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Research Article

Expression of MMP-2 and MMP-13 in Bullous Pemphigoid

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Abstract: ***Objective:*** To investigate the expression and significance of matrix metalloproteinase-2 (MMP-2) and matrix metalloproteinase-13 (MMP-13) in bullous pemphigoid (BP) skin lesions. ***Methods:*** Immunohistochemical SP method was used to detect the expression of MMP-2 and MMP-13 in 32 BP skin lesions, and compared with 15 normal skin tissues. ***Results:*** The expression of MMP-2 in the case group was significantly increased (38.56 ± 10.06) compared to the normal control group (21.20 ± 5.98); the expression of MMP-13 in the case group was significantly augmented (18.62 ± 5.90) compared to the normal control group (11.47 ± 8.484). The expressions of MMP-2 and MMP-13 in the skin lesions of patients with bullous pemphigoid were statistically different from those of normal people (both $P < 0.05$). Compared with the expression of MMP-2 and MMP-13 in bullous pemphigoid, the expression of MMP-2 and MMP-13 was moderately correlated (correlation coefficient was 0.523). ***Conclusion:*** The expression of MMP-2 and MMP-13 is significantly increased in bullous pemphigoid skin lesions, suggesting that they may play an important role in the pathogenesis of BP. There is a certain correlation between the expression of MMP-2 and MMP-13, suggesting that the high expression of MMP-13 may play a role in the mechanism that further leads to the high expression of MMP-2.

Keywords: Matrix metalloproteinase, MMP-2, MMP-13, Bullous pemphigoid

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1 Introduction

Matrix metalloproteinases, also known as matrix enzymes, belong to the zinc-calcium-dependent family of endopeptidases, and their main role is to degrade the extracellular matrix and promote the transformation of various biological factors[1,2]. Matrix metalloproteinases play an important role in normal physiological processes, such as embryo formation, development, tissue remodeling and others. It is also involved in many pathological processes including inflammation, tumors, and cardiovascular diseases[1,3-7]. MMP-2 and MMP-13, as members of the matrix metalloproteinase family, played an important role in the above process. Matrix metalloproteinase 2 (MMP-2) also known as gelatinase A can degrade gelatin and IV collagen fibers which are the main components of base cell membranes[9,10]. Matrix metalloproteinase 13 (MMP-13) also known as collagenase III can widely degrade various components of the basement membrane[11,12]. Bullous pemphigoid (BP) is an autoimmune sub-epidermal vesicular disease characterized by the deposition of autoantibodies on the basement membrane band which is more common in the elderly[11]. There are two main types of BP antigens which are BP180 and BP230. BP180 is currently considered to be the main antigen. Anti-BP180 antibody activates complements, recruits neutrophil and releases proteases to destroy hemidesmosomes and extracellular matrix components. The separation of the true epidermis occurs in the transparent plate of the basal layer, causing the formation of blisters under the epidermis[3]. The separation of the dermis and epidermis must be accompanied by the degradation of the cell-matrix, suggesting that MMP-2 and MMP-13 may play an important role in the occurrence and development of

bullous pemphigoid. To this end, we selectively monitor the expression of the MMP-2 and MMP-13 in bullous pemphigoid skin lesions based on previous studies, in order to confirm the role of matrix metalloproteinases in the disease, and further study the relationship between MMP-2 and MMP-13 and bullous pemphigoid.

2 Materials

a.)Cases and specimens: There are 32 cases of bullous pemphigoid with 15 cases in women and 17 cases in men. The age ranged from 34 to 87 years, with an average of 65.00 ± 15.11 years old. They all came from the Department of Dermatology of Cangzhou People's Hospital. They were diagnosed as bullous pemphigoid by clinical and histopathological examination, and they have not received any treatment. There were 15 normal controls, 7 females and 8 males, aged 28 to 81 years, with an average age of 59.90 ± 13.61 years. All patients were non-dermatological surgical patients in Cangzhou People's Hospital.

b.)Main reagents: Mouse anti-human MMP-2 and MMP-13 monoclonal antibodies (US R&D), goat anti-mouse IgG SP kit (Beijing Zhongshan Jinqiao Biotechnology Co., Ltd.).

3 Experimental method

Sp immunohistochemical staining: Follow the instructions of the Sp kit. The cells at the junction of the true epidermis stained with brown-yellow as positive, and the normal skin was not stained or the staining was not obvious. Analysis of staining results: The average number of 5 positive cells per 0.2 mm² area was counted with a single-blind method using a micrometer with a mesh eyepiece under a high-power lens (400 *). All operations are judged by the same experimenter. Statistical analysis used a t-test and Pearson correlation, $P < 0.05$ was considered statistically significant.

4 Results

Cells expressing MMP-2 and MMP-13 in bullous pemphigoid are mainly located in the epidermal site, especially MMP-13 is more pronounced near the basement membrane. In addition, MMP-2 is also expressed in the cuticle.

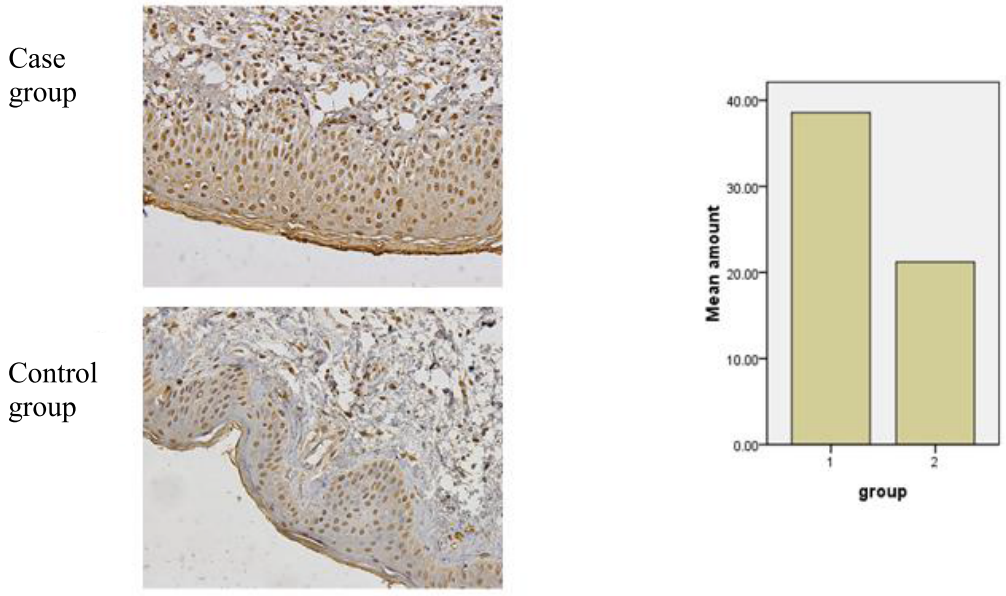

Figure 1. Expression of MMP-2

MMP-2 expression was significantly increased in the case group (38.56 ± 10.06) compared with the control group (21.20 ± 5.98).

The expression of MMP-13 in the case group (18.62 ± 5.90) was also significantly higher than in the control group (11.47 ± 8.484).

The expressions of MMP-2 and MMP-1 in the skin lesions of patients with bullous pemphigoid were statistically different from those of normal people (both $P < 0.05$).

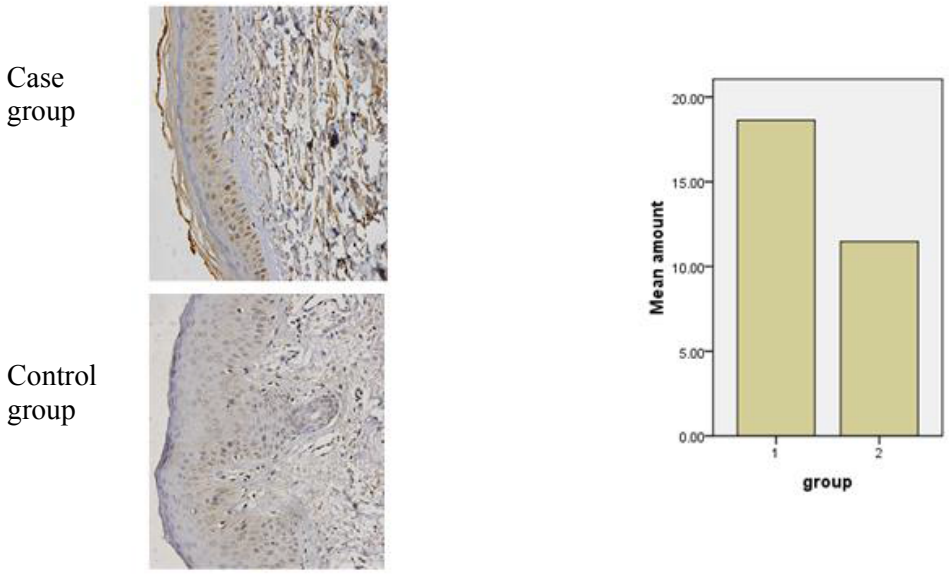

Figure 2. Expression of MMP-13

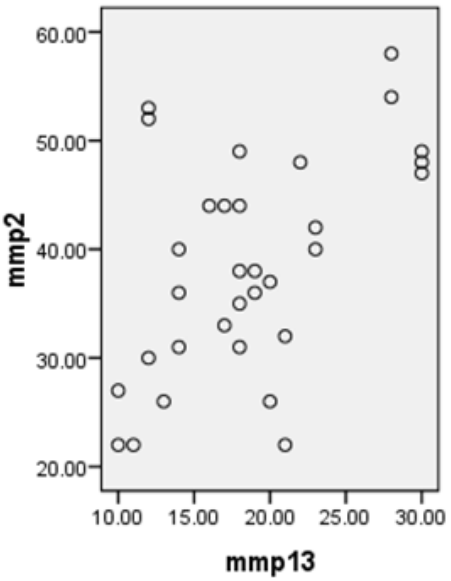

Figure 3. Relationship between MMP-13 and MMP-2

At the same time, comparing the expression of MMP-2 and MMP-13 in bullous pemphigoid, the expression of MMP-2 and MMP-13 was moderately correlated (correlation coefficient was 0.523).

5 Discussion

Currently, we understand that BP is an autoimmune sub-epidermal vesicular disease, and its pathogenesis is related to the destruction of basement membrane components. Autoantibodies bind to epidermal basement membrane antigens to activate a series of immunological and enzymatic phenomena which leads to the formation of vesicles. Some data have shown that MMPs are involved in the development of bullous pemphigoid skin lesions, but their role in this process is unclear. However, MMP-1, -2, -9, and -10 were detected in keratinocytes throughout the epidermis or base, and most enzymes were also detected in the blister site[17]. It has been reported that the separation of epidermis and dermis occurs in the basal layer, accompanied by a large number of inflammatory infiltrates and degradation of hemidesmosomes and extracellular matrix components. Proteolytic enzymes of inflammatory cells are involved in the formation of BP blisters. Proteolytic enzymes, including MMP-2, -9, and others have been detected in the vesicles and skin lesions of BP[3]. Under normal

circumstances, the expression and activity of MMPs are relatively stable through the regulation of transcription levels, zymogen activity, inhibitory effects of inhibitors, and cell phagocytosis. Abnormal expression and activity are closely related to many diseases[8]. In addition, foreign studies have reported that the basement membrane is composed of a variety of substances, such as collagen VI, collagen VII, laminin, fibrin, and others; MMP-2, -9 and -13 can reduce collagen VI which is the main component of cell basement membrane[14]. The current study found that the expression of MMP-2 and MMP-13 in bullous pemphigoid was significantly higher than that of normal people, suggesting that MMP-2 and MMP-13 may play an important role in the formation of bullous pemphigoid blisters. Another study found that the levels of MMP-2, -7, -9, -12 and -13 increased after asbestos-induced lung injury. The activity of MMPs may be related to the development of asbestos in the lung. MMPs can regulate inflammation and interstitial lung fibrosis development. MMP-2 and -13 play an important role in the process of pulmonary fibrosis[15]. Mechanistic depiction of the role of MMP-13 to activate the positive feedback pathway of MMP-2 and -9 activities. Asbestos-mediated pulmonary fibrosis is the same as that caused by paraquat and peroxide[15,16]. The results of this study indicate that there is a correlation between the expression of MMP-2 and MMP-13, suggesting that the high expression of MMP-13 may play a role in the mechanism that further leads to the high expression of MMP-2.

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