate that PD-1^+CD8^+ T cells present in the epidermis are more active than those in the dermis and represent effector cells rather than exhausted cells in psoriasis.

Several putative antigens have been proposed to be autoantigens in psoriasis. We showed that $CD8^+$ T cells, especially $CD8^+$ T_{RM} cells, have less diverse TCR Vβ repertoire than the overall skin-infiltrating T cells and $CD4^+$ T cells. Moreover, we found that TCR Vβ2 usage was significantly more frequent in PD-1^+ T_{RM} cells than PD-1^- counterpart. Importance of this observation is supported by recent identification of putative pathogenic T cell clones possessing a psoriasis-specific TCR sequence and increased usage of TCR Vβ2, Vβ6 and Vβ13 in psoriasis skin.

Since IL-17A blockade does not directly affect Th17/Tc17 cells, the reduction of infiltrating T cells after Secukinumab treatment is thought to be due to the disruption of keratinocyte feed-forward response. However, this does not fully explain the reason why T_{RM} cells proliferating *in situ* and not migrating out of the skin are markedly reduced after therapy. It is tempting to speculate that IL-17A blockade normalizes keratinocyte-derived putative autoantigens, resulting in decreased autoreactive T_{RM} cells activation and survival. Likewise, in this study, we supposed that Secukinumab normalizes the expression of putative psoriasis antigen and perhaps resulting in inhibiting proliferation of $Vβ2^+$ T_{RM} cells.

A question arises as to how the activity of PD-1^+ T_{RM} cells is controlled in the epidermis. PD-L1 expressed on keratinocytes directly downmodulates the excessive immune response induced by epidermal $CD8^+$ T cells. Here, we found that PD-L1 expression was depressed in the epidermis of active psoriasis in line with the previous study. Further studies are need to assess the impact of PD-L1 expression on keratinocytes in relation to the functional status of PD-1^+ T_{RM} cells in the epidermis.

[Conclusion]

In conclusion, the results of this study showed that epidermal PD-$1^+CD8^+CD103^+$ T cells are a functionally distinct subpopulation of epidermal T cells in psoriasis. These cells possess the canonical psoriasis-specific resident memory phenotype with IL-17A production and use skewed TCR Vβs such as Vβ2. This study provides an important

clue for the determination of the pathogenic cells with PD-1 marker. Further investigation on antigen recognition of these epidermal T-cell subsets in psoriasis may provide an answer to the long- standing question of the autoimmune property of psoriasis. Furthermore, elimination of undesired T_{RM} cells from psoriasis skin may be a strategy for an establishment of a novel therapy.