The role of polymorphism of interleukin-2, -10, -13 and TNF-α genes in cutaneous T-cell lymphoma pathogenesis

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Abstract

Introduction: As the pathogenesis of cutaneous T-cell lymphomas (CTCL) is not fully understood, inherited gene polymorphisms are considered to play a role in the development of lymphomas.

Aim: To investigate whether certain gene polymorphisms might be involved in the development of CTCL.

Material and methods: In the case-control study we compared the frequency of nine selected single nucleotide polymorphisms (SNP) of seven genes (rs1800587/–889 C/T of interleukin (IL)-1α, rs2069762/–330G/T and rs2069763/+166G/T of IL-2, rs1800925/–1112 C/T of IL-13, rs1800896/–1082 A/G of IL-10, rs4073/–251 A/T of IL-8, rs5370/K198N, rs180054/–1370T/G of endothelin-1 and rs1800629/–308 G/A of TNF-α) in 43 CTCL and Polish cases using the amplification refractory mutation system polymerase chain reaction method.

Results: We have found that two genotypes, –330GG of IL-2 and –1112TT of IL-13 both promoter variants associated with “hypertranscription phenotype”, were over-represented in CTCL patients compared to healthy controls, and they increase the risk of malignancy development (OR = 5.82, p = 0.001 for IL-2 –330 GG, and OR = 5.67, p = 0.0024 for IL-13 –1112 TT). On the other hand, high transcription –308A allele of the TNF-α gene and –1082GG of IL-10 genotype is less frequent in lymphoma patients and has protective effects on the development of CTCL (OR = 0.45, p = 0.0466 for –308A of TNF-α, and OR = 0.35, p = 0.0329 for –1082GG of IL-10 genes).

Conclusions: Our results indicate that hypertranscription promoter variants of IL-2 and IL-13 genes could be estimated as the risk factor for development of CTCL, while TNF-α and IL-10 variants have a protective effect.

Key words: cytokine gene polymorphisms, cutaneous T-cell lymphoma.

Introduction

Cutaneous T-cell lymphomas (CTCL) with the predominant subtype – Mycosis fungoides (MF) – are characterized by skin infiltration with skin homing lymphocytes CD4(+) [1]. Mycosis fungoides ranges from a localized, indolent process to an aggressive lymphoma with widespread cutaneous and extracutaneous involvement [1]. The pathogenesis of MF is complex and still unknown. The reason for evolution from a reactive process to the malignant transformation of skin-homing T cells in MF remains unclear. Cytokine production in the skin and blood is considered to be of major importance for the pathogenesis of CTCLs. Cytokine expression in CTCLs may be responsible for enhanced proliferation of the malignant cells and inhibition of the antitumor immune response. It is thought that as MF progresses, it becomes more Th2 polarized. The cytokine profile has switched from Th1 to Th2, production of proinflammatory cytokines has increased, which indirectly promotes the development of the autoimmune reaction [2, 3]. However, division of cytokine production depending on MF stage is not clear [4]. Moreover, it is believed that microenvironment (chemokines, cytokines, growth factors) is an important factor leading to MF development and progression [1, 5]. Not only does it stimulate lymphoma growth by produced cytokines but it also induces angiogenesis and inhibits anti-tumor response. An association of cytokine gene polymorphisms with susceptibility to autoimmune diseases [6, 7], skin dermatoses [8–10] in myeloproliferative and lymphoproliferative malignancies [11–13] and other immunological reactions has been reported. So far, studies on the role of inherited gene polymorphisms in the pathogenesis of CTCL have been rare. Some of the studies indicate a potential association of CTCL with polymorphisms of interleukin-6 (IL-6), metalloproteinase 2, angiotensin convertase and oncogene TP-53 [14–18].
Aim

The aim of the present study was to investigate whether a particular cytokine gene polymorphisms might be involved in the pathogenesis of CTCL.

Material and methods

Subjects

The study group included 43 patients (26 males, 17 females, mean age: 60.7 ±15.3 years, age range: 20–86 years) with CTCL (34 MF, 7 Sezary syndrome (SS), one case of NK/T cell lymphoma and one case of anaplastic CD3+ T-cell lymphoma) diagnosed and treated at the Department of Dermatology of the Medical University in Gdansk, in the case of endothelin-1 gene polymorphism, 60 patients (36 males, 24 females, mean age: 62.7 ±10.6, range: 20–86) were examined. Patients with CTCL were diagnosed on the basis of clinical, histopathological and immunohistochemical findings, according to the European Organization of Research and Treatment of Cancer (EORTC) criteria. Mycosis fungoides/SS patients were staged: IB (11 cases), IIA (4 cases), IIB (16 cases), III (3 cases) and IV (7 cases) according to the staging system proposed by the International Society of Cutaneous Lymphoma (ISCL) and the EORTC [19, 20]. Controls n = 84 (mean age: 27.46 ±7.88 years, range: 18–52) to 261 (mean age: 30.5 ±10.1 years, range: 18–62), depending on tested polymorphisms, were unrelated healthy individuals without personal or family history of chronic skin diseases and without personal history of malignancy (Table 1).

The study was approved by the local research ethics committee of the Medical University of Gdansk. The study was financed by the Polish Ministry of Science and Higher Education grant 02-0066/07/253.

DNA extraction and genotyping

Genomic DNA was isolated from the whole blood samples using Blood DNA Prep Plus according to the instructions of the manufacturer (A&A Biotechnology, Gdansk, Poland). Analysis of the polymorphic variants of the genes was performed by the amplification re-fractory mutation system polymerase chain reaction (ARMS-PCR), using self-designed specific sequences of oligonucleotides rs1800587/–889 C/T of interleukin (IL)-1α, rs2069762/–330G/T and rs2069763/–166G/T of IL-2, rs1800925/–1112 C/T of IL-13, rs1800896/–1082 A/G of IL-10, rs4073/–251 A/T of IL-8, rs5370/K198N, rs180054/–1370T/G of endothelin-1 gene and rs1800629/–308 G/A of TNF-α gene. As the internal amplification control of the primers, the growth hormone (GHI) gene was applied.

Statistical analysis

Statistical analysis was performed with the use of the Statistica 10 software package (StatSoft, Tulsa, OK, USA). Pearson’s χ² test was employed to examine the significance of the differences in the observed alleles and genotypes between groups. A logistic regression model was used to calculate the odds ratios (ORs) and the 95% confidence intervals (CIs). P-values below 0.05 were considered to be statistically significant.

Results

The study revealed that genotypes –330 GG and GT (p = 0.001 and p = 0.0001) of the IL-2 gene and –1112 TT (p = 0.0024) of the IL-13 gene are statistically more frequent in CTCL patients, whereas allele –308A of TNF-α (p = 0.0466) allele and IL-10 –1082 GG genotype (p = 0.0329) are less frequently present in the patients group (Table 1). Presence of IL-2 –330GG and IL-13 –1112 TT genotypes significantly increases the risk of CTCL (OR = 5.82, 95% CI: 1.87–18.11, p = 0.0024 for IL-2 –330GG genotype and OR = 5.67, 95% CI: 1.64–19.58, p = 0.006 for –1112TT genotype of the IL-13 gene). In contrast, TNF-α –308A allele and –1082GG genotypes have a protective effect (OR = 0.45, 95% CI: 0.2–1.00, p = 0.05 for TNF-α and OR = 0.35, 95% CI: 0.13–0.95, p = 0.04 for GG genotype of IL-10 genes). There were no statistically significant differences in the genotype and allele distribution of the polymorphism of the other examined cytokine genes between the studied CTCL population and the control group.

Discussion

The association of several diseases with allelic variations in cytokine genes has been reported but a possible association between IL-1α, IL-2, IL-8 and IL-13 gene polymorphisms and susceptibility to CTCL have not been studied yet. However, some studies have already investigated the genetic variant IL-10, TNF-α and endothelin-1 polymorphisms in CTCL [14, 15, 21].

In this study, we investigated alleles and genotypes of the TNF-α polymorphism (at the position –308 of the promoter region). The results have shown a protective association of CTCL and TNF-α –308A allele (high transcription variant). We found a protective association between CTCL and heterozygous and homozygous genotypes of TNF-α (–308AA and –308GA).

An association with the TNF-α gene polymorphism has been reported for lymphoproliferative malignancies. Kitzgibbon et al. [13] had revealed that polymorphisms in the promoter region of the TNF-α gene at position –308 are associated with an increased susceptibility for the development of follicular lymphoma. Also Tsukaszki et al. [12] had demonstrated a relationship between TNF-α –857T allele and adult T-cell leukemia/lymphoma. In the case of MF, Hodak et al. [21] had shown that no specific polymorphism in TNF-α locus was associated with patch stage MF.
Table 1. Frequency of interleukin-1α, -8, -10, -13, TNF-α and endothelin-1 gene polymorphisms in CTCL patients and healthy controls

| Variables                        | CTCL patients | Controls | P-value – χ² Pearson test |
|----------------------------------|---------------|----------|---------------------------|
| rs1800587 (-889 C/T) polymorphism in the promoter region of the interleukin-1α gene | n = 42        | n = 99   |                           |
| Genotypes:                      |               |          |                           |
| CC                              | 26 (61.90%)   | 51 (51.5%)| 0.26                      |
| CT                              | 14 (33.3%)    | 45 (45.5%)| 0.18                      |
| TT                              | 2 (4.80%)     | 3 (3.0%)  | 0.61                      |
| Alleles:                        | n = 84        | n = 198  |                           |
| C                               | 66 (78.5%)    | 147 (74.2%)| 0.44                      |
| T                               | 18 (21.5%)    | 51 (25.8%)|                           |
| rs2069762 (-330 G/T) polymorphism in the promoter region and rs2069763 (+166G/T) in exon 1 of the interleukin-2 gene | n = 42        | n = 87   |                           |
| Genotypes:                      |               |          |                           |
| GG                              | 11 (26.2%)    | 5 (5.8%)  | 0.001 (OR = 2.50, 95% CI: 1.15–5.45, p = 0.002) |
| GT                              | 8 (19.0%)     | 48 (55.2%)| 0.0001 (OR = 0.19, 95% CI: 0.08–0.46, p = 0.0002) |
| TT                              | 23 (54.8%)    | 34 (39.0%)|                           |
| Alleles:                        | n = 84        | n = 174  |                           |
| –330 G                          | 54 (64.3%)    | 58 (33.3%)| 0.000001 (OR = 3.60, 95% CI: 2.08–6.22, p < 0.0001) |
| –330 T                          | 30 (35.7%)    | 116 (66.7%)|                           |
| +166 G                          | 69 (82.1%)    | 123 (70.7%)| 0.0482 (OR = 1.9, 95% CI: 0.99–3.64, p = 0.05) |
| +166 T                          | 15 (17.9%)    | 51 (29.3%)|                           |
| rs4073 (-251 A/T) polymorphism in the promoter region of the interleukin-8 gene | n = 42        | n = 175  |                           |
| Genotypes:                      |               |          |                           |
| AA                              | 6 (14.3%)     | 42 (24.0%)| 0.17                      |
| AT                              | 21 (50.0%)    | 94 (53.7%)| 0.66                      |
| TT                              | 15 (35.7%)    | 39 (22.3%)| 0.07                      |
| Alleles:                        | n = 84        | n = 350  |                           |
| A                               | 33 (39.3%)    | 178 (51.8%)| 0.06                      |
| T                               | 51 (60.7%)    | 172 (49.1%)|                           |
| rs1800896 (-1082 A/G) polymorphism in the promoter region of the interleukin-10 gene | n = 43        | n = 173  |                           |
| Genotypes:                      |               |          |                           |
| GG                              | 5 (11.6%)     | 47 (27.2%)| 0.0329 (OR = 0.35, 95% CI: 0.13–0.95, p = 0.04) |
| GA                              | 30 (69.8%)    | 90 (52.0%)| 0.0361 (OR = 2.13, 95% CI: 1.04–4.35, p = 0.04) |
| AA                              | 8 (18.6%)     | 36 (27.2%)| 0.75                      |
| Alleles:                        | n = 86        | n = 346  |                           |
| A                               | 40 (46.5%)    | 162 (46.8%)| 0.96                      |
| G                               | 46 (53.5%)    | 184 (53.2%)|                           |
| rs1800629 (-308 G/A) promoter polymorphism of the TNF-α gene | n = 43        | n = 261  |                           |
| Genotypes:                      |               |          |                           |
| GG                              | 36 (83.7%)    | 178 (68.2%)| 0.0388 (OR = 2.4, 95% CI: 1.02–5.61, p = 0.04) |
| GA                              | 7 (16.3%)     | 80 (30.6%)| 0.05                      |
| AA                              | 0             | 3 (1.1%)  | 0.50                      |
| Alleles:                        | n = 86        | n = 522  |                           |
| A                               | 7 (8.0%)      | 86 (16.5%)| 0.0466 (OR = 0.45, 95% CI: 0.20–1.00, p = 0.05) |
| G                               | 79 (92.0%)    | 436 (83.5%)|                           |
| rs1800925 (-1112 C/T) polymorphism in the promoter region of the interleukin-13 gene | n = 42        | n = 175  |                           |
| Genotypes:                      |               |          |                           |
| CC                              | 18 (42.9%)    | 71 (40.6%)| 0.79                      |
| CT                              | 18 (42.9%)    | 99 (56.6%)| 0.11                      |
| TT                              | 6 (14.2%)     | 5 (2.8%)  | 0.0024 (OR = 5.67, 95% CI: 1.64–19.58, p = 0.006) |
genotype of the gene is lower in the lymphoma patients compared to the controls and could be estimated as a protective factor for CTCL developing. In our study, the –330G allele is more frequent in our patients, but does not have any influence on the serum IL-10 level [25, 26].

The role of polymorphism in the promoter region of the IL-10 gene in MF has been studied by Hodak et al., but no differences have been found between MF and healthy controls [21]. A polymorphic variant in the promoter region of IL-10 may alter the specific transcription factors recognition and consequently affect the rate of gene transcription. Our work indicates lower frequency of a high transcription –1082GG genotype in patients with CTCL. The results of Polish patients with B-cell NHL analysis, in contrast to our study, show that –1082G allele is more frequent in our patients, but does not have any influence on the serum IL-10 level [25, 26].

It has been reported that polymorphisms in the IL-2 gene are associated with various inflammatory diseases and cancers including rheumatoid arthritis, gastric cancer, NHL and atopic dermatitis (AD) [11, 27–29]. To the best of our knowledge, there had been no studies checking the association between IL-2 gene polymorphisms and CTCL. We have analyzed −330G/T and −166G/T polymorphisms of the IL-2 gene and found an association between CTCL and −330GG (high transcription rate) genotype of IL-2. This specific genotype of the IL-2 gene polymorphism is more common in patients with CTCL than in healthy controls. We can conclude that patients homozygous for G allele are more susceptible to CTCL than those homozygous and/or heterozygous for T allele. The GG genotype represents the potential to produce high levels of IL-2 whereas the TG and TT genotypes are associated with low production of this pro-inflammatory cytokine. The genetic polymorphism leading to increased IL-2 production may enhance susceptibility to CTCL.

Interleukin-13 is Th2 anti-inflammatory cytokine that is involved in mediating B cell and mast cell proliferation and IgE synthesis. Due to the key role in IgE synthesis, a lot of studies have focused on the association of IL-13 genes polymorphisms and the risk of allergic diseases such as asthma, allergic rhinitis or atopic dermatitis [31–33]. Glen et al. revealed that the −1112T allele is more frequent in AD patients than in healthy controls and that specific genotypes of IL-13 polymorphisms are associated with an increased serum total IgE concentration and course of atopic dermatitis [30]. Due to some similarities between AD and CTCL, such as Th2 dominance we investigated the correlation between IL-13 polymorphisms and the risk of CTCL development. We found a significant difference in the frequency of the genotype −1112TT (high transcription rate) of the IL-13 gene between patients with CTCL and healthy controls. Patients homozygous for T allele were at an increased risk of CTCL. As indicated by Nedoszytko et al. [34], the −1112CT/IL-13 gene polymorphism and the resulting “hypertranscription” may predis-

### Table 1. Cont.

| Variables | CTCL patients | Controls | P-value – χ² Pearson test |
|-----------|---------------|----------|--------------------------|
| Alleles:  | n = 84        | n = 350  | 0.42                     |
| C         | 54 (64.3%)    | 241 (68.9%) |                        |
| T         | 30 (35.7%)    | 109 (31.1%) |                        |

**rs3370 (K198N) polymorphism of the endothelin-1 gene**

| Genotypes: | n = 60 | n = 107 | P-value – χ² Pearson test |
|------------|--------|---------|--------------------------|
| GG         | 39 (65%) | 69 (64.5%) | 0.95                     |
| GT         | 21 (35%) | 35 (32.7%) | 0.76                     |
| TT         | 0       | 3 (2.8%)  | 0.19                     |

| Alleles: | n = 120 | n = 214 | P-value – χ² Pearson test |
|----------|---------|---------|--------------------------|
| G        | 99 (82.5%) | 173 (80.8%) | 0.71                     |
| T        | 21 (17.5%) | 41 (19.2%)  |                          |

**rs1800541 (−1370T/G) polymorphism in the promoter region of the endothelin-1 gene**

| Genotypes: | n = 60 | n = 107 | P-value – χ² Pearson test |
|------------|--------|---------|--------------------------|
| TT         | 29 (48.3%) | 41 (38.3%) | 0.21                     |
| TG         | 28 (46.7%) | 61 (57.0%) | 0.20                     |
| GG         | 3 (5%)   | 5 (4.7%)  | 0.92                     |

| Alleles: | n = 120 | n = 214 | P-value – χ² Pearson test |
|----------|---------|---------|--------------------------|
| T        | 86 (71.7%) | 143 (66.8%) | 0.36                     |
| G        | 34 (28.3%) | 71 (33.2%)  |                          |
pose for the development of systemic mastocytosis, the disease involving mast cells (MC) and their progenitors.

No differences in the frequency of the rest of gene polymorphisms studied (IL-1α, IL-8 and endothelin-1 gene) between the CTCL and control group have been found. It indicates lack of association between those gene polymorphisms and pathogenesis of CTCL. Regarding endothelin-1 gene, Vaska et al. also did not find any significant differences in genotype distributions and allelic frequencies between CTCL and non-CTCL patients [14]. However, some differences were found in genotype distributions of endothelin-1 gene polymorphism between patients treated with phototherapy and those without it [14]. It should be noted that we compared frequency of cytokine gene polymorphisms in CTCL patients treated and not treated and the healthy control group, what limited the interpretation. The differences in cytokine gene polymorphisms suggest that they are involved in CTCL pathogenesis. Specific cytokine gene polymorphism frequency should be evaluated concerning the early and advanced stages of cutaneous T-cell lymphomas. It is possible that the cytokine gene polymorphisms might determine progression of the disease.

There are differences in the age between patients and the control group, but these differences do not affect the results of the comparative study, because genetic polymorphisms could be estimated as one of additional risk factors, apart from the major ones (advanced stage, age > 60, large-cell transformation, and increased lactate dehydrogenase) in the pathogenesis of CTCL [35].

Conclusions

Our results suggest that polymorphisms of IL-2, IL-10, IL-13 and TNF-α genes are involved in the development of CTCL and indicate that hypertranscription promoter variants of IL-2 and IL-13 genes could be estimated as the risk factor for development of CTCL, while TNF-α and IL-10 variants have a protective effect.

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Conflict of interest

The authors declare no conflict of interest.

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