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Cytokine production profiles of a model for fluorouracil and UVB-induced discoid lupus erythematosus in TCR α chain knockout mouse

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Fluorouracil (FU) is well known to induce discoid lupus-like eruption at the sun exposure sites in Japan. It means the associations of UVB with drug induced DLE. It is still obscure which cytokines are involved in the development of DLE. To address the issue, we established a murine model of FU and UVB-induced discoid lupus and could show the Th1 dominant cytokine profiles in DLE model of TCR α chain KO mice treated with FU and UVB.

Key words : drug-induced DLE, UVB, TCR α chain KO mouse

INTRODUCTION

It is well known that drug-induced systemic lupus erythematosus (SLE) can be precipitated by many kinds of drug such as antiarrhythmic, antimicrobial, anticonvulsant, and antihypertensitive agents [1-4]. In contrast, there is little information of drug-induced discoid lupus erythematosus (DLE). Previously, we reported that it is well known in Japan that fluorouracil agents induce DLE-like eruptions [5]. The frequency of DLE-like eruption is about 10 % among all cases of drug eruptions induced by fluorouracil agents [5]. Drug induced DLE mainly develops at the sun exposure sites. In addition, in the development of DLE, antibody-dependent mechanisms are not suggested. The association of DLE with T cell activation is still obscure. From these backgrounds, we tried to establish drug-induced DLE model using fluorouracil, ultraviolet light B (UVB) and TCR α chain knockout (KO) mouse. Furthermore, we investigated which cytokines were involved in the development of drug-induced DLE.

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MATERIALS AND METHODS

Mice. C57BL/6J (B6) mice, TCR α chain KO mice of the B6 background and TCR δ chain KO mice of the B6 background were used in our experiments.

5-Fluorouracil injection and UVB irradiation.. FU was dissolved with phosphate-buffered saline (PBS) and two different concentration were made such as

1mg/ml (low dose) and 10mg/ml (high dose). We performed intraperitoneal injection of 0.2ml each mouse at the age of 10 week, every two day for 12wk. UVB ($200mJ/cm^2$) was irradiated on shaved dorsal skin 5 times a week for more 12wk. Experimental group was divided as follows; PBS injection group, FU (low or high) alone injection group, UVB irradiation group and the group of FU (low or high) injection + UVB irradiation. In the groups of FU + UVB, after 12 wk FU injection, UVB irradiation was started with FU injection for 12wk. Mice were sacrificed at the end of FU and UVB irradiation. We analyzed skin eruptions, hematoxylin eosin (HE) staining of skin and kidney, direct immunofluorescence (IF) test, anti-nuclear antibody (by indirect IF). The level of mRNA expression of TNF-α, IFN-γ, IL-2, IL-4, IL-10 , IL-12 and IL-18 of skin was determined by RT-PCR in each group of TCR α chain KO mice.

RESULTS AND DISCUSSION

B6 mice treated with FU (high) and UVB developed a slight erythema around the neck. TCR α chain KO mice treated with FU (low) + UVB showed rapidly and frequently marked erythema at the neck and back with positive subepidermal IgG deposits. In contrast, B6 mice treated with PBS or FU alone had no changes. B6 mice treated with UVB and TCR α chain KO mice treated with FU showed high frequency of hyperkeratosis and perivascular lymphoid cell infiltration. B6 mice treated with FU (high) + UVB and TCR α chain KO mice treated with FU (low) + UVB showed more frequently plugging, acanthosis, liquefaction degeneration than the groups without eruption. By RT-PCR methods, there are marked differences in cytokine production of skin lesions in each group of TCR α chain KO mice. The group treated with FU (low) alone or UVB only showed no remarkable cytokine production. However, the group with FU (low) + UVB showed Th1 type cytokine production predominantly. Especially, IFN-γ and TNF-α were significantly produced and a little production of IL-12 is also seen in this group. On the other hand, IL-10 and IL-18 was equally produced in each group of TCR α chain KO mice. The production of IL-4 was not seen in all groups. From these results, Th 1 type cytokine was suggested to play a major role in DLE model treated with FU and UVB.

Toro reported that skin lesion of DLE in human was associated with Th 1 type cytokines characterized by the expression of IL-2 and IFN-γ [6]. Our experimental result of cytokines was accordance with their results of human. In the mechanisms of drug-induced DLE, it was suggested that keratinocytes injured by FU and UVB showed Th 1 type response in relation to γ δ T cell.

CONCLUSION

1) We could establish a murine model of discoid lupus erythematosus in C57BL background TCR α chain KO mice treated with fluorouracil and UVB.

2) UVB irradiation could frequently induce hyperkeratotic and severe erythematous LE- like lesions in TCR α chain KO mice which were pre-treated with fluorouracil.

3) Histological findings in DLE like lesions induced in TCR α KO mice were similar to those of DLE in human.

4) TNF-α, IFN-γ and IL-12 was suggested to be involved in the skin lesions of drug-induced DLE.

5) IL-2, IL-4 and IL-10 showed no remarkable changes between control and DLE model of TCR α chain KO mice.

6) Th 1 type cytokines, rather than Th 2 cytokines were likely to be involved in drug-induced DLE model.

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