Vitiligo skin is imprinted with resident memory CD8 T cells expressing CXCR3

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Introduction

- Vitiligo: the most common depigmenting disorder
- Hallmark of vitiligo: **loss of melanocytes**
- Near-orphan status for drug development
- T cell infiltration in peri-lesional skin of patients
- Recurrence of vitiligo often in the same area, suggesting the involvement of resident memory T cells (T_{RM})
- Dysregulation of T_{RM} harmful in the context of inflammatory disorders, such as psoriasis

Aim of the study

To decipher the phenotype and function of skin infiltrating T cells in vitiligo patients, and to compare such infiltrate to the one observed in psoriasis, the archetype of a skin inflammatory disorder

I. Vitiligo is enriched with populations of skin CD8 T_{RM} cells expressing CXCR3

(A). Immunofluorescence microscopy analysis of CD8, CD69, CD103, and/or CXCR3 expression in skin biopsies from a healthy control, patients with stable or active vitiligo, or psoriasis. Scale bar represents 50µm.
(B-D). T cells were isolated from controls healthy skin, perilesional skin of patients with stable or active vitiligo, and psoriasis skin. The proportion of CD8 T_{EM} cells expressing (B) CD69 and CD103 or (C) CXCR3 was determined by flow cytometry. (D) Frequency of CXCR3⁺ cells within CD8 T_{EM} cells. Each symbol represents one specimen. The mean ± s.e.m. is shown. *p<0.05, **p<0.01, ***p<0.001.

II. Melanocyte-specific vitiligo skin CD8 T_{EM} cells display increased expression of CXCR3

The relative frequency of HLA-A2 restricted melanocyte-specific CD8 T_{EM} cells within CXCR3⁺ and CXCR3⁻ subsets was evaluated by flow cytometry in the skin of patients with stable (n=5) or active vitiligo (n=5) using HLA-A2 pentamer loaded with the melanocyte peptides gp100, MART-1, or tyrosinase. The mean ± s.e.m. is shown. *p<0.05.

III. Vitiligo skin CD8 T_{EM} cells exhibit a skewed inflammatory cytokine profile with moderate cytotoxic activity

(A). T cells were isolated from controls healthy skin, perilesional skin of patients with stable or active vitiligo, and psoriasis skin. The proportion of IFN-γ, TNF-α, IFN-γ/TNF-α or IL-17 producing, skin-infiltrating CD8 T cells was evaluated by flow cytometry.
(B-C). Expression of granzyme B was assessed on freshly isolated T cells from the skin of healthy controls, patients with a stable or active vitiligo, psoriasis, or lupus. Representative granzyme B staining is shown in panel (B). Each symbol represents one specimen. The mean ± s.e.m. is shown. *p<0.05, **p<0.01, ***p<0.001.

Conclusion

- Perilesional skin from vitiligo patients contains significant infiltrate characterized by a combination of CD103⁺ and CD103⁻ CD69⁺ CD8 T_{RM} cells, reinforcing the concept of vitiligo as an immune memory skin disease
- Remaining CD8 T_{RM} cells in patient perilesional skin could be an important mediator for disease flares
- Most skin infiltrating CD8 T_{RM} cells in vitiligo bear expression of CXCR3
- Cytotoxicity is not the only mechanism involved in melanocyte disappearance in vitiligo and IFN-γ and TNF-α produced by skin CXCR3⁺ T cells could play a more important role
- Targeting T_{RM} cells could be an attractive strategy in vitiligo

References : Bertolotti et al. *Pigment Cell Melanoma Res.* 2014; Boniface et al. *Clin Rev Allergy Immunol* 2017; Clark. *Sci. Transl. Med.* 2015; Le Poole et al. *Am. J. Pathol.* 1996; Picardo et al. *Nat. Rev. Dis. Primers*, 2015; Rashighi et al. *Science Transl. Med.* 2014; Van den Wingaard et al. *Lab Invest* 2000