学位論文の要旨

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学位論文名　Roles of Proinflammatory Cytokines and The Fas/Fas Ligand Interaction in The Pathogenesis of Inflammatory Myopathies

発表雑誌名（巻，初頁～終頁，年）　Immunology (in press)

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論文内容の要旨

INTRODUCTION

The immunologic response is a central event in the pathogenesis of inflammatory myopathies, which include polymyositis (PM) and dermatomyositis (DM). Regarding the underlying mechanism, we have previously reported that Fas-mediated apoptosis of muscle fibers occurs in both PM and DM. In addition, many invading $CD4^+$ T cells, as well as $CD8^+$ T cells, are detected in the inflamed tissues of PM, and Fas ligand (FasL) is preferentially expressed on $CD4^+$ T cells. Despite reports showing the expression of Fas and FasL, it remains unclear whether

Fas-mediated apoptosis occurs in inflamed muscle tissues, and the roles that the Fas/FasL interaction plays in disease pathogenesis have not been fully elucidated.

When cross-linked with FasL, Fas transduces an apoptotic signal. In the present study, we investigated whether proinflammatory cytokines influence Fas-mediated apoptosis of muscle fibers, since they have been detected in the inflamed tissues of inflammatory myopathies. We also tested the hypothesis that the Fas/FasL interaction in the lesions of inflammatory myopathies results in the activation of inflammatory responses, by focusing on interleukin (IL)-23 and Th17, which is a new helper T-cell subset that is responsible for autoimmune and inflammatory responses.

MATERIALS AND METHODS

Human skeletal muscle cells: Human skeletal muscle myoblast cells (purchased from Lonza) were cultured in gelatin-coated plastic dishes with DMEM that contained 10% heat-inactivated FBS, 10% heat-inactivated donor horse serum, 2 mM L-glutamine, 100 U/ml penicillin, 100 μg/ml streptomycin, and 1.25 mg/ml amphotericin B.

Patients: The study was approved by the Ethics Review Board of Shimane University Faculty of Medicine (Study No. 373) Muscle biopsy specimens were taken from 9 patients with polymyositis (PM), 3 patients with dermatomyositis (DM); and 3 control subjects with normal histological findings. The controls had no clinical evidence of muscle disease. Each diagnosis was confirmed clinically and with routine histologic preparations of the muscle biopsy. All of the patients were designated as

'definite' according to the criteria of Bohan and Peter.

RESULTS AND DISCUSSION

In vitro culturing of muscle cells with the proinflammatory cytokines interferon-γ, tumor necrosis factor-α, and interleukin (IL)-1β synergistically increased Fas expression, susceptibility to Fas-mediated apoptosis, and the expression of cytoplasmic caspases 8 and 3. In addition, culturing of muscle cells with activated $CD4^+$ T cells induced muscle cell apoptosis, which was partially inhibited by anti-FasL antibody. We also tested the possibility that Th17, which is an IL-17-producing helper T-cell subset that plays crucial roles in autoimmune and inflammatory responses, participates in the pathogenesis of inflammatory myopathies. Interestingly, in vitro culturing of dendritic cells with anti-Fas IgM or activated $CD4^+$ T cells induced the expression of mRNA for IL-23p19, but not for IL-12p35, in addition to proinflammatory cytokines. Furthermore, IL-23p19 and IL-17 mRNAs were detected in the majority of biopsy samples from patients with inflammatory myopathies.

CONCLUSION

Taken together, these results suggest that proinflammatory cytokines enhance Fas-mediated apoptosis of muscle cells, and that the Fas/FasL interaction between invading dendritic cells and $CD4^+$ T cells induces local production of IL-23 and proinflammatory cytokines, which can promote the proliferation of Th17 cells and enhance Fas-mediated apoptosis of muscle cells, respectively.