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New Phenomenon

# The imbalance of IL-18/IL-18BP in patients with systemic juvenile idiopathic arthritis

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Systemic JIA (SJIA) is one subtype of juvenile idiopathic arthritis (JIA) that is a leading cause of short-term and long-term disability in children [1]. Although SJIA represents only 10%–20% of all cases of JIA, it accounts for more than two-thirds of the mortality associated with this condition [2]. The etiology and pathogenesis of SJIA remain unknown. Further understanding of SJIA pathogenesis may facilitate new therapeutic approaches.

Interleukin-18 (IL-18) was originally identified as an interferon gamma (IFN)-γ-inducing factor, and IL-18 can induce INF-γ production by splenocytes, hepatic lymphocytes, and type 1T helper (Th1) cell clones [3]. IL-18 levels have been shown to be abnormal in some inflammatory diseases and in autoimmune diseases. IL-18 expression has been reported to be up-regulated in lupus nephritis (LN), type 1 diabetes, and other autoimmune diseases [4]. IL-18 binding protein (IL-18BP) is a circulating decoy receptor that binds to IL-18 with high affinity. IL-18BP can efficiently antagonize the biological activities of IL-18 [5]. Experiments have shown that IL-18BP could prevent or attenuate the development of some autoimmune diseases [6].

Currently, the balance between IL18 and IL-18BP in SJIA patients remains unknown. The hypothesis that an imbalance between IL-18 and IL-18BP may play an important role in SJIA was demonstrated in the present study by comparing the plasma levels and mRNA expression of IL-18 and IL-18BP in peripheral blood mononuclear cells from active patients, remission patients, and healthy children.

Forty-five acute-phase SJIA patients (20 males and 25 females; age range 1–16 years, median 9 years) were enrolled in this study. Twenty-three SJIA cases (11 males and 12 females; age range 1–16 years, median 10 years) in remission were also included in this study. Twenty healthy children (11 males and 9 females; age range 1–16 years, median 9 years) were recruited by family members and friends of the investigators. Approval for this research was obtained from the Medical Ethics Committee of the Qilu Hospital and Second Hospital of Shandong University.

We measured the IL-18 levels with a commercial enzyme-linked immunosorbent assay (ELISA) (USCNLIFTM; Wuhan EIAab Science Co., Wuhan, China). The lower detection limit of the assay was 15.6 pg/ml. An ELISA (Human IL-18BPa DuoSet; R&D Systems, Minneapolis, USA) was used to detect IL-18BP. Multiplex real-time PCR was performed for *IL-18*, *IL-18BP*, and the endogenous control (*β-actin*) on an ABI PRISM®7500 Sequence Detection System (Applied Biosystems, Foster City, USA) using SYBR® Green (Toyobo, Japan) as a double-strand DNA-specific binding dye.

It was found that plasma IL-18 and IL-18BP levels were higher in patients with acute SJIA ($n = 45$) than those in healthy children ($n = 20$) or in the remission group ($n = 23$). The patients in remission had similar plasma levels of IL-18 and IL-18BP compared with healthy children. The expression levels of *IL-18* mRNA in the patients with active SJIA were 4.8-fold higher than those in the healthy control group ($P < 0.05$), and the levels of *IL-18* mRNA in the remission group were 2.8-fold higher than those in the healthy control group [$P < 0.05$; **Fig. 1(A)**]. The expression levels of *IL-18BP* mRNA in the active SJIA group were 2.2-fold higher than those in healthy controls ($P < 0.05$), and the expression levels in the remission group were 1.9-fold higher than those in healthy controls [$P < 0.05$; **Fig. 1(B)**]. The ratio of IL-18/IL-18BP levels and of IL-18/IL-18BP mRNA expression in the plasma was higher in the SJIA patients than in the remission group or in the healthy children [$P < 0.05$; **Fig. 1(C,D)**]. The ratio of plasma IL-18/IL-18BP was positively correlated with the erythrocyte sedimentation rate (ESR), serum ferritin (SF) (**Fig. 2**). The ratio of plasma IL-18/IL-18BP and the clinical symptom of more than three systems with lesions were positively correlated ($r = 0.431$, $P < 0.01$). The ratio of plasma IL-18/IL-18BP had no correlation with C-reactive protein.

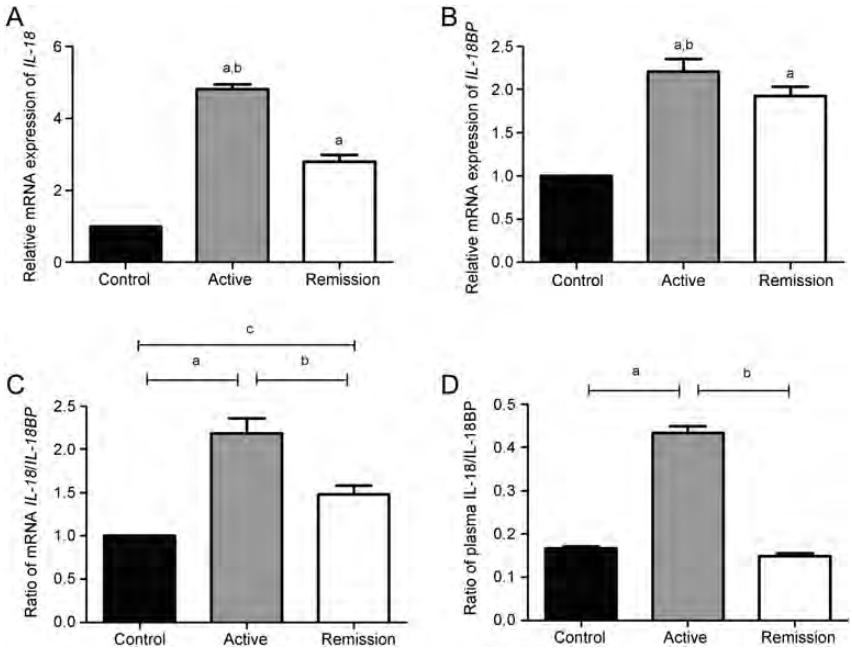


**Figure 1 The expression of IL-18 and IL-18BP mRNA and plasma level in active SJIA patients, in remission SJIA patients, and healthy controls**
(A) The relative mRNA expression levels of *IL-18* in peripheral blood mononuclear cells from SJIA patients compared to healthy controls ($^{a}P < 0.05$ compared with control; $^{b}P < 0.05$ compared with remission groups; one-way analysis of variance). (B) The relative mRNA expression levels of *IL-18BP* in peripheral blood mononuclear cells from SJIA patients compared with healthy controls ($^{a}P < 0.05$ compared with control; $^{b}P < 0.05$ compared with remission groups; one-way analysis of variance). (C) The ratio of *IL-18/IL-18BP* mRNA expression in peripheral blood mononuclear cells in active SJIA patients, in remission SJIA patients, and healthy controls ($^{a}P < 0.05$ compared with control groups; $^{b}P < 0.05$ compared with remission groups; $^{c}P < 0.05$ compared with control groups; one-way analysis of variance). (D) The ratio of IL-18/IL-18BP plasma levels in active SJIA patients, in remission SJIA patients, and healthy controls ($^{a}P < 0.05$ compared with control groups; $^{b}P < 0.05$ compared with remission groups; one-way analysis of variance).

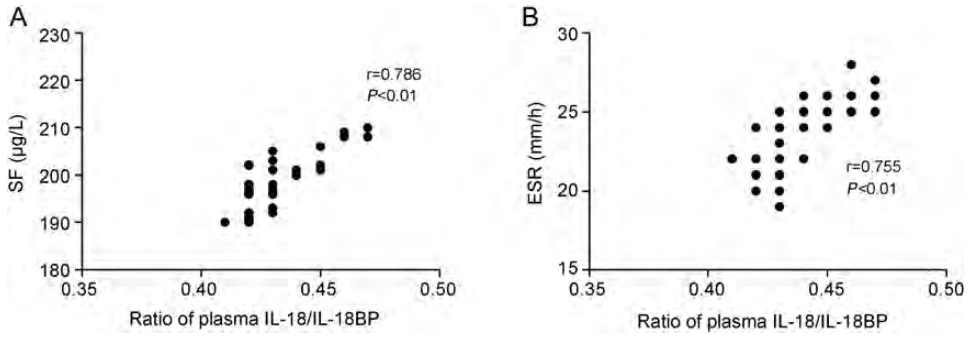


**Figure 2 The ratio of plasma IL-18/IL-18BP is correlated with SF and ESR in active patients**

The imbalance of IL-18/IL-18BP might play an important role in the pathogenesis of SJIA and it might go hand-in-hand with the severity of SJIA. The balance of IL-18/IL-18BP could possibly become a new indicator to estimate the disease state of SJIA, and regulating the balance of IL-18/IL-18BP could be a therapeutic strategy for the treatment of SJIA. There are still issues need to be resolved and confirmed, including the following questions: What are the explicit mechanisms of IL-18 and IL-18BP during the onset of SJIA? What is the relation between the IL-18/IL-18BP ratio and NK cells? What are the most reasonable and effective methods to regulate the balance of IL-18/IL-18BP, and how can we find them? Providing the answers to these questions require further research.

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