MDR1-expressing T cells accumulate in the resolved skin of psoriatic plaque after treatment with topical corticosteroid but not with anti-IL-17A mAb

Toshiharu Fujiyama[1], Kazuo Kurihra[1], Takatsune Umayahara[1], Taisuke Ito[1], Hideo Hashizume[2], Yoshiki Tokura[1]
[1]Department of Dermatology, Hamamatsu University School of Medicine
[2]Department of Dermatology, Iwata city Hospital.

Background.

Topical corticosteroid is a widely used for treatment of psoriasis. However, its long-term use may bring about resistance to the treatment. We have previously shown that multiple drug resistance 1 (MDR1)-expressing T cells infiltrate in the skin lesions of psoriasis, especially at the skin treated with a corticosteroid. (Figure 1) Corticosteroids are a substrate of MDR1, and possible association of MDR1+ T cells and corticosteroid resistance has been documented in some diseases. Since MDR1+ T cells in psoriatic skin include large number of IL-17A and IL-22-producing cells (Figure 2), they can be associated with corticosteroid resistance. In this study, we sought to clarify whether the blockade of IL-17A by Secukinumab affects MDR1 expression.

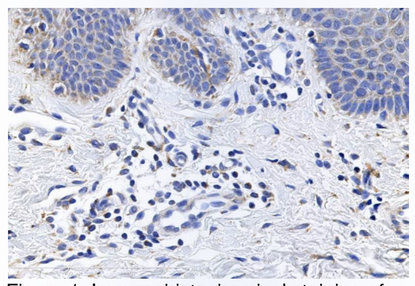


Figure 1. Immunohistochemical staining of MDR-1 using corticosteroid treated psoriatic skin sample. Some lymphocytes are positive for MDR-1.

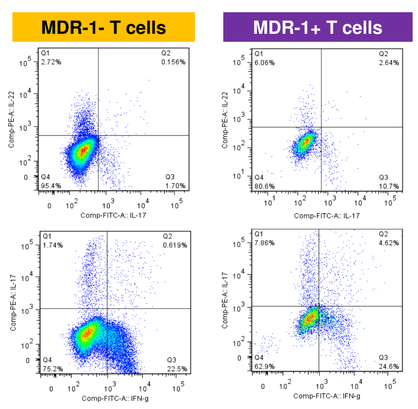


Figure 2. Cytokine profile of MDR-1 +/- T cells.

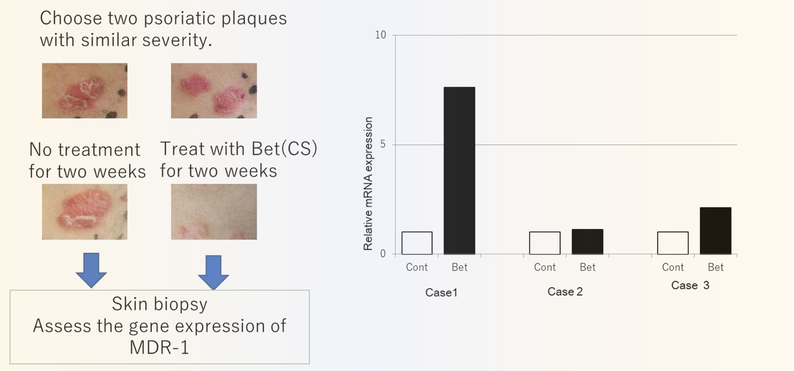


Figure 3. MDR-1 gene expression in corticosteroid treated/non-treated psoriatic skin.
Topical treatment of corticosteroid upregulated the gene expression of MDR-1 in all three cases.

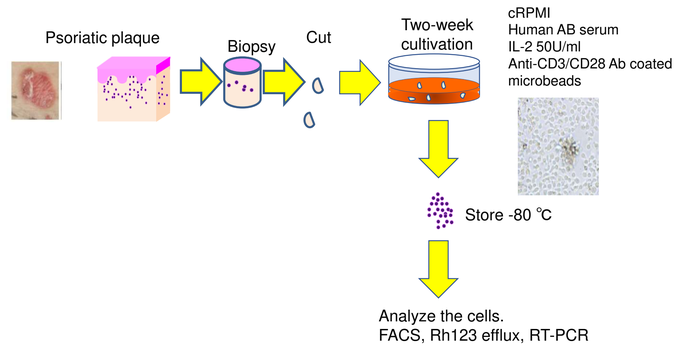
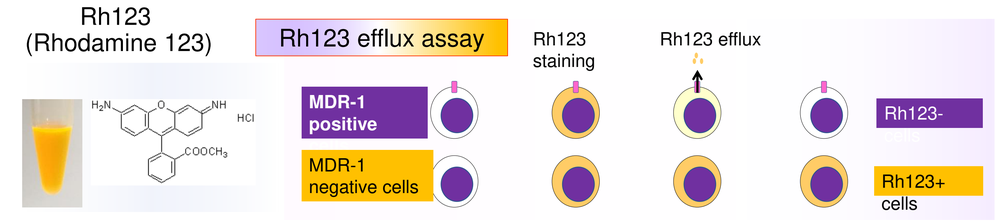


Figure 4. Ex-vivo expansion of skin infiltrating T cells. A half of the 4mm-punch biopsy specimen is cultivated in cRPMI containing IL-2 and anti-CD3/CD28 mAb coated microbeads for 2 weeks.

Patients and method.

We analyzed stocked T cells expanded by IL-2 and anti-CD3/CD28 mAb-coated microbeads from biopsy specimens (Figure 3) taken from the skin of 7 patients treated with topical corticosteroid for two weeks and from the skin of 6 patients treated with Secukinumab for four weeks (Epidermal thickness 0.046±0.017 vs 0.136±0.099). The function of MDR1 was investigated by Rh123 efflux assay.



Rh123 is a non-toxic fluorescent dye λex/em 505/534 nm.
Rh123 is a substrate of MDR1. The function of MDR-1 can be assessed by Rh123 efflux assay.
Figure 5. Rh123 efflux assay and MDR1.

Results.

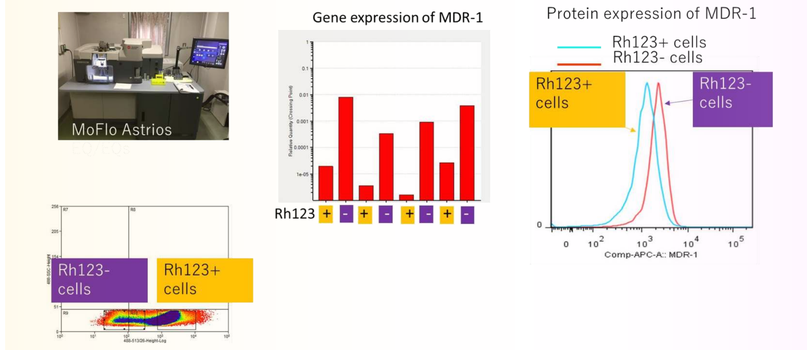


Figure 6. Rh123 negative cells express MDR-1.

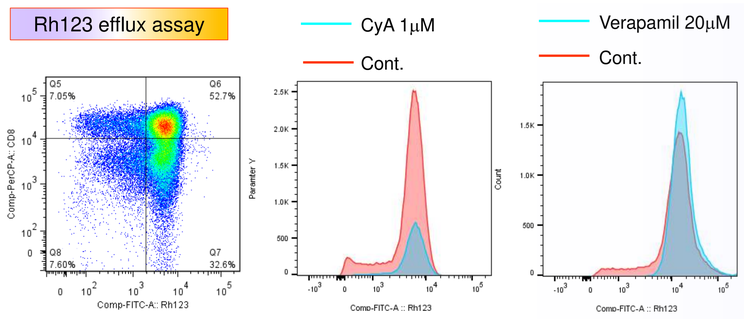


Figure 7. The function of MDR-1 is inhibited by CyA and Verapamil.

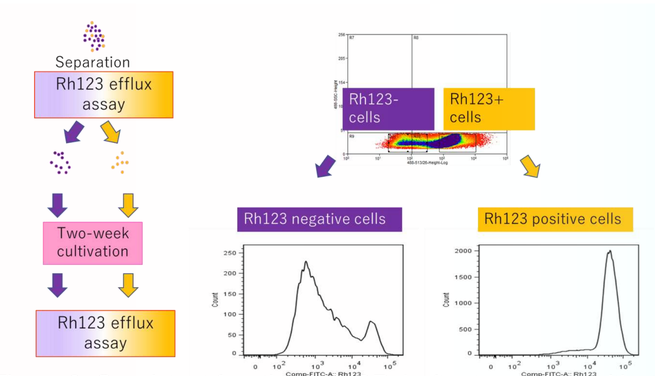


Figure 8. Consistent function of MDR-1 after two-week cultivation.

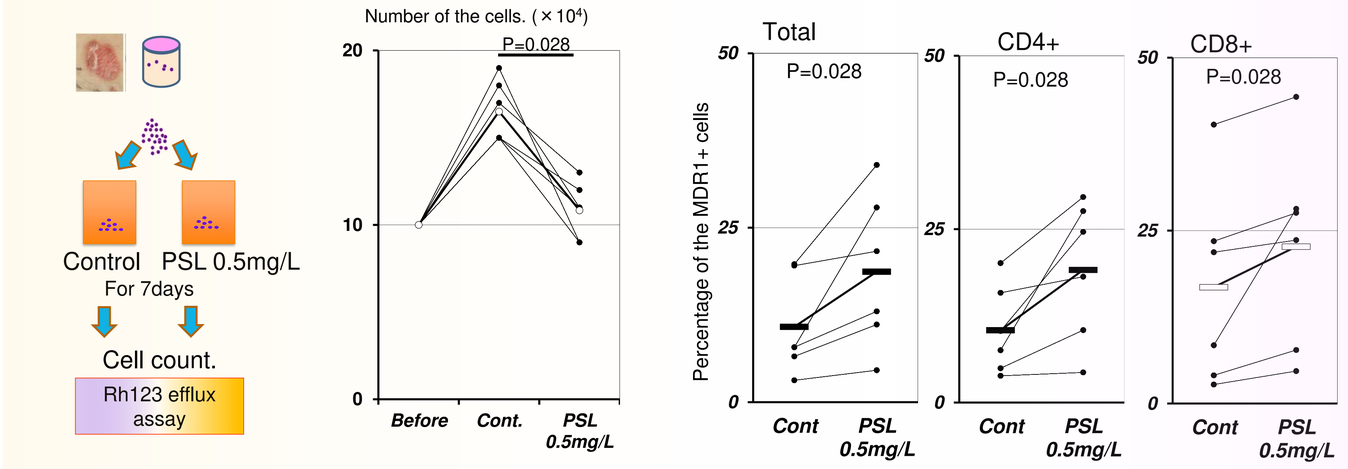


Figure 9. In vitro treatment of prednisolone(PSL) 0.5mg/L 7days induce MDR1 in T cells.

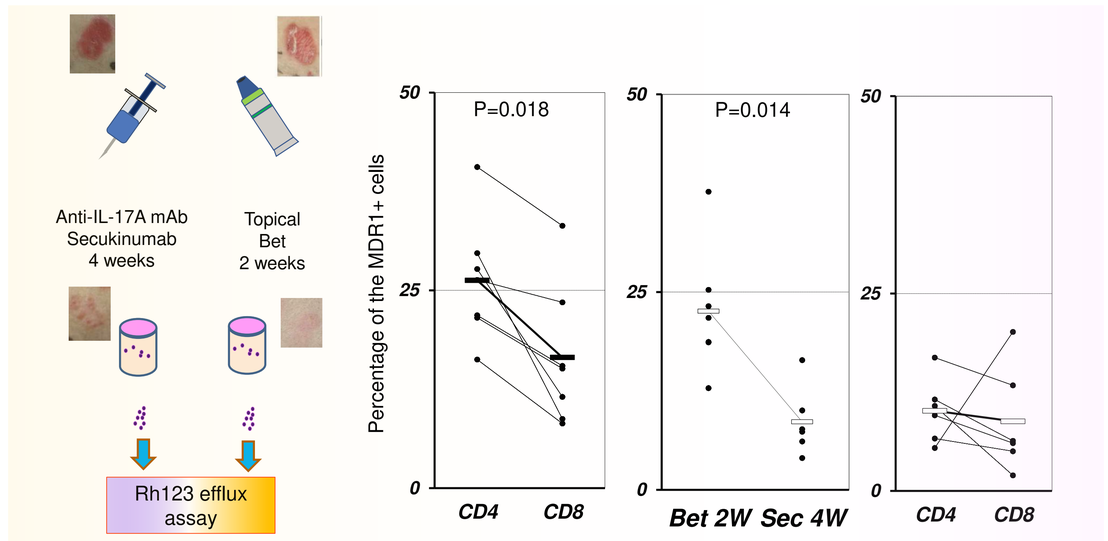


Figure 10. MDR1+ T cells increased after the treatment of the topical corticosteroid, but not after the treatment with anti-IL-17A mAb.

Discussion.

Rh123^{dim} cells expressed *ABCB1* gene, while Rh123^{hi} cells did not. In addition, verapamil, a specific inhibitor of MDR1 depressed the efflux of Rh123 at 94.0±2.3 percent, and thus, we considered Rh123^{low} cells as MDR1+ cells. *In vitro* treatment of a corticosteroid significantly increased the frequency of MDR1+ cells (P=0.028). The frequency of MDR1+ T cells was significantly higher in the corticosteroid-treated skin than in Secukinumab-treated patients' skin (P=0.014). Notably, this difference was more apparent in CD4+ T cells than in CD8+ T cells. Our results suggest that, unlike corticosteroid-treated skin, MDR1+ T cells do not accumulate in the skin of Secukinumab-treated patients.

Conclusion. While anti-IL-17A mAb more strongly improves psoriasis than do topical corticosteroids, it renders remaining skin T cells susceptible to corticosteroid treatment.

Conflict of interest. The authors have no conflict of interest to declare associated with this study. We use stored samples obtained from clinical studies conducted by Novartis Co. and LEO Pharma Co.