Psoriasis is a chronic inflammatory skin disease, and immunological disorder plays a crucial role in the pathogenesis of psoriasis. Antimicrobial peptides (AMPs), including cathelicidin (LL-37) and human beta-defensin (HBD)-3, are not only the basis of innate immunity but also a bridge to activate adaptive immunity. In the immune response, several inflammatory cytokines, including tumor necrosis factor-α, interleukin (IL)-6, IL-10, IL-17, IL-22, and IL-23, are involved in the occurrence and development of psoriasis. Guttate psoriasis was known to have a better prognosis than other types of psoriasis with a rapid regression and a longer remission period. However, 33.0% to 68.3% of guttate psoriasis subsequently develops into chronic plaque psoriasis during the follow-up period of at least 1 or 10 years. However, the association of pathogenesis between guttate and plaque psoriasis is not clear, and most studies only focus on inflammatory cytokine changes in plaque psoriasis rather than in guttate psoriasis. This study aimed to compare the levels of serum inflammatory cytokines and AMPs of the variants (plaque vs. guttate) of psoriasis vulgaris, specifically some potential treatment targets, and to reveal the pathogenesis in different clinical manifestations.

This study was approved by the Ethical Committee of the Peking University People’s Hospital (No. 2020PHB034-01). All patients signed a written informed consent. A retrospective selection of patients and controls from the dermatology outpatient clinic of the Peking University People’s Hospital from January 2017 to August 2018 was performed. Fifty-three patients with psoriasis vulgaris (20 with guttate psoriasis, 13 with mild plaque psoriasis, and 20 with moderate-severe plaque psoriasis) and 24 controls were enrolled in the study. The diagnosis of psoriasis was confirmed using clinical and histopathological criteria. The guttate group comprised patients whose lesions were papules with diameters of <1 cm, whereas the plaque group comprised patients with at least one lesion with a long axis of >5 cm. Based on the clinical classification of the American National Psoriasis Foundation, body surface area (BSA) was used to classify patients with plaque psoriasis into two sub-groups: the mild plaque group (lesion involvement below 3% of BSA) and the moderate-severe plaque group (lesion involvement above 3% of BSA). The major inclusion criteria were as follows: no local or systemic treatment for at least 4 weeks before study entry; no significant infection or immune suppression; and no history of specific medical diagnoses with renal, hepatic, cardiovascular, pulmonary, rheumatic, or endocrine involvement. The control group comprised healthy volunteers with no history of specific medical diagnoses with renal, hepatic, cardiovascular, pulmonary, rheumatic, or endocrine involvement.

Venous blood samples (5–10 mL) were collected into vacuum tubes under sterile conditions from both the patient and control groups. Serum was obtained by spinning the samples in a centrifuge, then immediately frozen at −70°C, and stored until analysis. Quantitative analysis was performed by enzyme-linked immunosorbent assay with commercially available kits to measure serum IL-10 (Biovendor, Czech Republic), IL-17 (RD systems, Minneapolis, MN, USA), IL-22 (RD systems), IL-23 (RD systems), IL-37 (Hy Justin Biotech, Uden, Netherlands), and HBD-3 (Antigenix America Inc., NY, NY, USA) levels, according to the manufacturer’s instructions.

Data analysis were performed and graphs were plotted using GraphPad Prism version 5 (GraphPad Software, San Diego, CA, USA) and Statistical Package for the Social Sciences software ver. 24 (International Business Machines Corporation, Chicago, IL, USA). Data are represented as medians (interquartile range). P < 0.05 was considered significant. The two-tailed Kruskal-Wallis test with the post-hoc Bonferroni was used for comparison of param-


The mean age of patients was 38.85 ± 13.39 years, including 22 females and 31 males. The mean age of controls was 47.58 ± 16.30 years, including 15 females and 9 males. No statistically significant difference was noted between the mean age and sex in each group (P > 0.05). The demographical characteristics of psoriasis patients and controls are presented in Supplementary Table 1, http://links.lww.com/CMAJ/A386.

Serum levels of cytokines and AMPs were analyzed in four groups: guttate psoriasis, mild plaque psoriasis, moderate-severe plaque psoriasis, and controls [Table 1]. Serum IL-10 levels were significantly higher in the guttate psoriasis group than those in controls (P < 0.05). In contrast, the serum HBD-3 levels were significantly lower in the guttate psoriasis group than those in controls (P < 0.05). In the mild plaque psoriasis group, the levels of few inflammatory cytokines increased, but the serum IL-22 levels were significantly higher in the mild plaque psoriasis group than those in controls (P < 0.05). In the mild plaque psoriasis group, the levels of few inflammatory cytokines increased, but the serum IL-22 levels were significantly higher in the mild plaque psoriasis group than those in controls (P < 0.05). IL-10, IL-17, IL-22, and IL-23 levels were also higher in the moderate-severe plaque psoriasis group than those in controls (P < 0.05). Furthermore, IL-22 and IL-23 levels were significantly higher in the moderate-severe plaque psoriasis group than those in the guttate psoriasis group (P < 0.01). Although IL-17 and IL-23 levels were also higher in the moderate-severe plaque psoriasis group than those in the mild plaque group, only the difference in IL-23 levels was statistically significant (P < 0.05).

The correlations in the serum levels of cytokines and AMPs are presented in Supplementary Figure 1, http://links.lww.com/CMAJ/A386. In guttate psoriasis patients, the circulating IL-17 levels were significantly and positively correlated with IL-22 levels (r = 0.658, P < 0.01). In patients with moderate-severe plaque psoriasis, serum IL-10 levels had a positive correlation with IL-17 (r = 0.450, P < 0.05) and IL-22 levels (r = 0.452, P < 0.05). However, in patients with mild plaque psoriasis, serum IL-23 levels were negatively correlated with LL-37 levels (r = -0.539, P < 0.05).

The pathogenic mechanisms of psoriasis are sustained by the activation of inflammatory pathways. IL-23/17 axis is crucial in stimulating and maintaining inflammation in plaque psoriasis.[1] Our present datum confirmed that serum IL-17 and IL-23 levels were higher in the moderate-severe plaque psoriasis group than those in controls. However, in the guttate psoriasis group, serum IL-17 and IL-23 levels are controversial. IL-17 and/or IL-23 levels were higher or had no significant difference in the guttate psoriasis patients compared with those in plaque psoriasis patients.[5] In our study, the circulating IL-17 and IL-23 levels in the moderate-severe plaque psoriasis group were higher than those in the guttate psoriasis group, and the difference in IL-23 levels demonstrated a significant difference. Therefore, the possible reason for these different results is the insufficient analysis about plaque psoriasis subgroups according to disease severity. Considering our results, the IL-23/17 axis mainly affects plaque psoriasis instead of guttate psoriasis; hence, the biologics of anti-IL-17 or anti-IL-23 should not be used in guttate psoriasis patients. Moreover, serum IL-23 levels, rather than serum IL-17 levels, were significantly higher in the moderate-severe plaque psoriasis group than those in the mild psoriasis group. Thus, IL-23 may play an important role in regulating and maintaining psoriasis.

Nowadays, it was revealed that the pathogenesis of psoriasis is related to immunological imbalance.[5] IL-10 and IL-22, both as IL-10 family cytokines, participate in psoriasis pathogenesis. They exert essential functions to maintain tissue homeostasis during infection and inflammation.[4] Yan et al.[5] found that the numbers of Foxp3+ Tregs in skin lesions and peripheral blood were higher in plaque psoriasis than in normal control and guttate psoriasis. Hence, they hypothesized that the number of Foxp3+ Tregs, one of the IL-10-producing cells,[1] is increased in a feedback manner crucial in stimulating and maintaining inflammation in plaque psoriasis. In our study, the circulating IL-17 and IL-23 levels were higher in the moderate-severe plaque psoriasis group than those in controls. However, in the guttate psoriasis group, serum IL-17 and IL-23 levels are controversial. IL-17 and/or IL-23 levels were higher or had no significant difference in the guttate psoriasis patients compared with those in plaque psoriasis patients. In our study, the circulating IL-17 and IL-23 levels in the moderate-severe plaque psoriasis group were higher than those in the guttate psoriasis group, and the difference in IL-23 levels demonstrated a significant difference. Therefore, the possible reason for these different results is the insufficient analysis about plaque psoriasis subgroups according to disease severity. Considering our results, the IL-23/17 axis mainly affects plaque psoriasis instead of guttate psoriasis; hence, the biologics of anti-IL-17 or anti-IL-23 should not be used in guttate psoriasis patients. Moreover, serum IL-23 levels, rather than serum IL-17 levels, were significantly higher in the moderate-severe plaque psoriasis group than those in the mild psoriasis group. Thus, IL-23 may play an important role in regulating and maintaining psoriasis.

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| Table 1: Levels of specific serum cytokines and AMPs in each group (pg/mL). |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Items           | Guttate psoriasis (n = 20) | Mild plaque psoriasis (n = 13) | Moderate-severe plaque psoriasis (n = 20) | Controls (n = 24) | Statistics | P value |
| IL-10           | 0.91 (0.46–1.24)‡ | 0 (0–1.33)‡ | 1.09 (0.54–1.61)‡ | 0 (0–0.89) | 17.262 | 0.001 |
| IL-17           | 2.19 (0–6.17)‡ | 0 (0–37.38)‡ | 8.51 (1.64–21.73)‡ | 0 (0–6.53) | 8.369 | 0.039 |
| IL-22           | 0 (0–5.75)‡ | 10.3 (0–31.58)‡ | 8.25 (0.54–47.21)‡ | 0 (0–0) | 27.275 | <0.001 |
| IL-23           | 0 (0–3.8)‡ | 0 (0–0)‡ | 12.19 (0.30–21.71)‡ | 0 (0–3.56) | 19.063 | <0.001 |
| LL-37           | 203.09 (7.25–467.27)‡ | 417.17 (205.25–654.63) | 278.60 (96.60–802.67) | 475.82 (247.29–916.09) | 6.241 | 0.100 |
| HBD-3           | 92.7 (70.94–107.18)‡ | 133.08 (108.46–152.80) | 114.36 (73.75–173.22) | 140.75 (127.83–195.32) | 9.351 | 0.025 |

Data are expressed as median (interquartile range). Kruskal-Wallis test. †P < 0.05. ‡P < 0.01. † †P < 0.001, compared with controls. † † †P < 0.001, compared with mild plaque psoriasis. † † † †P < 0.01, compared with guttate psoriasis. AMPs: Antimicrobial peptides; IL: Interleukin; LL: Cathelicidin; HBD: Human beta-defensin.
blocking IL-22 was not successful in plaque psoriasis.\textsuperscript{[1]} Hence, IL-22 may not be a key cytokine in psoriasis. Moreover, IL-22 was not involved in guttate psoriasis pathogenesis.

Although extensive studies reported that LL-37 and HBD-3 are overexpressed in psoriatic lesions, there are few data on circulating AMPs, specifically in guttate psoriasis. Our results showed that the circulating AMP levels were lower in the guttate psoriasis group than in controls, which may be related with the high incidence of acquiring \textit{Streptococcus pyogenes}-associated throat infection in guttate psoriasis. Furthermore, we found that serum AMP levels were lower in the plaque psoriasis group than in controls, but the difference was not statistically significant between the two groups. We presumed that there were some antibodies that combined with AMPs to consume them, such as complement antibodies in lupus erythematosus. Similarly, Anderson \textit{et al}\textsuperscript{[6]} found that there was a strong and specific expression of psoriasis in psoriatic epidermis, but psoriasis levels were lower in patients with psoriatic epidermis than those in controls, and these levels decreased with increasing disease severity. They concluded that this is possibly attributed to the presence of psoriasis-specific autoantibodies.

In conclusion, this study compared circulating cytokines and AMP levels in several types (plaque \textit{vs.} guttate) of psoriasis vulgaris. The results showed that the immune responses were changing in different phenotypes and different severities. The serum AMP levels were lower and IL-10 levels were higher in the guttate psoriasis group than those in controls, but circulating IL-17 and IL-23 levels did not differ with those in controls. Serum IL-23 levels demonstrated a more noticeable difference between the mild and moderate-severe plaque psoriasis groups than serum IL-17 levels. Furthermore, this difference may provide an evidence for a potential targeted therapy for guttate psoriasis and plaque psoriasis.

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\textbf{Conflicts of interest}

None.

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