Association of ERAP1 gene polymorphisms with the susceptibility to psoriasis vulgaris

A case–control study

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**Abstract**
Psoriasis vulgaris (PsV), also known as plaque psoriasis, is a life-threatening autoimmune skin disease. Inflammatory factors may contribute to the development of PsV. Present study aimed to explore the association of endoplasmic reticulum aminopeptidase 1 (ERAP1) gene polymorphisms (rs26653 and rs27524) with PsV susceptibility in a Chinese Han population. Subgroup analysis was also performed based on the onset of PsV.

Present case–control study included 143 patients with PsV and 149 healthy controls. Direct sequencing method was used for genotyping ERAP1 polymorphisms. Chi-squared test was used to estimate the association between ERAP1 polymorphisms and PsV susceptibility. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to assess association strength.

The polymorphism rs26653 was positively correlated with PsV susceptibility (CC vs GG, P = .047, OR = 1.964, 95% CI = 1.006–3.834; C vs G, P = .042, OR = 1.403, 95% CI = 1.011–1.946). Meanwhile, its CC genotype and C allele were positively associated with the early onset of PsV (P = .036, OR = 2.080, 95% CI = 1.044–4.145; P = .034, OR = 1.443, 95% CI = 1.028–2.024) and increased PsV risk in the subgroup with family history (P = .029, OR = 2.149, 95% CI = 1.075–4.296; P = .027, OR = 1.466, 95% CI = 1.044–2.059).

**Abbreviations:** CHB = Chinese Han in Beijing, CIs = confidence intervals, EO-PsV = early onset psoriasis vulgaris, ERAP1 = endoplasmic reticulum aminopeptidase 1, GWAS = genome wide association study, HLA = human leukocyte antigen, HWE = Hardy–Weinberg equilibrium, INF = interferon, LO-PsV = late onset psoriasis vulgaris, MHC = major histocompatibility complex, NF-κB = nuclear factor kappa B, ORs = odds ratios, PsV = psoriasis vulgaris, SNPs = single-nucleotide polymorphisms.

**Keywords:** ERAP1, polymorphisms, psoriasis vulgaris, subgroup analysis

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**1. Introduction**
Psoriasis vulgaris (PsV) is one of the most common long lasting inflammatory skin diseases.\(^1\) PsV usually affects back, scalp, elbows, and knees,\(^2\) and is characterized by erythema and plaques. PsV may attack people of all ages, but mainly in young adults. According to onset age, PsV could be divided into early onset PsV (EO-PsV) and late onset PsV (LO-PsV).\(^3\) PsV, a life-threatening disease, is intractable and tends to relapse. Even worse, PsV may cause different complications.\(^4\)

PsV decreases the life quality of its patients, and imposes heavy mental pressure and economic burden on family member.\(^5\) Epidemiology study has suggested that PsV exhibits high prevalence globally.\(^6\) The pathogenesis of PsV is not fully understood, but it is well known that vascular remodeling, epidermal hyper-proliferation and inflammation are major histopathology for PsV. PsV is universally considered to be a genetic disease which is affected by ethnicity, region, and environment factors.\(^7\) T-cells mediate the proliferation of cutaneous cells in patients with PsV.\(^9\) Many elements in immune system may contribute to the development of PsV.\(^10\)

Endoplasmic reticulum aminopeptidase 1 (ERAP1), an aminopeptidase induced by γ-interferon (INF), belongs to the zinc finger metal matrix peptidase M1 family.\(^11\) As a cytokine receptors on cell surface, ERAP1 may act as an antigen-processing machinery involved in proteins’ process and transport.\(^12\)\(^,\)\(^13\) Additionally, ERAP1 also participates in the trimming of HLA class-I-binding precursors and regulates the function of natural killer cells.\(^14\)\(^,\)\(^15\) Besides, ERAP1 has been reported to take part in psoriasis.\(^17\)\(^,\)\(^18\) ERAP1 gene is located at chromosome 5q13. Many polymorphisms in ERAP1 gene have been identified to be possibly able to alter proteins’ conformational structure, specificity, and activity.\(^14\) Nonsynonymous single-nucleotide polymorphisms (SNPs), rs26653 (Arg127Pro), rs30187 (Lys528Arg), and rs27044 (Asp730Glu) have been found in different exons in ERAP1 gene. Genome-wide association study (GWAS) found that rs27524 is an additional
psoriasis-associated variant. And some polymorphisms are significantly associated with human leukocyte antigen (HLA)-C*06 in patients with psoriasis. All the evidences suggested that ERAP1 gene polymorphisms played a crucial role in inflammatory response in PsV.

Polymorphism distributions are usually different between regions. In current study, we selected 2 SNPs not widely studied in China, rs26653 and rs27524, to detect their association with PsV susceptibility in a Chinese Han population.

2. Materials and methods

2.1. Study subjects

A total of 143 patients with PsV were recruited from Linyi People’s Hospital. Healthy individuals without systemic autoimmune disorders and skin lesions were enrolled as control group. Healthy controls were matched with the cases in both age and gender. These participants were Chinese Han people. The current study was approved by the Ethic committee of Linyi People’s Hospital. Informed consent was signed by each participant. Demographic and clinical characteristics were recorded through questionnaire.

2.2. Genotyping

Blood samples were collected from each subject and processed with EDTA. Then genomic DNA was extracted using DNA extraction kit (TIANGEN, Beijing, China) according to the manufacturer’s specification.

The PCR primers for ERAP1 gene rs26653 and rs27524 polymorphisms were designed using Primer Premier 5.0 (Table 1). ERAP1 gene polymorphisms were amplified through PCR and sequenced adopting direct sequencing method.

2.3. Statistical analysis

The conformity to Hardy–Weinberg equilibrium (HWE) was examined to detect the representativeness of the subjects. Genotype and allele frequencies were calculated through direct counting. Correlation between ERAP1 gene polymorphisms and PsV susceptibility was assessed using odds ratios (ORs) with corresponding 95% confidence intervals (CIs). All of the calculations were performed with PASW 18.0. All the tests were 2-tailed, and P-values < .05 were considered as statistical significance.

3. Results

3.1. Characteristics of subjects

Age and gender showed no significant difference between case and control groups. As for the age of onset, it was below 40 years in 125 (87.41%) patients (EO-PsV) and over 40 in 18 (12.59%) cases (LO-PsV). Among the patients, the onset age and disease duration were 30.52 ± 9.14 and 11.32 ± 6.19 years, respectively. Only 19 patients had the family history of PsV, while none of the controls had the family history (Table 2).

3.2. Association of ERAP1 gene SNPs with the susceptibility to PsV

Genotype distributions of ERAP1 gene rs26653 and rs27524 SNPs did not deviate from HWE in control group (Table 3, P > .05), revealing that the controls were representative for general population.

The frequencies of the GG, GC, and CC genotypes of rs26653 SNP were 25.17%, 51.05%, 23.78% in patients with PsV, and 34.90%, 48.32%, 16.78% in healthy controls. Besides, the CC genotype and C allele were significantly more frequent in patients with PsV than in healthy controls, indicating that they could significantly increase PsV susceptibility (P = .047, OR = 1.964, 95% CI = 1.006–3.834; P = .042, OR = 1.403, 95% CI = 1.011–1.946). As for rs27524 SNP, its AA genotype and A allele exhibited higher frequencies in patients with PsV than in the controls, but the difference was not significant (20.98 vs 14.09, P = .076). While the frequencies of the GG and GA genotypes and the G allele were similar between case and control groups (P > .05 for all). So rs27524 SNP might had no significant association with PsV risk (Table 3).

3.3. Subgroup analysis on the association between ERAP1 SNPs and PsV risk

The CC genotype and C allele of rs26653 SNP were significantly correlated with increased risk of EO-PsV (Table 4, P = .036, OR = 2.080, 95% CI = 1.044–4.145; P = .034, OR = 1.443, 95% CI = 1.028–2.024). No association was observed between rs26653 SNP and LO-PsV; nor was between rs27524 SNP and either EO-PsV or LO-PsV. However, the AA genotype and A

| Table 1 | Primer sequences of ERAP1 gene polymorphisms. |
|---------|-----------------------------------------------|
| rs ID   | Region | Allele | Variation | Primer sequence | Annealing (°C) |
| rs26653 | Exon2   | C/G     | Arg127Pro | F: 5'-GAGGCAGATTGCTAGAGGAGA-3' | 55 |
|         |         |         |          | R: 5'-GCCTGTGGCTTCTGTGA-3' | |
| rs27524 | 3'UTR   | A/G     | None      | F: 5'-GGAAGGCTACTOSGAGAAGAACC-3' | 60 |
|         |         |         |          | R: 5'-CCGAAAGATTGACGTAATGAAA-3' | |

| Table 2 | Characteristics of subjects. |
|---------|-------------------------------|
| Characteristic | Case n = 143 (%) | Control n = 149 (%) | P  |
| Age       | 42.39 ± 12.12 | 41.28 ± 11.59 | .790 |
| Gender    | .884 |
| Male      | 78 (54.55) | 80 (53.69) | |
| Female    | 65 (45.45) | 69 (46.31) | |
| Duration of PsV | 11.32 ± 6.19 | 10.54 ± 6.14 | .036 |
| Onset age | 30.52 ± 9.14 | 27.32 ± 9.14 | |
| Family history | 19 | 0 | |
| PsV types |     |
| EO-PsV   | 125 (87.41) | |
| LO-PsV   | 18 (12.59) | |

EO-PsV = early onset PsV, LO-PsV = late onset PsV, PsV = psoriasis vulgaris.
allele of rs27524 SNP showed a tendency toward being related to EO-PsV, which might become significant in a larger sample size.

Subgroup analysis based on gender revealed no significant association of rs26653 and rs27524 SNPs with PsV susceptibility, either in males or in females (Table 5, \( P > 0.05 \)).

Subgroup analysis based on family history showed that rs26653 CC genotype was distinctly correlated with enhanced PsV risk in the patients with family history (Table 6, \( P = 0.029 \), OR = 2.149, 95% CI = 1.075–4.296). Such association was also observed for rs26653C allele (\( P = 0.027 \), OR = 1.466, 95% CI = 1.044–2.059). No obvious association was detected between rs26653 SNP and PsV risk in patients without family history. While rs27524 SNP had no significant association with PsV risk in either of the subgroups with and without family history (\( P > 0.05 \)).

4. Discussion

Disorders in immune system in regard to skin cells (especially the excessive and rapid growth of epidermal layer during wound repair) may lead to skin diseases, including PsV.\(^{[23–26]}\) Presently, PsV has been regarded as a complex and multifactorial disease, and its pathogenesis is reportedly associated with hereditary factors, immune or inflammatory factors, life style, and other environmental factors.\(^{[23–26]}\) Hyper-proliferative and infiltrating keratinocytes interact with activated immune cells and thus result in PsV onset.\(^{[27]}\) A variety of immune cells play important roles in PsV pathogenesis. These immune cells, moving from dermis to epidermis, secrete cytokines, and participate in different immune pathways.\(^{[10]}\) Various immune pathways have been proved to be involved in PsV, including TH17 pathway, passive immunity pathway, and nuclear factor kappa B (NF-κB) subunit 1 and interferon signaling pathways.\(^{[3,28–31]}\) Immune or inflammatory genes involved in these pathways may be associated with the occurrence of PsV.

The ERAP1 could regulate the link between peptides and major histocompatibility complex (MHC) class I molecules, such as HLA-C.\(^{[32]}\) It has been reported that mutations in ERAP1 gene are correlated with PsV susceptibility only in people harboring certain alleles of the HLA-C.\(^{[21]}\) GWAS and meta-analysis found that mutations in ERAP1 gene were distinctly related to the development of PsV.\(^{[21,23]}\) In addition, ERAP1 gene rs26653 SNP was positively associated with different inflammatory diseases, such as ankylosing spondylitis and inflammatory bowel disease.\(^{[33]}\) Therefore, it is reasonable to speculate that ERAP1 gene SNPs might be correlated with PsV susceptibility in Chinese populations.

### Table 3

| Genotype/allele | Case n = 143 (%) | Control n = 149 (%) | \( P \) | OR (95% CI) |
|-----------------|------------------|---------------------|--------|-------------|
| rs26653         |                  |                     |        |             |
| GG              | 36 (25.17)       | 52 (34.90)          | –      | –           |
| GC              | 73 (51.05)       | 72 (48.32)          | .162   | 1.465 (0.857–2.501) |
| CC              | 34 (23.78)       | 25 (16.78)          | .047   | 1.964 (1.006–3.934) |
| G               | 145 (50.70)      | 176 (59.06)         | –      | –           |
| C               | 141 (49.30)      | 122 (40.94)         | .042   | 1.403 (1.011–1.948) |
| \( P_{\text{HWE}} \) |                 | 0.993               |        |             |
| rs27524         |                  |                     |        |             |
| GG              | 44 (30.77)       | 57 (38.26)          | –      | –           |
| GA              | 69 (48.25)       | 71 (47.65)          | .380   | 1.259 (0.753–2.106) |
| AA              | 30 (20.98)       | 21 (14.09)          | .076   | 1.851 (0.935–3.662) |
| G               | 157 (54.90)      | 185 (62.08)         | –      | –           |
| A               | 129 (45.10)      | 113 (37.92)         | .078   | 1.345 (0.967–1.871) |
| \( P_{\text{HWE}} \) |                 | .883                |        |             |

90% CI = 95% confidence interval, OR = odds ratio, \( P_{\text{HWE}} = \) \( P \)-value for Hardy–Weinberg equilibrium, PsV = psoriasis vulgaris.

### Table 4

| Genotype/allele | EO-PsV n = 125 (%) | LO-PsV n = 18 (%) | Control n = 149 (%) | \( P \) | OR (95% CI) | \( P \) | OR (95% CI) |
|-----------------|--------------------|------------------|--------------------|--------|-------------|--------|-------------|
| rs26653         |                    |                  |                    |        |             |        |             |
| GG              | 31 (24.80)         | 5 (27.78)        | 52 (34.90)         | –      | –           | –      | –           |
| GC              | 63 (50.40)         | 10 (55.56)       | 72 (48.32)         | .177   | 1.468 (0.839–2.566) | .522   | 1.444 (0.466–4.477) |
| CC              | 31 (24.80)         | 3 (16.67)        | 25 (16.78)         | .036   | 2.080 (1.044–4.145) | .773   | 1.248 (0.276–5.642) |
| G               | 125 (50.00)        | 20 (55.56)       | 176 (59.06)        | –      | –           | –      | –           |
| C               | 125 (50.00)        | 16 (44.44)       | 122 (40.94)        | .034   | 1.443 (1.028–2.024) | .687   | 1.154 (0.575–2.317) |
| rs27524         |                    |                  |                    |        |             |        |             |
| GG              | 38 (30.40)         | 6 (33.33)        | 57 (38.26)         | –      | –           | –      | –           |
| GA              | 60 (48.00)         | 9 (50.00)        | 71 (47.65)         | .385   | 1.268 (0.742–2.165) | .738   | 1.204 (0.405–3.582) |
| AA              | 27 (21.60)         | 3 (16.67)        | 21 (14.09)         | .065   | 1.929 (0.955–3.894) | .702   | 1.357 (0.311–5.923) |
| G               | 136 (54.40)        | 21 (58.33)       | 185 (62.08)        | –      | –           | –      | –           |
| A               | 114 (45.60)        | 15 (41.67)       | 113 (37.92)        | .069   | 1.372 (0.975–1.931) | .662   | 1.169 (0.579–2.361) |

90% CI = 95% confidence interval, EO-PsV = early onset PsV, LO-PsV = late onset PsV, OR = odds ratio, PsV = psoriasis vulgaris.
Table 5
Subgroup analysis of association between ERAP1 single-nucleotide polymorphisms and PsV susceptibility based on gender.

| Genotype/allele | Male Case n=78 (%) | Male Control n=80 (%) | Female Case n=65 (%) | Female Control n=69 (%) | P | OR (95% CI) | P | OR (95% CI) |
|-----------------|-------------------|----------------------|---------------------|------------------------|----|-------------|----|-------------|
| rs26653         |                   |                      |                     |                        |    |              |    |              |
| GG              | 19 (24.36)        | 29 (36.25)           | 17 (26.15)          | 23 (33.33)             |    | –           |    | –           |
| GC              | 40 (51.28)        | 39 (48.75)           | 33 (50.77)          | 34 (47.83)             | .226| 1.565 (0.756–2.340) | .453| 1.353 (0.613–2.984) |
| CC              | 19 (24.36)        | 12 (15.00)           | 15 (23.08)          | 13 (18.84)             | .059| 2.417 (0.958–6.099) | .368| 1.561 (0.591–4.126) |
| G               | 78 (60.00)        | 97 (76.63)           | 67 (51.54)          | 79 (57.26)             |    | –           |    | –           |
| C               | 78 (60.00)        | 63 (39.37)           | 63 (48.46)          | 59 (18.84)             | .057| 1.540 (0.986–2.405) | .348| 1.259 (0.778–2.038) |
| rs27524         |                   |                      |                     |                        |    |              |    |              |
| GG              | 23 (24.99)        | 31 (38.75)           | 21 (32.31)          | 26 (37.68)             |    | –           |    | –           |
| GA              | 38 (48.72)        | 38 (47.50)           | 31 (47.69)          | 33 (47.83)             | .404| 1.348 (0.668–2.720) | .695| 1.163 (0.546–2.476) |
| AA              | 17 (21.79)        | 11 (13.75)           | 13 (20.00)          | 10 (14.49)             | .120| 2.083 (0.821–5.283) | .352| 1.610 (0.589–4.398) |
| G               | 84 (63.85)        | 100 (62.50)          | 73 (56.15)          | 85 (61.59)             |    | –           |    | –           |
| A               | 72 (46.15)        | 60 (37.50)           | 57 (43.85)          | 53 (38.41)             | .119| 1.429 (0.912–2.238) | .366| 1.252 (0.769–2.039) |

Table 6
Subgroup analysis of association between ERAP1 single-nucleotide polymorphisms and PsV susceptibility based on family history.

| Genotype/allele | Family history | No n=124 (%) | Yes n=19 (%) | Control | With family history | P | OR (95% CI) | P | OR (95% CI) |
|-----------------|----------------|--------------|-------------|---------|---------------------|----|-------------|----|-------------|
| rs26653         |                |              |             |         |                     |    |              |    |              |
| GG              |               | 30 (24.19)   | 6 (31.58)   | 52 (42.60) | –                   | .146| 1.517 (0.864–2.661) | .735| 1.204 (0.412–3.520) |
| GC              |               | 63 (50.81)   | 10 (52.63)  | 72 (48.32) | .029               | 2.149 (1.075–4.296) | .958| 1.040 (0.240–4.504) |
| CC              |               | 31 (25.00)   | 3 (15.79)   | 25 (16.78) | –                   | .366| 1.252 (0.769–2.039) | .891| 1.049 (0.529–2.079) |
| G               |               | 123 (49.60)  | 22 (57.89)  | 176 (59.06) | –                   | .919| 1.234 (0.774–2.264) | .875| 0.918 (0.314–2.682) |
| C               |               | 125 (40.40)  | 16 (42.11)  | 122 (40.94) | .072               | 1.093 (0.793–1.503) | .514| 1.610 (0.589–4.398) |
| rs27524         |                |              |             |         |                     |    |              |    |              |
| GG              |               | 37 (29.84)   | 7 (36.84)   | 57 (38.26) | –                   | .226| 1.565 (0.756–2.340) | .453| 1.353 (0.613–2.984) |
| GA              |               | 61 (49.19)   | 8 (42.11)   | 71 (47.69) | .360               | 1.324 (0.774–2.264) | .875| 0.918 (0.314–2.682) |
| AA              |               | 26 (20.97)   | 4 (21.05)   | 21 (14.09) | .072               | 1.090 (0.793–1.503) | .514| 1.610 (0.589–4.398) |
| G               |               | 135 (54.44)  | 22 (57.89)  | 185 (62.08) | –                   | .226| 1.565 (0.756–2.340) | .453| 1.353 (0.613–2.984) |
| A               |               | 113 (45.56)  | 16 (42.11)  | 113 (37.92) | .071               | 1.370 (0.973–1.930) | .617| 1.191 (0.600–2.362) |

Han population. In the present study, we selected 2 SNPs with the minor allele frequencies >.5 in CHB (Chinese Han in Beijing) to verify the hypothesis.

We found that the CC genotype of rs26653 SNP increased PsV susceptibility by 1.964 times. At the same time, the degree of increase in disease risk by its C allele was up to 1.403 times. These findings partly accorded with those from a previous study by Lysell et al which found that rs26653 was strongly correlated with psoriasis susceptibility in their studied population. Our subgroup analysis found significantly enhanced disease risk related to rs26653 CC genotype for EO-PsV, and its C allele elevated the disease susceptibility by 1.443 folds for EO-PsV. However, no significant association was observed for LO-PsV. We failed to find any significant association for ERAP1 SNPs with PsV risk, in either male or female subgroup. While the CC genotype and C allele of rs26653 SNP increased PsV risk in patients with the family history by 2.149 and 1.466 times, respectively. Besides, rs26653 was obviously associated with the response to ustekinumab therapy among patients with psoriasis.

Minor allele of rs27524 SNP had higher frequency in patients with PsV than in healthy controls. There was a tendency for the relationship of ERAP1 gene rs27524 SNP with increased PsV risk, though without statistical significance. No significant association was discovered of rs27524 SNP with PsV types, genders, or with or without family history. Our findings accorded with those from a previous study by Lysell and colleagues in a Sweden population. But divergence still exists. For instance, Yang et al suggested that rs27524 SNP was distinctly associated with PsV risk. In addition, GWAS demonstrated that rs27524 A allele was significantly associated with classical Hodgkin lymphoma, another inflammatory disease.

In summary, rs26653 SNP may be positively correlated with PsV susceptibility in Chinese Han population. Several limitations in present study should be stated. First of all, sample size was not large enough that might reduce analysis power. Secondly, only 1 ethnic group was included in our study, and this situation might limit the application range of our results. Thirdly, the results were not adjusted for potentially confounding factors. Additionally, gene–environment interactions were not taken into account in the current study. Therefore, well designed studies with enlarged sample size and ethnicity number are needed to further verify our findings in the future.

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References

[1] Griffiths CE, Barker JN. Pathogenesis and clinical features of psoriasis. Lancet 2007;370:263–71.
[2] Paltrafman AC, McNamne KE, McCann FE. New developments in the management of psoriasis and psoriatic arthritis: a focus on apropilast. Drug Des Devel Ther 2013;7:201–10.
[3] Henseler T, Christophers E. Psoriasis of early and late onset: characterization of two types of psoriasis vulgaris. J Am Acad Dermatol 1983;13:450–6.
[4] Boehncke WH, Buerger C, Boehncke S. Co-morbidities in psoriasis patients. Hautarzt 2009;60:116–21.
[5] Karinkhaki C, Boysen LN, Margolis DJ, et al. Comparing cutaneous research funded by the National Institute of Arthritis and Musculoskeletal and Skin Diseases with the 2010 Global Burden of Disease results. PLoS One 2014;9:e102122.
[6] Parisi R, Symmons DP, Griffiths CE, et al. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. J Invest Dermatol 2013;133:377–85.
[7] Menter A, Gottlieb A, Feldman SR, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. J Am Acad Dermatol 2008;58:826–50.
[8] Ayubyi A, Shirbeigi L, Egbaliljan F. Psoriasis and topical Iranian traditional medicine. Iran J Med Sci 2016;41:S54.
[9] Lovato P, Norsgaard H, Tokura Y, et al. Calcipotriol and betamethasone dipropionate exert additive inhibitory effects on the cytokine expression of inflammatory dendritic cell-Th17 cell axis in psoriasis. J Dermatol Sci 2016;81:153–64.
[10] Balwag J, Barnes DH, Johnston A. Cytokines in psoriasis. Cytokine 2015;73:342–50.
[11] Chang SC, Momburg F, Bhutani N, et al. The ER aminopeptidase, ERAP1, trims precursors to lengths of MHC class I peptides by a “molecular ruler” mechanism. Proc Natl Acad Sci U S A 2005;102:17107–12.
[12] Thuring C, Pollin E, Greinon L, et al. HLA class I is most tightly linked to levels of tapasin compared with other antigen-presenting proteins in glosloblastoma. Br J Cancer 2015;113:952–62.
[13] Steinbach A, Winter J, Reuschbach M, et al. ERAP1 overexpression in HPV-induced malignancies: a possible novel immune evasion mechanism. Oncoimmunology 2017;6:e1336594.
[14] Chen H, Li L, Weimershau M, et al. ERAP1-ERAP2 dimers trim MHC I-bound precursor peptides; implications for understanding peptide editing. Sci Rep 2016;6:28902.
[15] Tran TM, Hong S, Edwin JL, et al. ERAP1 reduces accumulation of aberrant and disulfide-linked forms of HLA-B27 on the cell surface. Mol Immunol 2016;74:10–7.
[16] Cifaldi L, Romana P, Falco M, et al. ERAP1 regulates natural killer cell function by controlling the engagement of inhibitory receptors. Cancer Res 2015;75:824–34.
[17] Sukhov A, Adamopoulos IE, Maverakis E. Interactions of the immune system with skin and bone tissue in psoriatic arthritis: a comprehensive review. Clin Rev Allergy Immunol 2016;51:87–99.
[18] Enouchidou I, Kamal RP, Seregin SS, et al. Cutting edge: coding single nucleotide polymorphisms of endoplasmic reticulum aminopeptidase I can affect antigenic peptide generation in vitro by influencing basic enzymatic properties of the enzyme. J Immunol 2011;186:1909–13.
[19] Urayama KY, Jarrett RF, Hjalgrim H, et al. Genome-wide association study of classical Hodgkin lymphoma and Epstein-Barr virus status-defined subgroups. J Natl Cancer Inst 2012;104:240–53.
[20] Das A, Chakraborty J, et al. Associations of ERAP1 coding variants and domain specific interaction with HLA-C *06 in the early onset psoriasis patients of India. Hum Immunol 2017;78:724–30.
[21] Strange A, Capon F, Spencer CC, et al. A genome-wide association study identifies new psoriasis susceptibility loci and an interaction between HLA-C and ERAP1. Nat Genet 2010;42:985–90.
[22] Raychaudhuri SK, Maverakis E, Raychaudhuri SR, et al. Diagnosis and classification of psoriasis vulgaris, HLA and ERAP1. J Invest Dermatol 2012;132:1221–32.
[23] Herzinger T, Kleuser B, Schafer-Korting M, et al. Sphingosine-1-phosphate signaling in the skin. Am J Clin Dermatol 2007;8:329–45.
[24] Antiga E, Volpi W, Cardilicchia E, et al. Etanercept downregulates the Th17 pathway and decreases the IL-17/IL-10+ cell ratio in patients with psoriasis vulgaris. J Clin Immunol 2012;32:1221–32.
[25] Kim J, Krueger JG. Highly effective new treatments for psoriasis target the IL-23/Th17 T cell autoimmune axis. Annu Rev Med 2017;68:255–69.
[26] Manolache L, Petrescu-Sceleeanu D, Benea V, Life events involvement in psoriasis onset/recurrence. Int J Dermatol 2010;49:636–41.
[27] Harden JL, Krueger JG, Bowcock AM. The immunogenetics of psoriasis: a comprehensive review. J Autoimmun 2015;64:66–73.
[28] Chiricozzi A, Saric T, et al. The ER aminopeptidase ERAP1 enhances or limits antigen presentation by trimming epitopes to 8-9 residues. Nat Immunol 2002;3:1177–84.
[29] Wu P, Ma G, Zhu X, et al. Cyr61/CCN1 is involved in the pathogenesis of psoriasis vulgaris via promoting IL-8 production by keratinocytes in a JNK/NF-kappaB pathway. Clin Immunol 2016;174:53–62.
[30] York IA, Chang SC, Saric T, et al. The ER aminopeptidase ERAP1 limits antigen presentation by trimming epitopes to 8-9 residues. Nat Immunol 2002;3:1177–84.
[31] Kucukshahin O, Ates A, Turkcapar N, et al. Association between single nucleotide polymorphisms in prospective genes and susceptibility to ankylosing spondylitis and inflammatory bowel disease in a single centre in Turkey. Turk J Gastroenterol 2016;27:317–24.
[32] Lysell J, Padyukov L, Kosclu et al. Genetic association with ERAP1 in psoriasis is confined to disease onset after puberty and not dependent on HLA-C*06. J Invest Dermatol 2013;133:411–7.
[33] Masouri S, Stefanaki I, Nitisos G, et al. A pharmacogenetic study of psoriasis risk variants in a Greek population and prediction of responses to anti-TNF-alpha and anti-IL-12/23 agents. Mol Diagn Ther 2016;20:221–5.
[34] Yang Q, Liu H, Qiu L, et al. Investigation of 20 non-HLA (human leucocyte antigen) psoriasis susceptibility loci in Chinese patients with psoriatic arthritis and psoriasis vulgaris. Br J Dermatol 2013;168:1060–5.