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Review

Role of the appendix in the pathogenesis of ulcerative colitis

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Abstract. Although human appendix has been considered as a vestigial remnant, recent observations have focused attention on the role of the appendix in the pathogenesis of ulcerative colitis (UC). Many case-control studies suggest that previous appendectomy is rare in UC patients. This inverse relation is limited to patients who undergo appendectomy before the age of 20 years. Moreover, several investigators reported the improvement of UC after appendectomy, especially in young patients. In the appendix of UC patients, the CD4/CD8 ratio is significantly increased, and the proportion of CD4+CD69+ (early activation antigen) T cells, but not of CD4+HLA-DR+ (mature activation antigen) T cells, is also significantly increased. These findings suggest that the appendix may be a priming site in the development of UC. Further studies including analysis of CD4+ and CD8+ T cells are necessary to clarify the role of the appendix in the pathogenesis of UC.

Key words: Appendix – Appendectomy – Ulcerative colitis – Activated T cell – CD4+ T cell

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Mucosal T cells

Although the pathogenesis of ulcerative colitis (UC) has not been determined, an abnormal mucosal immune response plays a major role in the development and pathophysiology of UC [12, 26]. Extensive infiltration of lymphocytes, especially CD4+ T cells [17], has been observed in the inflamed mucosa of UC patients [32]. Activated CD4+ T cells exhibit increased cytotoxic activity [28] and secrete cytokines that enhance the inflammatory state resulting in tissue injury [2, 6]. Although the triggering factor for UC is still unknown, cytokine imbalance and the production of inflammatory mediators by activated CD4+ T cells play an important role in the pathogenesis of UC. T helper type 2 (Th2) cells and their cytokines, particularly interleukin (IL)-4, have been suggested to enhance the development of UC [22].

Recently, regulatory T cells, characterized by the expression of cell surface markers CD4 and CD25, have been shown to actively suppress immune responses, and lack of regulatory T cells leads to organ-specific autoimmunity [33]. On the other hand, a subpopulation of CD8+ T cells also suppresses the response of activated CD4+ T cells and B cells through an interaction that depends on expression of the major histocompatibility complex (MHC) class Ib molecule Qa-1, the mouse homolog of human leukocyte antigen (HLA)-E [9]. However, the precise role of these regulatory T cells in UC remains unclear.

Several studies concerning T cell subsets in the resected appendix have been performed previously [11], but very few have focused on the activation status of the immune cells in the appendix as well as in the uninflamed mucosa. Recent investigations including TCR-α deficient mice colitis models suggest that non-pathogenic enteric bacterial flora may be involved in the induction of

colitis [15, 30]. However, it is unclear which part of the colon is involved in priming luminal antigens as the inductive site.

CD4/CD8 ratio

We investigated the CD4/CD8 ratio in the inflamed and uninflamed colonic mucosa, especially in the appendiceal mucosa, of UC patients in order to clarify the role of the appendix in the development of UC [14]. UC patients were divided into 5 groups according to the activity and extent of the disease: active pancolitis (A-Pan), active left-sided colitis (A-Lt), A-Lt with appendiceal involvement (A-Lt/Ap), inactive pancolitis (I-Pan), and inactive left-sided colitis (I-Lt).

The CD4/CD8 ratio in the appendix significantly increased both in A-Lt and A-Lt/Ap compared with that in controls. The ratio in the appendix also tended to increase in A-Pan compared with that in controls. Interestingly, as the CD4/CD8 ratio in the appendix increased, the ratio in the rectum tended to increase, suggesting that some relations might be present in the immune responses between the appendix and the rectum.

In the normal appearance transverse colon of A-Lt/Ap, the CD4/CD8 ratio significantly increased compared with that in controls. In the entire colon, the CD4/CD8 ratio tended to increase in A-Lt/Ap compared with that in A-Lt, but it was significant only in the transverse colon. Matsumoto et al. [13] also reported that the histological inflammation grade in the entire colon was higher in A-Lt/Ap than that in A-Lt. The grade was significant both in the inflamed appendiceal orifice and in the uninflamed ascending colon. The CD4/CD8 ratio therefore may represent the inflammation degree in the mucosa.

Even in the inactive UC groups, the CD4/CD8 ratio significantly increased in the rectum compared with that in controls. Most patients with inactive UC have low-grade inflammation, and it is possible that symptomatic relapse occurs only when the inflammatory process reaches a critical intensity [31]. Also, because inflammation is a continuous process, direct assessment of the level of inflammatory activity may provide a quantitative pre-symptomatic measure of imminent clinical relapse of the disease [3]. In our study, the increased CD4/CD8 ratio suggested that the significant immuno-imbalance was persistent in the inactive rectum. Because patients with inactive UC even receiving maintenance therapy are easy to relapse [3], we suspect that the disease can relapse when the immuno-imbalance is persistent in the rectum.

Activated T cells

We also investigated the proportion of early and late activated CD4+ T cells in colonic mucosa of UC patients with CD69 as an early activation antigen and HLA-DR as a late activation antigen, respectively [14]. In the appendix, the proportion of CD4+CD69+ T cells significantly increased in all UC groups, even in the inactive UC groups, compared with that in controls. In the transverse colon, the proportion did not significantly increase in any UC groups compared with that in controls. In the rectum, the proportion significantly increased only in A-Pan, but not in the other groups, compared with that in controls. The proportion of CD4+HLA-DR+ T cells significantly increased only in the rectum of A-Pan, but not in the other areas of any groups compared with that in controls. These findings suggest that the appendix may be a priming site in the development of UC.

In TCR-α deficient mice, the pathological T cells are initially concentrated in the appendix [29]. Mucosal TCRαβ+ T cells, including CD4+ T cells, in IL-2 deficient mice appear in the colon prior to the manifestation of colitis [28]. An increase of identical T cell clones involved in the development of inflammation is detectable in the uninflamed appendix and the inflamed colon of UC patients as well as in TCR-α deficient mice [16, 21]. Therefore, the increased CD4+CD69+ T cells indicate that CD4+ T cells may be initially activated in the appendix, and may re-circulate to the entire colon and rectum (increased CD4/CD8) prior to the manifestation of UC, and inflammation originating from the rectum extends to the entire colon. The reason why the inflammation begins in the rectum is unknown.

Previous appendectomy

Although human appendix is considered as a vestigial remnant [20], recent observations have focused attention on the role of the appendix in the pathogenesis of UC. Many case-control studies suggest that previous appendectomy is rare in UC patients [1, 24, 25], raising the possibility that appendectomy protects against the subsequent development of UC [4, 18, 23, 27]. Patients with previous appendectomy also have a delayed onset of UC [23, 27], a reduced need for immuno-suppression therapy and proctocolectomy [4, 23], and a reduced relapse rate and extent of UC [18].

Previous appendectomy for an inflammatory condition (appendicitis or lymphadenitis), but not for nonspecific abdominal pain, is associated with a low risk of subsequent UC [1]. The findings suggest that the inflammatory condition preceding the appendectomy, rather than the appendectomy itself, is inversely related to the subsequent development of UC. This inverse relation is limited to patients who undergo appendectomy before the age of 20 years. Although these findings support that the appendix may be related to the pathogenesis of UC, the immunological role of human appendix is unknown.

Appendectomy in experimental model

Appendectomy in T-cell receptor (TCR)-α deficient mice, which spontaneously develop colitis resembling human ulcerative colitis at 24–30 weeks of age, suppresses the development of experimental colitis [15]. When the mice underwent appendectomy at a young age (3–5 weeks), the number of mesenteric lymph node cells at 6–7 months were markedly less than in the sham-operated mice. Furthermore, appendectomy at a young age, but not at older age (>6 weeks), suppressed the development of the colitis. These

results suggest that appendix is the priming site of cells involved in the disease process, and plays an important role in the development of colitis in the mice.

Therapeutic appendectomy

We first reported the improvement of UC (A-Lt/Ap) without medication during the 3 years after appendectomy in a young patient (21-year-old), and proposed that appendectomy may have a place as a therapeutic strategy in UC patients [19]. Järnerot et al. [10] also performed laparoscopic appendectomy in 6 patients with refractory UC (2 A-Pan and 4 A-Lt), and found that one young patient (26-year-old) was in remission with continued maintenance treatment, but 5 patients (mean age; 50.8 years, range; 44–56 years) had relapse of the disease. Histological analysis of the resected appendix showed mucosal erosions and moderate infiltrations of CD4+ T cells in our patient [19], but did not show any inflammation in all patients as reported by Järnerot et al. [10]. They concluded that appendectomy does not influence the course of established UC in a consistent way [10], which supports our results in the study [14].

Eri et al. [5] also reported the clinical course of 6 patients (mean age; 30.5 years) with refractory UC (5 A-Lt and 1 A-Lt/A) after laparoscopic appendectomy, and found that 5 patients were in complete clinical remission, and one patient had improved. Histological analysis of the resected appendix showed colitis-type inflammation (ulcerative appendicitis), containing a highly activated lymphocyte population, in the 5 patients. Recently, Jo et al. [11] reported the clinical course of 9 patients (mean age; 32.5 years, range; 13–48 years) with mildly activated UC (4 A-Pan and 5 A-Lt) after appendectomy, and found that 2 A-Lt patients with ulcerative appendicitis had improved, but the disease remained active in the other patients (3 A-Lt without ulcerative appendicitis and 4 A-Pan).

Hallas et al. [7] reported the nationwide study with complete follow-up of 202 patients (mean age; 43.3 years) with UC who underwent appendectomy after their onset of UC, and concluded that appendectomy has no beneficial effect on admission rates in UC patients. Although appendectomy is associated with a low risk for subsequent UC only in young patients [5, 10, 11, 19], especially before the age of 20 years [1], no stratification of data for any age had been performed [7]. Later, Hallas et al. [8] supported that appendectomy would be useful against UC in young subjects by analyzing those who underwent appendectomy before the age of 30 years. These findings and our results [14] indicate that appendectomy may be performed in young UC patients with ulcerative appendicitis.

Conclusion

In conclusion, appendectomy may be a benefit therapy in young UC patients with ulcerative appendicitis. Apart from the rectum, the appendix may be a priming site in the development of UC, and should no longer be considered an evolutionary redundancy. Further studies including analysis of CD4+ and CD8+ T cells are necessary to clarify the role of the appendix in the pathogenesis of UC.

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