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ORIGINAL ARTICLE

$CD8^+CD28^+/CD8^+CD28^-$ T cell equilibrium can predict the active stage for patients with inflammatory bowel disease

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KEYWORDS
Inflammatory bowel disease;
CD8+ T cells;

Summary
Background/aim: The balance of blood $CD8^+CD28^+/CD8^+CD28^-$ T cells has been verified to be vital for patients with ulcerative colitis (UC), but their role in inflammatory bowel disease (IBD) remains unknown. This investigation aimed to evaluate the efficiency of the balance in predicting the active stage in IBD patients.

Abbreviations: BA, biological agent; CD, Crohn's disease; CRLRs, cumulative remission lasting rates; FUPT, follow-up point-in-time; IBD, inflammatory bowel disease; LTR, lasting time of remission; RAS, reason for active stage; UC, ulcerative colitis.

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Immunologic balance;
Active stage;
Lasting time of remission

Methods: Fifty-three IBD subjects, including 31 UC and 22 Crohn's disease (CD) patients, were enrolled, and their peripheral blood $CD8^+CD28^+$ and $CD8^+CD28^-$ T cell levels were tested using flow cytometry. The risk factors related to prognosis were compared between UC and CD patients. A 1-year follow-up was performed for all the IBD patients, and the $CD8^+$ T cells and their ratio were compared at the 3rd, 6th, 9th, and 12th months during follow-up. The sensitivity and specificity of the $CD8^+$ T cell level and balance were analyzed through receiver operator characteristic (ROC) curves. The cumulative remission lasting rates (CRLRs) under the different factors were analyzed using the Kaplan—Meier method.

Results: Higher prescription rates of immunosuppressants, steroids, probiotics, and biological agents (BAs) were found in CD subjects in comparison to UC subjects ($P = 0.005$, 0.024, 0.034, and 0.001), as was a higher active rate during follow-up (95.5% of CD patients vs 67.7% of UC patients, $P = 0.035$). The $CD8^+CD28^+$ T cell level and the $CD8^+CD28^+/CD8^+CD28^-$ T cell ratio were significantly higher in UC patients than in CD patients, but the reverse was true for $CD8^+CD28^-$ T cells during follow-up at the 9th and 12th month (all $P < 0.05$). The diagnostic models of the initial $CD8^+CD28^+$ and $CD8^+CD28^-$ T cell numbers and the $CD8^+CD28^+/CD8^+CD28^-$ T cell ratio in predicting the active stage were found to be significant, with areas under the curves (AUCs) of 0.883, 0.098, and 0.913 for UC subjects (with 95% CI: 0.709—0.940, 0.009—0.188, and 0.842—1.003; $P = 0.001$, 0.00, and 0.000) and 0.812, 0.078, and 0.898 for CD subjects (with 95% CI: 0.683—0.957, 0.003—0.158, and 0.837—0.998; $P = 0.003$, 0.00, and 0.000). The cut-off values showed that when the ratios were 1.30 for UC and 1.22 for CD patients, the best sensitivity and specificity were observed, with 91.6% and 89.0% for UC and 88.5% and 85.1% for CD, respectively. The CRLRs were significantly higher in female, non-BA-treated, non-surgical IBD subjects when compared to male, BA-treated, surgical subjects ($P = 0.031$, 0.000, and 0.000). The number of $CD8^+CD28^+$ and $CD8^+CD28^-$ T cells and the $CD8^+CD28^+/CD8^+CD28^-$ T cell ratio were correlated with BA treatment and surgery (all $P < 0.05$).

Conclusion: The $CD8^+CD28^+/CD8^+CD28^-$ T cell balance, expected to be a novel immunologic marker, presented a satisfactory efficiency with high sensitivity and specificity in predicting the active stage in UC and CD patients, and the balance was closely related to the use of BAs and surgery.

Introduction

Due to the increasingly high incidence rate, 1.37 per 100,000 individuals in Asia and 3.44 per 100,000 in China [1], preventive actions for inflammatory bowel disease (IBD) are urgent! Many factors, both internal and external, can influence the prognosis, primarily the remission and active stages, of IBD patients [2], but more extensive studies are required to determine which factors can predict the exacerbation or improvement of IBD. More importantly, the heterogeneity, especially the effect of genetic burden on disease phenotypes, between ulcerative colitis (UC) and Crohn's disease (CD) is a confounding factor in IBD prognosis evaluation [3,4].

It has been acknowledged that immunological disorder is the kernel mechanism for IBD [5]. Among the numerous immunocytes, $CD8^+$ T cells are the ideal lymphocyte subset to predict prognosis in both UC and CD from diagnosis, and assessing $CD8^+$ T cells is expected to be a major step toward personalized therapy [6]. Coincidentally, we have reported that the balance of blood $CD8^+CD28^+/CD8^+CD28^-$ T cells plays a vital role in IBD, and a balance tilting toward $CD8^+CD28^+$ T cells was beneficial for patients with UC [7]. Based on these findings, we thus supposed that the balance of $CD8^+CD28^+/CD8^+CD28^-$ T cells affects the outcome of IBD, and we observed UC and CD patients through a one-year follow-up period. As hypothesized, the $CD8^+CD28^+/CD8^+CD28^-$ T cell balance was confirmed to predict a subsequent active stage with high sensitivity and specificity for both UC and CD patients. This study was conducted as follows.

Clinical data and methods

Patient's data

This investigation was approved by the Ethics Committee of Nanfang Hospital, Southern Medical University. IBD patients were determined according to local endoscopy, pathology, and pharmacy records [1] from the Gastroenterology and Emergency departments of Nanfang Hospital, Southern Medical University from October 2012 to November 2013. IBD cases with tumor, tuberculosis, autoimmune diseases, pregnancy, or poor compliance were excluded [8]. Based on the above-mentioned criteria, there were 53 subjects enrolled, aged 13—71 years old, including 31 UC and 22 CD subjects, 33 male and 20 female subjects, 14 subjects in remission, and 39 subjects in the active stage.

Observation and comparison of factors

Internal factors, including gender, age, onset age, course of disease, occupation, stage, and family history, were compared between UC and CD patients [9], as were external factors (mainly therapeutic factors) that included treatment with 5-aminosalicylic acid (5-ASA), immunosuppressants,

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