Interferon- γ deficiency attenuates skin fibrosis in a murine model of chronic graft-versus-host disease-like scleroderma

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Introduction

There are few effective treatments for sclerotic skin disorders including systemic scleroderma, chronic graft-versus-host disease (GVHD) and morphea. Because IFN γ directly inhibits the proliferation of skin fibroblasts and the production of collagen *in vitro*, IFN γ is known as an antifibrotic factor. However, administration of recombinant IFN γ could not inhibit fibrosis in patients with systemic scleroderma¹⁾. Our study aims to elucidate the role of IFN γ on skin fibrosis, and established a new murine model of scleroderma.

Methods

Chicken ovalbumin (OVA)-specific CD8 T cell (OT-I cell)-transferred transgenic mice that express membrane-bound OVA under the control of a keratin 14 promoter (K14-mOVA Tg mice), were used²⁾. We transferred wild-type or IFN γ -KO OT-I cells to K14-mOVA Tg mice respectively, and compared the severity of skin fibrosis between the two groups.

Results

● OT-I cell- transferred K14-mOVA Tg mice develop acute GVHD-like mucocutaneous erosive disease 14 days after the transfer, and present chronic GVHD-like scleroderma 28 days after the transfer.

● IFN γ -KO OT-I cells induced acute GVHD-like mucocutaneous lesions and lichenoid tissue reaction/interface dermatitis (LTR/IFD) as severe as wild-type (WT) OT-I cells did in K14-mOVA Tg mice 14 days after transfer.

● IFN γ -KO OT-I cells induced milder scleroderma and skin fibrosis than WT OT-I cells did in K14-mOVA Tg mice 28 days after transfer.

● The mRNA expressions of TGF β 1 on day 14, and Col1a2, α SMA on day 28 in skin were decreased in IFN γ -KO OT-I cell-transferred K14-mOVA Tg mice (IFN γ -KO group) compared with WT OT-I cell-transferred K14-mOVA Tg mice (WT group).

● Macrophages have been reported to produce TGF β induced by IFN γ in skin or lung fibrosis model³⁻⁵⁾. In our murine model, the mRNA expression of TGF β 1 on day 14 in keratinocytes was decreased in IFN γ -KO group compared with WT group. It indicates that keratinocytes may be another source of TGF β production.

● Infiltration of IFN γ -KO OT-I cell in skin was less than WT OT-I cell at late phase (day 14-28). The mRNA expression of CXCL9, CXCL10, and CXCL11 in skin was decreased in IFN γ -KO group compared with WT group at late phase.

Conclusions

- Skin manifestations of OT-I cell-transferred K14-mOVA Tg mice at late phase is a novel skin fibrosis model.
- In this model, IFN γ secreted from autoaggressive CD8 T cells induces skin fibrosis by upregulate TGF β 1 production. Keratinocytes, which is the target of autoaggressive CD8 T cells (OT-I cells), may be one of the sources that produce TGF β 1 in skin as well as macrophages. However, further *in vitro* experiments are needed to investigate whether keratinocytes produce TGF β 1 reacting to IFN γ directly.
- IFN γ also implicates to the recruitment of autoaggressive CD8 T cells in skin by CXCL9, CXCL10, and CXCL10.

References

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There is no COI to declare in this study.