学 位 論 文 の 要 旨

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学 位 論 文 名	Alterations of Peripheral Blood $CD5^+$ B Cells in Inflammatory Bowel Disease
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INTRODUCTION

Ulcerative colitis (UC) and Crohn's disease (CD) are two major forms of inflammatory bowel disease (IBD) whose etiologies have not been fully revealed. The intestinal immune system is generated by a variety of cells, including T and B cells, dendritic cells (DCs), and macrophages. Interference with normal interactions among those immune cells and luminal antigens leads to chronic mucosal inflammation, which is directly involved in the pathogenesis of IBD. Previous studies have mainly focused on T cells, DCs, and macrophages to elucidate the immunological disorders of IBD, whereas little is known regarding the role of B cells in its pathogenesis. B cells are divided into different subpopulations based on the phenotypic and functional characteristics of CD5, a cell surface antigen. $CD5^+$ B cells comprise a unique subset of B cells that modulates innate as well as autoimmune systems, and their major function is to produce polyreactive immunoglobulins in a T cell-independent manner. These antibodies have broad specificities against a variety of pathogen-associated molecules and regulate innate immune response in mucosal compartments of the body. $CD5^+$ B cells also produce autoreactive antibodies, which are associated with the development of several kinds of autoimmune diseases. These various immune functions of $CD5^+$ B cells may be related to the

pathogenesis of IBD, which has been reported to represent a group of immune-mediated disorders associated with innate immunity as well as autoimmunity. The aim of this study was to investigate alterations of the circulating $CD5^+$ B cell subset in patients with IBD by evaluating various clinical parameters, including therapeutic regimens.

MATERIALS AND METHODS

Thirty-four patients with UC, 19 patients with CD, and 46 healthy control subjects were enrolled in this study. $CD5^+$ B cells in peripheral blood collected from each subject were analyzed by flow cytometry using anti-CD19 and anti-CD5 monoclonal antibodies. To clarify significant factors related to the presence of the circulating $CD5^+$ B cell subset in the IBD patients, multiple regression analysis was performed using several clinical parameters. In an *in vitro* examination, dexamethasone-induced apoptosis in peripheral blood B cells was examined by detecting cell surface binding of the annexin-V antibody with flow cytometry.

RESULTS AND DISCUSSION

In the present study, the age and gender of the control subjects did not have an influence on the circulating $CD5^+$ B cell subset. The concentrations of $CD5^+$ B cells in peripheral blood from the IBD patient groups were lower than that in the healthy subjects, with a significant reduction observed in samples from the UC patients (control 40.2% vs. UC 27.2%, $p < 0.01$). Multiple regression analysis showed that the presence of UC, corticosteroid therapy, and number of white blood cells (WBC) each had a significant effect to decrease the number of circulating $CD5^+$ B cells in the IBD patients. We also evaluated the correlation between the $CD5^+$ B cell subset and corticosteroid therapy or number of WBC. $CD5^+$ B cells were significantly lower in patients who received corticosteroid therapy. On the other hand, even in UC patients who did not receive corticosteroid therapy, the $CD5^+$ B cell subset was significantly decreased as compared to the healthy controls (40.2% vs. 34.1%, $p < 0.01$). Furthermore, $CD5^+$ B cells and the number of WBC collected from IBD patients had a significantly

negative correlation in both UC ($p < 0.01$) and CD patients ($p < 0.05$). These findings suggest that the $CD5^+$ B cell subset may have some roles in the pathogenesis of IBD. In addition, since the decrease in the $CD5^+$ B cell subset was more predominant as compared to that of the $CD5^-$ B cell subset during an active stage of IBD, it is possible that various mediators induced by intestinal inflammation suppress the self-replenishing function of $CD5^+$ B cells or may accelerate the migration of $CD5^+$ B cells from peripheral blood to the intestines. However, the essential role of $CD5^+$ B cells in the pathogenesis of IBD is not fully explained by these speculations, because the distribution and migration systems of this subset in the human body are largely unexplained.

In an *in vitro* study, we investigated whether corticosteroid therapy predominantly induces apoptosis of $CD5^+$ B cells among whole B cells. Corticosteroid treatment induced apoptosis of $CD19^+$ B cells, while that was also observed in both $CD5^+$ and $CD5^-$ B cells, suggesting that corticosteroids do not selectively target $CD5^+$ B cells for cell death. Corticosteroids have other various effects, such as lymphocyte maturation, homing, trafficking, and recirculation, which may have an influence on the decrease in number of circulating $CD5^+$ B cells in treated individuals.

Finally, we investigated alterations of the peripheral blood $CD5^+$ B cell subset in IBD patients by evaluating clinical parameters, including therapeutic regimens. The circulating $CD5^+$ B cell subset was decreased in UC patients, and corticosteroid therapy was a significant parameter to decrease circulating $CD5^+$ B cells in both UC and CD. Further examinations regarding $CD5^+$ B cells may reveal the immunological pathogenesis of IBD and lead to development of new therapeutic strategies.

CONCLUSION

Circulating peripheral blood $CD5^+$ B cells may be involved in the pathogenesis of UC and modulation of this subset by corticosteroid therapy may have a role in treatment of IBD patients.