Original Article
IL-6/STAT3 signaling pathway is activated in plasma cell mastitis

Yang Liu[1], Jian Zhang[1], Yu-Hui Zhou[1], Yi-Na Jiang[2], Wei Zhang[1], Xiao-Jiang Tang[1], Yu Ren[1], Shui-Ping Han[3], Pei-Jun Liu[4], Jing Xu[5], Jian-Jun He[1]

[1]Department of Breast Surgery, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, China; [2]Department of Pathology, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, China; [3]Department of Pathology, School of Medicine, Xi'an Jiaotong University, Xi'an, Shaanxi, China; [4]Translational Medical Center, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, China; [5]Department of Geriatrics, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, China

Abstract: Plasma cell mastitis (PCM), a particular type of mastitis, mainly occurs in females at nonpregnant and nonlactating stages. The infiltration of abundant plasma cells and lymphocytes is the hallmark of the disease. The incidence rate of PCM increased gradually and its pathogenesis remained unclear. In this study, we investigated the expression of IL-6/STAT3 signaling pathway, which is vital not only for the differentiation of plasma cells but also for survival of plasma cells and T lymphocytes, in 30 PCM cases, 10 acute mastitis cases and 10 normal breast tissues by immunohistochemical analysis. IL-6 level was significantly higher in PCM patients than in acute mastitis patients or normal group. The positive rate of IL-6 and p-STAT3 staining in PCM samples was 93.3% (28/30) and 70% (21/30), respectively, and there was a significant positive association between IL-6 and p-STAT3 staining (r=0.408, P=0.025). In PCM group, the rate of nipple retraction was 40% (12/30). Significantly higher IL-6 expression was found in PCM patients with nipple retraction than in other PCM patients. However, no significant difference in IL-6 or p-STAT3 staining was detected between PCM patients experiencing recurrence and other PCM patients. In addition, Bcl-2 level was higher in PCM patients than in acute mastitis patients or normal group, but there was no difference in Bcl-2 immunostaining between PCM patients experiencing recurrence and other PCM patients. These indicate that IL-6/STAT3 signaling is activated in PCM and may play an important role in the pathogenesis of PCM.

Keywords: Plasma cell mastitis, IL-6, STAT3, immunohistochemistry

Introduction

Plasma cell mastitis (PCM), a particular type of mastitis, mainly occurs in females at nonpregnant and nonlactating stages [1, 2]. In 1850, Burkitt described the pathological features of PCM for the first time [3]. With the progression of PCM, discharge stimulants would overflow from the dilated ducts, resulting in inflammation with plenty of plasma cells. Thus the disease was named PCM [4].

At present, surgical excision is the most common treatment for PCM [1, 5, 6]. However, PCM could recur even after the mammary gland is completely resected [7]. The recurrence rate of PCM is nearly 28% after the excision of the lac-tiferous ducts, and will raise to 79% if the lactiferous ducts are not excised [8]. Recurrence of PCM will result in repeated incision and may lead to breast deformation [9]. The incidence of PCM is approximately 5% of the incidence of breast cancer [10]. Recently, the incidence rate of PCM increases gradually and PCM develops even in women at adolescent or menopausal stage [11]. However, the etiology and pathogenesis of PCM remain largely unclear.

Plasma cells are derived from B lymphocytes and play important role in humoral immune responses. There are almost no plasma cells in normal breast tissue and plasma cells will die rapidly when either isolated ex vivo [12] or generated in vitro [13]. The infiltration of a large
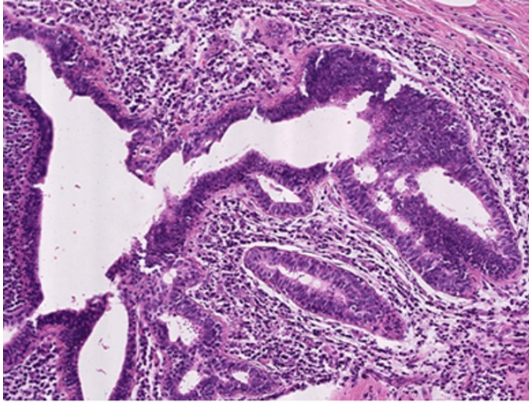
Figure 1. Representative HE staining of PCM tissues. Original magnifiation: 200×.

number of plasma cells, B lymphocytes and T lymphocytes is the hallmark of PCM [14]. Thus we hypothesized that secreted chemokines may promote the differentiation of plasma cells and maintain the survival of plasma cells. Interleukin-6 (IL-6) is a pro-inflammatory cytokine produced mostly by the lymphocytes, fibroblasts and myeloid cells and has been characterized as a potent activator of Signal Transducer and Activator of Transcription 3 (STAT3) [15]. IL-6/STAT3 signaling pathway is vital not only for the differentiation of plasma cells but also for plasma cells survival [16, 17]. Moreover, IL-6/STAT3 signaling protects T cells against apoptosis [18]. These studies suggest that IL-6/STAT3 pathway may play an important role in the development of PCM.

In this study, we determined the activation of IL-6/STAT3 pathway in PCM by immunohistochemical analysis of IL-6 and p-STAT3 in tissues from PCM patients, and used tissues from acute mastitis patients and normal breast tissues as the controls. We also analyzed the correlation of IL-6 expression with the recurrence and nipple retraction of PCM.

Materials and methods

Materials

30 cases of PCM were obtained from the surgical pathology files of First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, China. Of these, all were females with the age of 37.23±10.54 years. Meanwhile, 10 cases of acute mastitis and 10 cases of normal breast tissue were collected as the controls, with the age of 31.5±9.18 and 45.34±12.32 years, respectively. Specimens for hematoxylin-eosin (HE) staining and immunohistochemistry were immediately fixed in 10% buffered formalin and embedded in paraffin.

Immunohistochemical staining

Immunohistochemical staining was performed on tissue sections of 5 µm thin by using avidin-biotin complex method. Sections were dried at 65°C for 1 h, deparaffinized with xylene for 30 min and rehydrated in a graded ethanol series (100%, 95%, 90%, 85%, 70%). The tissue sections were washed in phosphate-buffered saline (PBS) and endogenous peroxidase was blocked by 3% hydrogen peroxide at room temperature for 20 min, followed by washing with PBS. Then tissue sections were treated in a microwave oven using 10 mmol/L citrate buffer (PH 6.0) (for IL-6 and Bcl-2 staining) or 1 mmol/L Tris/EDTA buffer (PH 9.0) (for p-STAT3 staining) for 20 min. Subsequently, the sections were pre-incubated with non-immune goat serum for 20 min at room temperature and then were incubated overnight at 4°C with IL-6 polyclonal antibody (1:500, Abcam, Cambridge, UK), phospho-STAT3-Tyr705 rabbit monoclonal antibody (1:200, Cell Signaling, Boston, USA) or Bcl-2 polyclonal antibody (1:100, Bio-World, Ohio, USA). After rinsing 3 times with PBS, sections were incubated with biotinylated goat-anti-rabbit antibody for 30 min at 37°C, followed by staining with DAB. Finally, the sections were counterstained with hematoxylin, dehydrated and mounted. PBS was used to substitute primary antibody as negative controls.

Immunohistochemical scoring

All tissue sections were analyzed using an Olympus CX21 microscope independently by two experienced pathologists who were blind to clinical data of the patients. Cells were counted with a 40× objective and five counted areas were randomly selected. For each area, both the percentage of positive cells and the intensity of staining were considered [19]: percentage score =0 if <1%, 1 if >1%<25%, 2 if >25%<50%, 3 if >50%<75%, 4 if >75%; intensity score =1 (weak), 2 (moderate), and 3 (strong). A final classification was obtained by multiplying percentage and intensity. When 1% or more of the cells in a given specimen stained positive, it was defined as positive staining.
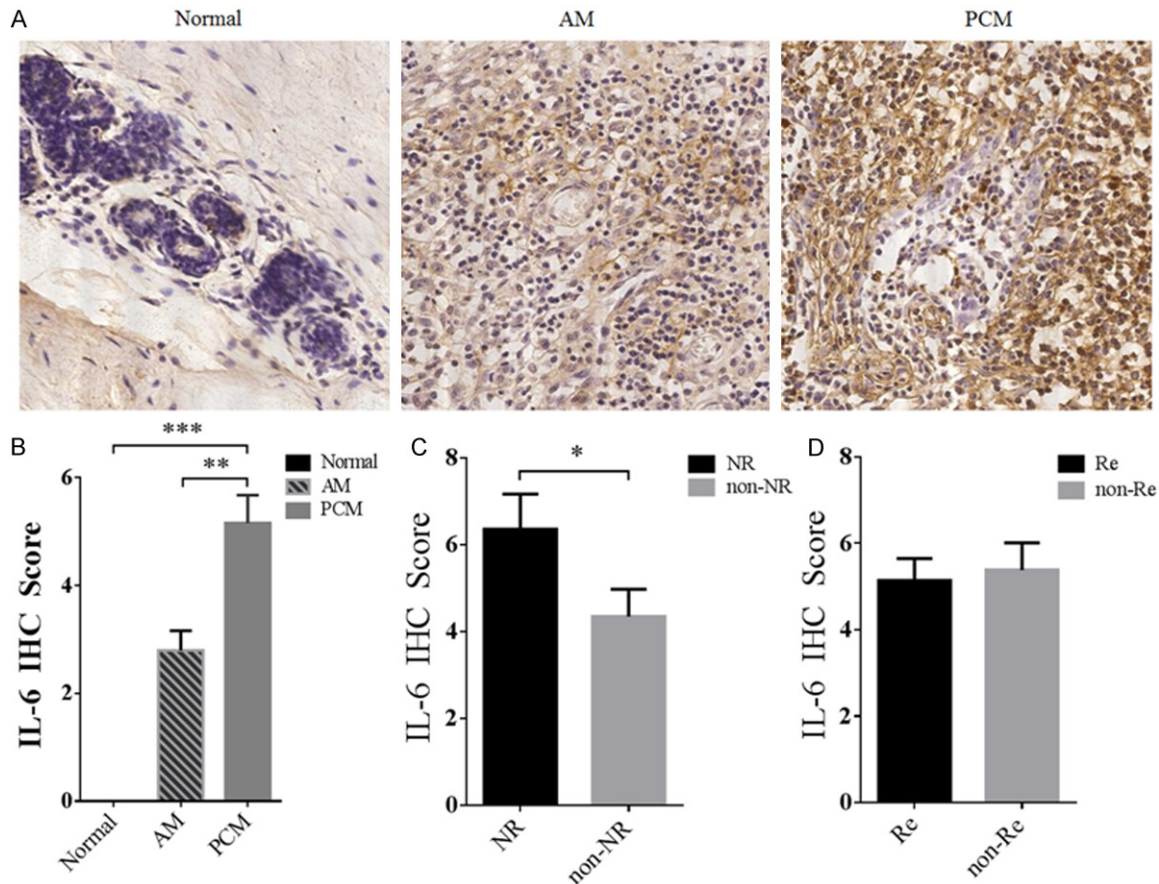
Figure 2. Immunohistochemical analysis of IL-6. A. Staining of IL-6 in PCM, acute mastitis (AM) and normal breast tissues. Original magnifiation: 400×. B. IL-6 staining was stronger in PCM than in acute mastitis patients (AM) (P=0.003) or normal group (P<0.001). C. IL-6 staining was stronger in PCM patients with nipple retraction (NR) than in other PCM patients (non-NR) (P=0.043). D. No significant difference in IL-6 staining was detected between PCM patients experiencing recurrence (Re) and other PCM patients (non-Re) (P=0.743). Data were presented as mean ± standard error of mean (SEM).

Statistical analysis

Statistical analyses were performed using SPSS 13.0 software package (IBM Corporation, Armonk, NY, USA). Comparison between two groups was made using the Mann-Whitney rank sum test, and comparison among three groups was made using Kruskal-Wallis one way analysis of variance. The correlation between IL-6 and p-STAT3 staining was assessed using Spearman's rank order correlation test. A value of *P*<0.05 was considered statistically significant.

Results

Histopathological analysis of PCM cases

Plentiful lipid debris was observed in the dilated mammary ducts in all PCM cases. Repre-

sentative histopathologic changes of PCM were shown in **Figure 1**, including irregular ductal hyperplasia, ductal dilatation and the infiltration of plasma cells, lymphocytes and macrophages. The ratio of plasma cells was over 50% in each PCM case.

Immunohistochemical analysis of IL-6

To explore whether the expression of IL-6 was aberrant in PCM patients, we compared the expression of IL-6 in 30 PCM patients with 10 patients with acute mastitis and 10 normal breast tissues. IL-6 immunostaining was detected in ductal epithelium and inflammatory cells of both PCM and acute mastitis, and it was predominantly located in the cytoplasm (**Figure 2A**). The expression of IL-6 in normal breast tissue was negative (**Figure 2A**). Significantly stronger IL-6 staining was detected in
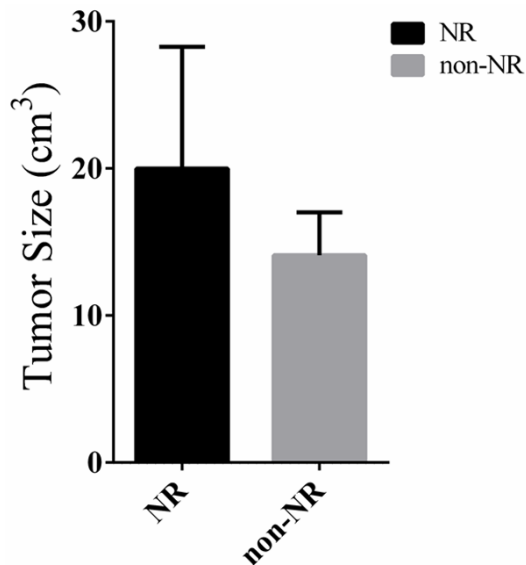
Figure 3. No significant difference was found in tumor size between PCM patients with nipple retraction (NR) and other PCM patients (non-NR) (P=0.461).

PCM patients than in acute mastitis patients (P=0.003) or normal group (P<0.001) (**Figure 2B**).

In PCM group, the rate of nipple retraction was 40% (12/30). Significantly higher IL-6 expression was found in PCM patients with nipple retraction than in other PCM patients (P=0.043) (**Figure 2C**). No significant difference was found in tumor size between PCM patients with nipple retraction and other PCM patients (P=0.461) (**Figure 3**).

The recurrence rate of PCM was 20% (6/30). We found no significant difference in IL-6 immunostaining between PCM patients experiencing recurrence and other PCM patients (P=0.743) (**Figure 2D**).

Immunohistochemical analysis of p-STAT3

To explore the role of IL-6/STAT3 signaling in PCM, we performed immunohistochemical analysis of p-STAT3. p-STAT3 was detected in ductal epithelial and inflammatory cells, predominantly located in the cytoplasm and the nucleus (**Figure 4**). The positive rate of p-STAT3 staining was 70% (21/30) in PCM patients, and IL-6 staining was positive among all 21 patients with positive p-STAT3 staining. The age of patients with positive and negative p-STAT3 staining was 36.14±8.2 years and 38.11±

14.69, respectively, and there was no significant difference (P=0.176). The positive rate of IL-6 expression was 93.3% (28/30) in PCM cases. By Spearman's rank correlation test, a significant positive correlation was found between IL-6 and p-STAT3 staining in PCM (r=0.408, P=0.025) (**Table 1**).

The recurrence rate of 9 patients with negative staining of p-STAT3 was 33% (3/9), higher than the overall recurrence rate. However, no significant correlation was found between recurrence and p-STAT3 staining in PCM cases (P=0.247) (**Table 2**).

Immunohistochemical analysis of Bcl-2

To explore the anti-apoptosis effect of IL-6/STAT3 signaling pathway in PCM, we determined the expression of Bcl-2 in 30 PCM patients compared with 10 acute mastitis patients and 10 normal breast tissues. Positive Bcl-2 staining was detected in ductal epithelium and inflammatory cells of both PCM and acute mastitis tissues, predominantly in the cytoplasm (**Figure 5A**). Bcl-2 was barely detectable in normal breast tissues. Significantly higher expression of Bcl-2 was detected in PCM patients compared to acute mastitis patients (P=0.039) or healthy control group (P<0.001) (**Figure 5B**). However, no significant difference in Bcl-2 immunostaining was observed between PCM patients experiencing recurrence and other PCM patients (P=0.273) (**Figure 5C**).

Discussion

IL-6 is a pleiotropic cytokine that plays a crucial role in a variety of inflammatory diseases and has been characterized as a potent activator of STAT3 [15, 20]. IL-6/STAT3 signaling pathway can promote the differentiation of plasma cells and inhibit apoptosis [16, 17, 21]. To our knowledge, this is the first report to analyze the activation of IL-6/STAT3 signaling in PCM. By immunohistochemical analysis we found that IL-6 expression was significantly higher in PCM than in acute mastitis and normal group. In addition, p-STAT3, an indicator of the activation of STAT3, was detected in 70% patients of PCM. Moreover, we observed a positive correlation between IL-6 and p-STAT3 staining.

IL-6 mainly activates JAK (Janus kinase)/STAT signal pathway via the binding to gp130 and
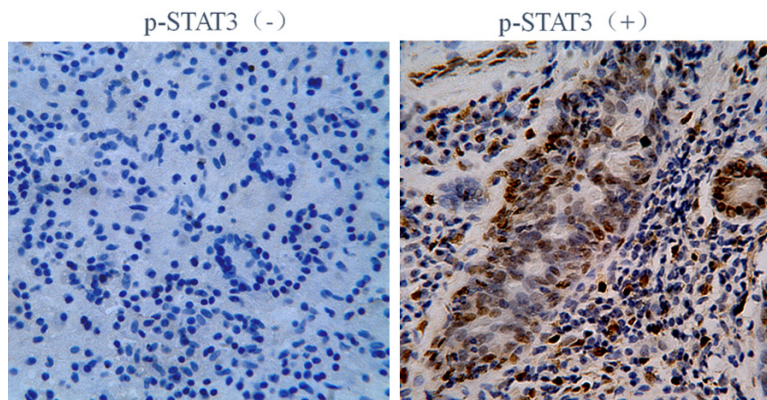
Figure 4. immunostaining of p-STAT3 in PCM. Original magnifiation: 400×.

Table 1. Correlation between IL-6 and p-STAT3 staining in PCM

IL-6	p-STAT3		r	P
	+	-		
+	21	7	0.408	0.025
-	0	2		

Table 2. Correlation between recurrence and p-STAT3 staining in PCM

Recurrence	p-STAT3		r	P
	+	-		
+	3	3	-0.218	0.247
-	18	6		

then mediates various cellular function [15, 22]. The transcription factors B lymphocyte induced maturation protein 1 (Blimp-1) and X-box binding protein 1 (XBP-1) are both essential for the differentiation of plasma cells [17, 21]. IL-6/STAT3 pathway can induce Blimp-1 expression through the activation of STAT3. Blimp-1, the master regulator of plasma cell differentiation, induces the transcription of Xbp-1 and promotes plasma cell differentiation [23, 24]. Interestingly, XBP-1 increases the production of IL-6, forming a positive feed-forward loop [25]. Furthermore, IL-6/STAT3 pathway maintains the survival of plasma cells [16]. In this study, our results suggest that IL-6/STAT3 pathway is activated in PCM and may play a vital role in inflammatory response, which is consistent with previous studies on plasma cells.

In this study, we found the expression of IL-6 and the activation of STAT3 in ductal epithelium. In epithelial cells IL-6/STAT3 pathway acti-vation can result in increased expression of intercellular adhesion molecule-1 (ICAM-1), which is overexpressed in ductal epithelium in PCM [26, 27]. ICAM-1 is induced by multiple factors and one of them is the activation of lymphocytes [28]. Induction of ICAM-1 in ductal epithelium may promote infiltrating inflammatory cell homing to the ductal epithelium and then lead to obvious degenerative changes [29].

IL-6/STAT3 pathway rescues T cells and plasma cells from apoptosis, and promotes chronic inflammatory cells infiltration [30, 31]. The infiltration of plasma cells, T lymphocytes and B lymphocytes, the major cell types present in human breast tissue, is mainly observed in PCM. Bcl-2 is a protein that regulates the survival of lymphocytes in a mitochondria-dependent way and has been detected in plasma cells isolated from bone marrow, blood and tonsils [32]. The important anti-apoptotic role of Bcl-2 in plasma cells has been extensively demonstrated [33, 34]. Therefore, we performed immunohistochemical analysis of Bcl-2 in the three groups. The results showed Bcl-2 expression was significantly higher in PCM than in acute mastitis or normal group. Higher expression of Bcl-2 can maintain the survival of inflammatory cells, resulting in the accumulation of massive inflammatory cells. These results indicate that IL-6/STAT3 pathway may inhibit apoptosis of T cells and plasma cells in PCM through upregulating the expression of Bcl-2.

The blockage of major ducts that results from nipple retraction is a crucial cause of PCM [9]. Thus we compared the expression of IL-6 between PCM patients with nipple retraction and other PCM patients. The results showed significantly higher IL-6 expression in PCM patients with nipple retraction than in those without nipple retraction. These data suggest that certain substances in the mammary ducts caused by nipple retraction may result in the production of abundant IL-6 and cause the infiltration of plasma cells, T lymphocytes and B lymphocytes. Therefore, IL-6 plays a vital role in the pathogenesis of PCM.
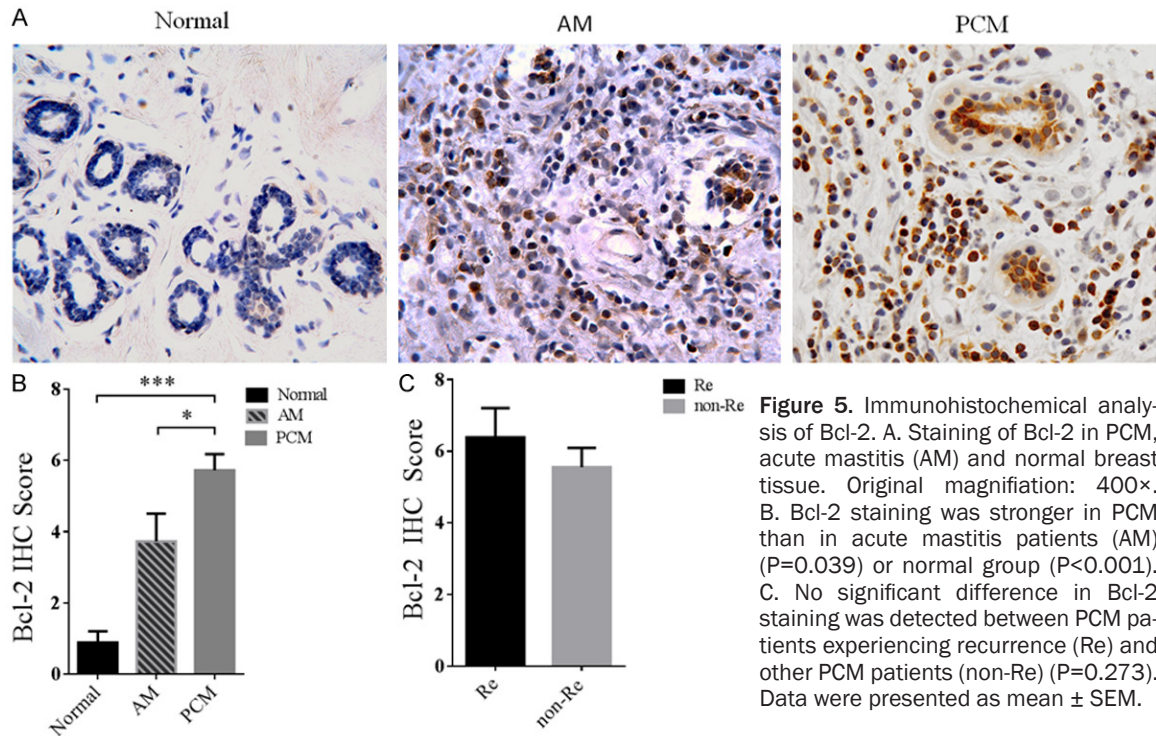
Figure 5. Immunohistochemical analysis of Bcl-2. A. Staining of Bcl-2 in PCM, acute mastitis (AM) and normal breast tissue. Original magnifiation: 400×. B. Bcl-2 staining was stronger in PCM than in acute mastitis patients (AM) (P=0.039) or normal group (P<0.001). C. No significant difference in Bcl-2 staining was detected between PCM patients experiencing recurrence (Re) and other PCM patients (non-Re) (P=0.273). Data were presented as mean ± SEM.

It is well-known that recurrence is the worst characteristic of PCM. In our study, the recurrence rate of PCM was 20%, a little lower than the reported data [8]. We compared the expression of IL-6 between PCM patients experiencing recurrence and other PCM patients and the results showed no significant difference. There was also no significant correlation between the recurrence and p-STAT3 immunostaining (STAT3 activation) in PCM. Furthermore, no significant difference in Bcl-2 immunostaining was detected between PCM patients experiencing recurrence and other PCM patients. These data suggest that the anti-apoptotic effect of IL-6/STAT3 pathway may be irrelevant to the recurrence of PCM and other factors may contribute to the recurrence. For example, the autoimmune theory has been proposed to account for the recurrence of PCM [35].

The present study has some limitations. First, the number of PCM cases was slightly insufficient. Considering the low incidence of PCM, more cases may be difficult to obtain. Second, this study is descriptive. While immunohistochemical analysis suggested the involvement of IL-6/STAT3 pathway in PCM, further studies are necessary to confirm the exact role of IL-6/STAT3 signaling in the pathogenesis of PCM.

In conclusion, we detected higher levels of IL-6, p-STAT3 and Bcl-2 in PCM and found a positive correlation between IL-6 and p-STAT3 immunostaining. Moreover, increased expression of IL-6 was detected in PCM patients with nipple retraction. These data indicate that IL-6/STAT3 signaling is activated and may be involved in the pathogenesis of PCM. Therefore, the components of IL-6/STAT3 pathway present novel therapeutic targets for PCM.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Jian-Jun He, Department of Breast Surgery, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an 710061, China. Tel: +86 29 85324609; Fax: +86 29 85324609; E-mail: chinahjj@163.com

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