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Commentary Open Access

Electron Transfer Flavoprotein Subunit Beta is Involved in Behcet's Disease

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Abstract

This article aim to make a comment on the previous study published entitled "electron transfer flavoprotein subunit beta (ETFB) is a candidate endothelial cell autoantigen in Behcet's Disease (BD)". Recently, serum IgG levels of anti-ETFB in BD patients from Shanxi Dayi Hospital were evaluated. The level of IgA against ETFB was also measured in Intestinal Behcet's disease. In addition, correlation of human ETFB, HSP60 and hnRNP-A2/B1 was analyzed. This result verified our previous conclusion. We also discovered that ETFB might be related with mucosal immune, and the pathology of intestinal BD may be related with the infection of intestinal microorganism.

Keywords: Behcet's disease; AECA; ETFB; Microorganism infection

Commentary

The purpose herein is to introduce the second part about ETFB in Behcet's Disease.

In our previous study, a candidate endothelial cell autoantigen was identified in Chinese patients with BD. Briefly put, Western blotting was firstly performed to screen candidate autoantigens and the putative antigen was identified by LC-MALDI-TOF/TOF. Next, the protein was cloned, expressed and purified. Finally, an optimized ELISA was developed to evaluate positive rate of corresponding antibody in a large number of clinical samples.

As a consequence, a 28 kDa antigen was identified as ETFB. The positive rate of anti-ETFB antibody was 38 of 92 BD patients (41%) and 1 of 90 healthy controls (1%) [1].

Endothelial cell (EC) and anti-endothelial cell antibodies (AECA) in BD

BD is a crossed disorder between vasculitis and autoimmunity [2,3]. Several findings revealed that AECAs may be pathogenic in vasculitis by activating cytokine production, endothelial cells and inducing the leucocyte adhesion on endothelial surfaces. The direct cytotoxicity of AECAs were also suggested in the autoimmune process of BD [4].

BD and microorganism infection

Most researchers believed BD is related to the infection of microorganism [5]. It was reported that *S. sanguis* mainly inhabits the mucous membrane of the colon, mouth and throat as viridans group streptococci, the role of which in BD immunopathogenesis has reported in several studies before [6-8]. The HSP65 of *S. sanguis* detected from the BD patients' sera is highly homologus with human HSP60 [8]. Also, it is demonstrated that there is a cross reactivity between the antibodies from BD patients' sera and *S. sanguis* or some recombinant peptides of HSP65 from *S. sanguis* [9,10]. Another investigation revealed streptococcal HSP-65 may cross-react with human hnRNP-A2/B1 in BD [11].

Recently, serum IgG against ETFB was evaluated in BD patients from Shanxi Dayi Hospital. The level of IgA against ETFB was also measured in Intestinal Behcet's disease. In addition, to confirm Dr. Dongsik Bang's finding that BD patients from Korea has significant positive correlation between hnRNP-A2/B1 and HSP65 [8,12], the correlation of ETFB, hnRNP-A2/B1 and HSP60 was analyzed.

The result indicated that the positive rate of anti-ETFB was 7 in 18 (38%) in BD patients from Shanxi Dayi Hospital, 4 in 16 (25%) in Sjogren's syndrome and 0 of 16 in healthy controls. There is significant difference between BD and healthy controls (Figure 1). The reactivity of serum IgA against human recombinant ETFB in intestinal Behcet's disease is significantly higher than in normal BD and healthy individuals (Figure 2). A high correlation between ETFB, hnRNP-A2/B1 and HSP60 was observed in China intestinal BD patients (Figure 3).

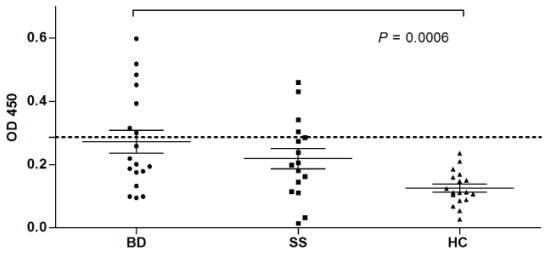

Figure 1: The positive rate of anti-ETFB in clinical samples. An optimized ELISA was performed to detect the reactivity of the serum IgG against EFTB. The result showed that the positive rate of anti-ETFB was 7 in 18 (38%) in BD patients from Shanxi Dayi Hospital, 4 in 16 (25%) in Sjogren's syndrome and in 0 of 16 healthy controls. There is significant difference between BD and healthy controls (P<0.0001). The data are shown as the mean ± SD. The cut-off value for the positive result was shown as mean + 3 SD, which was denoted with horizontal dotted line. BD: Behcet's Disease; SS: Sjogren's Syndrome; HC: Healthy Controls.

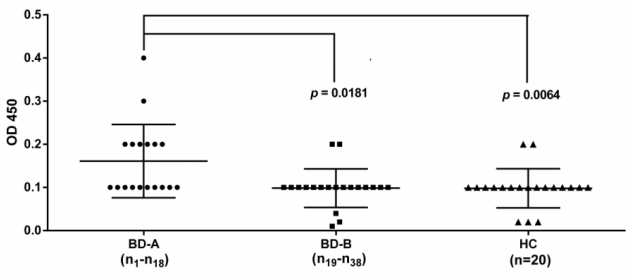

Figure 2: Reactivity of serum IgA antibodies against ETFB. ELISA was performed to evaluate the reactivity of serum IgA antibody against human recombinant EFTB. The result showed that the level of serum IgA against human recombinant ETFB in intestinal BD was significant higher than in normal BD (P=0.0181) and healthy controls (P=0.0064). BD-A: Intestinal Behcet's Disease; BD-B: Normal Behcet's Disease; HC: Healthy Controls.

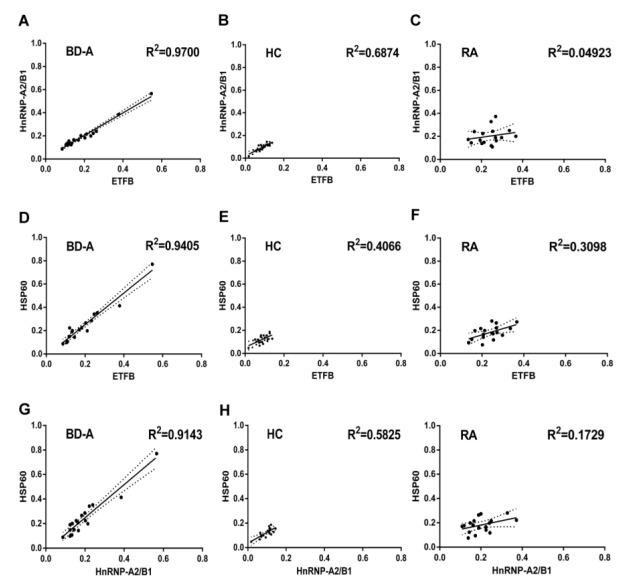

Figure 3: Correlation of ELISA using recombinant human ETFB, HSP60 and hnRNP-A2/B1. (A, B, C) Optical densities obtained from ELISA against recombinant human hnRNP-A2/B1 were correlated with those against the recombinant human ETFB in intestinal BD (R^2=0.9700, P<0.0001), healthy controls (R^2=0.6874, P<0.0001) and RA (R^2=0.04923, P=0.3762). (D, E, F) HSP60 was related with ETFB in intestinal BD (R^2=0.9405, P<0.0001), healthy controls (R^2=0.4066, P=0.0044), RA (R^2=0.3098, P=0.0164). (G, H, I) Correlation of HSP60 and hnRNP-A2/B1 in intestinal BD (R^2=0.9143, P<0.0001), healthy controls (R^2=0.5825, P=0.0002), RA (R^2=0.1729, P=0.0861). BD-A: Intestinal Behcet's Disease; HC: Healthy Controls; RA: Rheumatoid Arthritis.

In conclusion, the positive rate of serum IgG further confirmed our previous result. The reactivity of serum IgA against human recombinant ETFB in intestinal Behcet's disease is significantly higher than in normal BD, which demonstrated that ETFB protein might be related with mucosal immune, and the pathology of intestinal BD might be related to the infection of intestinal microorganism. There is a high correlation between ETFB, hnRNP-A2/B1 and HSP60, which hints us that among genetically predisposed individuals, environmental factor, especially infection of microorganism, might play a major role in intestinal BD pathogenesis.

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