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Quantitative analysis of transforming growth factor beta isoforms mRNA TGF-β1-3 in the patients with psoriasis

Ilościowa analiza profilu ekspresji mRNA izoform TGF-β1-3 u pacjentów z łuszczycą

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Słowa kluczowe
łuszczyca, TGF-β, marker molekularny

Summary

Introduction. Psoriasis is a dermatosis connected with changes in the concentrations of pro-inflammatory cytokines. One of them is a beta transforming growth factor (TGF-β), which appears in three isoforms in humans (TGF-β1-3). TGF-β has antiproliferative properties towards keratinocytes of epidermis. Great disease spread, arduousness of its symptoms and the fact that molecular changes precede phenotypic changes make us looking for new molecular markers.

Aim. The aim of the paper was to evaluate of changes in the expressions of genes encoding *TGF-β1-3* isoforms in psoriatic patients when compared with healthy persons and indicate possibilities to use the cytokine as a new complementary molecular marker.

Material and methods. The group was composed of 32 psoriatic patients, and the control group consisted of 20 of healthy volunteers. All persons were taken their whole blood, form which total RNA was extracted that constituted the matrix in RTqPCR reaction.

Results. Statistically significant differences of expressions were determined between the evaluated groups with the use of the Mann-Whitney U test ($p < 0.05$): for *TGF-β1* $p = 0.00005$; *TGF-β2* $p = 0.007$; *TGF-β3* $p = 0.007$. All three isoforms *TGF-β* (*TGF-β1* > *TGF-β3* > *TGF-β2*) were detected in both healthy persons and psoriatic patients.

Conclusions. The achieved results indicate that determination of *TGF-β1-3* expression may become a useful, new molecular marker in psoriasis, integrating into the strategy of treatment personalisation. It may be stated that such determination would not be very burdensome or troublesome from the patient's point of view.

Streszczenie

Wstęp. Łuszczyca to dermatoza związana ze zmianami stężeń prozapalnych cytokin. Jedną z nich jest transformujący czynnik wzrostu beta (TGF-β), który u człowieka występuje w trzech izoformach (TGF-β1-3). TGF-β charakteryzuje się właściwościami antyproliferacyjnymi w odniesieniu do keratynocytów naskórka. Duże rozpowszechnienie, uciążliwość objawów oraz fakt, że zmiany molekularne wyprzedzają zmiany fenotypowe skłaniają do szukania nowych markerów molekularnych.

Cel pracy. Celem pracy była ocena zmian profilu ekspresji genów kodujących izoformy *TGF-β1-3* u osób chorujących na łuszczycę w porównaniu z osobami zdrowymi oraz wskazanie możliwości wykorzystania tej cytokiny jako nowego uzupełniającego markera molekularnego.

Conflict of interest
Konflikt interesów
None
Brak konfliktu interesów

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Materiał i metody. Grupę badaną stanowiły 32 osoby chorujące na łuszczycę, a grupę kontrolną 20 zdrowych ochotników. Od wszystkich osób pobrano pełną krew, z której ekstrahowano całkowity RNA, stanowiący matrycę w reakcji RTqPCR.

Wyniki. Statystycznie istotne różnice ekspresji między badanymi grupami określano testem U Manna-Whitneya ($p < 0,05$): dla *TGF-β1* $p = 0,00005$; *TGF-β2* $p = 0,007$; *TGF-β3* $p = 0,007$. U osób zdrowych i chorych na łuszczycę stwierdzono występowanie wszystkich trzech izoform *TGF-β* (*TGF-β1* > *TGF-β3* > *TGF-β2*).

Wnioski. Uzyskane wyniki wskazują, że oznaczanie ekspresji *TGF-β1-3* może być użytecznym, nowym markerem molekularnym w łuszczycy, wkomponowując się w strategię personalizacji leczenia. Można stwierdzić, iż tego typu oznaczenie nie byłoby zbyt obciążające i kłopotliwe z punktu widzenia pacjenta.

INTRODUCTION

Psoriasis is a chronic, immunologic, multi-factor pro-inflammatory skin disorder found worldwide in 1-3% population (1-3). Two main age groups among psoriatic patients may be identified: 20-30 years of age and 50-60 years of age. In clinical terms, psoriasis involves papular lesions on erythematous background, coated with white silvery scale, localised on the hairy areas of the head and covering symmetrically the extensory parts of the upper and lower limbs, as well as the lumbo-sacral area. The dermatosis occurs in the following varieties: psoriasis vulgaris (90% of all cases), palmoplantar pustular psoriasis, general psoriasis pustulosa, psoriasis unguium, erythrodermic psoriasis and psoriatic arthritis (2).

The characteristic feature in psoriasis is parakeratosis, i.e. approximately 8-times accelerated partial keratosis, triggered with distorted proliferation and keratinocyte differentiation in the basal layer of the skin. Moreover, changes in the cytokine secretion profile, incorrect proliferation and differentiation of epidermal cells, as well as intensified angiogenesis (1, 4-6).

One of the cytokines that plays a significant role in the dermatosis is a beta transforming growth factor (TGF-β), which appears in three isoforms in mammals: TGF-β1 is mainly located in stratum corneum and stratum granulosum of the skin, TGF-β2 in stratum spinosum and TGF-β3 was detected in the basal layer and below (6). It plays a key role in many physiological and pathological processes (7). The beta transforming growth factor shows ant-proliferative properties towards keratinocytes in epidermis (8), it can inhibit the cycle in the epithelial cells of such organs, like, for instance: lungs, liver, spleen, prostate, ovaries and epidermal cells, as well as in the progenitor blood cells – lymphatic and hematopoietic cells (9).

TGF-β1 is the isoform of the said cytokine that was the most characterised and described. It acts as a strong inhibitor of cell proliferation, since it stops the G1 phase of the cellular cycle and stimulates directly formation of new blood vessels (10).

TGF-β1 is synthesized in the progenitor form and as a result of maturity an inactive complex is formed: matured TGF-β1 – LAP (11, 12), which is released form the extracellular matrix. Proteases take part in the removal process of TGF-β1 during the latent cycle (4) and activation occurs extracellularly, when TGF-β1 is released from the complex (11, 13). Molecular form of TGF-β begins to activate on the cell surface, when the soluble peptide TGF-β binds with TGFβRII receptor, an active serine-threonine kinase, which – in turn – leads to the recruitment and phosphorylation of TGF-β RI. TGF-β then transmits the signal inside the cell through the phosphorylation of proteins: Smad2 and Smad3. Then the proteins form a complex with Smad4, which gather inside the nucleus and act as transcription agents (1, 14).

AIM

The aim of this paper is to determine the transcription activity of genes encoding isoforms of the beta transforming growth factor *TGF-β1-3* in psoriatic patients when compared with healthy persons (constituting the control group), and thus to assess the possibilities to make use of the changes in the expression profiles of the tested isoforms as the complementary molecular markers in the diagnostic and treatment of psoriasis.

MATERIAL AND METHODS

The study was conducted with the agreement of the Committee of Bioethics in Katowice – Resolution No. KNW/0022/KB1/59/I/13/14 of 27.05.2014.

The first stage involved qualification of persons to the sample and control groups, basing on the inclusion and exclusion criteria, included in tables 1 and 2, respectively.

The sample group was composed of 32 patients (20 men and 12 women), who gave their informed consent to participate in the study, aged 53.9 ± 10.4, with diagnosed psoriasis. These persons were hospitalised at the Dermatology Ward and treated in the Outpatient's Dermatology Clinic.

In turn, the control group consisted of 20 healthy volunteers, who did not have psoriasis and who did not use corticosteroids, for any reasons, during 3 months preceding the study (9 women, 11 men) aged 46 ± 10. The material for study was 5 ml of whole blood taken from persons qualified to the sample and control groups.

The first stage of the molecular analysis involved isolation of total RNA from the whole blood with the use of FENOZOL reagent (A & A Biotechnology, Gdańsk, Poland), according to the guidelines included in the protocol. Extracts of nucleic acid were then assessed

Tab. 1. Criteria of inclusion to and exclusion from the study group

Criteria of inclusion to the study group	Criteria of exclusion from the study group
patient's voluntary informed consent to participate in the study	no patient's voluntary informed consent to participate in the study
moderate, severe form of psoriasis (PASI > 10, DLQI > 10, BSA > 10)	mild form of psoriasis, to be treated in an outpatient's mode or with the use of a photo therapy
age 30-60 years	age below 30 or over 60 years
normal results of laboratory tests showing preserved kidney function (creatinine within the scope of reference values)	uncontrolled high arterial hypertension or no therapeutic effect, pressure charges, renal failure
preserved 3-month period during which the patient did not use general corticosteroid therapy or immunosuppressive medicines	immunosuppressive therapy or general corticosteroid therapy during the study or during the last 3 months preceding the study
negative history of a current or past tumour	current tumour, lymphoproliferative disorders
no detected lymphoproliferative disorders (normal blood cell count results)	serious inflammatory diseases – rheumatoid arthritis and systemic lupus erythematosus, presence of such diseases, like Marfan syndrome, muscular dystrophy, sarcopenia, immediate post-operative conditions, skeletal muscle injuries

Tab. 2. Criteria of inclusion to and exclusion from the control group

Criteria of inclusion to the control group	Criteria of exclusion from the control group
volunteer's voluntary informed consent to participate in the study	no volunteer's voluntary informed consent to participate in the study
no diagnosed psoriasis or other skin diseases	current immunosuppressive therapy for any reason or general corticosteroid therapy during the study or during the last three months
age 30-60 years	age below 30 or over 60 years
preserved 3-month period, at least, during which the volunteer did not use general corticosteroid therapy or immunosuppressive therapy for any reason	serious inflammatory diseases – rheumatoid arthritis and systemic lupus erythematosus and immediate post-operative conditions, skeletal muscle injuries

in quantitative terms through electrophoresis in 0.8% agarose gel in qualitative terms through spectrophotometry (GeneQuant II, Pharmacia Biotech).

The next stage of the molecular analysis involved qualitative amplification reaction with reverse transcription (RTqPCR) for mRNA for the following genes: *TGF-β1*, *TGF-β2*, *TGF-β3* in the presence of β-actin (ACTB) and GAPDH to control endogenous reactions. Table 3 presents the sequence of used starters. The analysis was conducted with the use of Opticon™ DNA Engine Sequence Detector (MJ Research Inc., Watertown, MA, USA) with the use of reagent set – SYBR Green Quantitect RT-PCR Kit (Qiagen, Valencia, CA, USA). Thermal conditions for the conducted reaction were as follows: reverse transcription (RT) reaction was conducted in the temperature of 50°C for 30 minutes, amplification was conducted in the following temperatures: 95°C for 15 minutes; 42 two-stage cycles: 94°C for 30 second and 60°C for 60 seconds and final extension: 72°C for 30 seconds. The specificity of RTqPCR reactions was assessed through division of amplimers in 6% and determination of the reaction product melting temperature.

Tab. 3. Stater sequences used in qRT-PCR reaction

mRNA	Oligonucleotide sequence
TGF-β1	Forward: 5'TGAACCGGCCTTTCCTGCTTCTCATG3' Reverse: 5'GCGGAAGTCAATGTACAGCTGCCGC3'
TGF-β2	Forward: 5'TACTACGCCAAGGAGGTTTACAAA3' Reverse: 5'TTGTTCAGGCACTCTGGCTTT3'
TGF-β3	Forward: 5'CTGGATTGTGGTTCCATGCA3' Reverse: 5'TCCCCGAATGCCTCACAT3'
GAPDH	Forward: 5'-GAAGGTGAAGGTCGGAGTC-3' Reverse: 5'-GAAGATGGTGATGGGATTC-3'
ACTB	Forward: 5'-TCACCCACACTGTGCCCATCTACGA-3' Reverse: 5'-CAGCGGAACCGCTCATTGCCAATGG-3'

forward – forward primer, reverse – reverse primer

RESULTS

Transcription activity of the genes under study was presented as the number of mRNA copies of a specific gene, converted into 1 μg of total RNA. The statistical analysis was performed with the use of Statistica 12 PL (StatSoft, Tulsa, Oklahoma, USA), assuming the statistical gravity factor $p < 0.05$. Descriptive statistics of mRNA expression profile: *TGF-β1*, *TGF-β2*, *TGF-β3* were presented in the form of a mediane and upper and lower quartiles of the number of transcript copes in 1 μg of total RNA (tab. 4). Graphic interpretation of the number of copier of the individual isoforms in the sample and control groups were shown in figure 1a-c. Statistically significant differences for a given transcript between the sample and control groups were verified with the use of the Mann-Whitney U test ($p < 0.05$).

The analysis of expression profile of the transcripts under study showed that all three isoforms of *TGF-β1-3* are present in both healthy persons and psoriatic patients. Differences in the transcription activity of the said genes were observed between the sample and control groups. The following regularity may be observed the sample and control groups in the number of the individual TGF-β isoforms: *TGF-β1* > *TGF-β3* > *TGF-β2*. Reduced *TGF-β1* and *TGF-β3* expression was observed when compared with the control group.

Tab. 4. mRNA transcription activity: *TGF-β1*, *TGF-β2*, *TGF-β3* in the sample and control groups (number of mRNA copies of the gene in 1 μg of total RNA)

Group	Control			Sample		
mRNA	**median**	**lower quartile**	**upper quartile**	**median**	**lower quartile**	**upper quartile**
TGF-β1	3 060 000	1 890 000	11 500 000	497 000	190 000	873 000
TGF-β2	1250	696	2720	6790	1160	46 800
TGF-β3	677 500	270 000	2 280 000	227 500	85 650	738 500

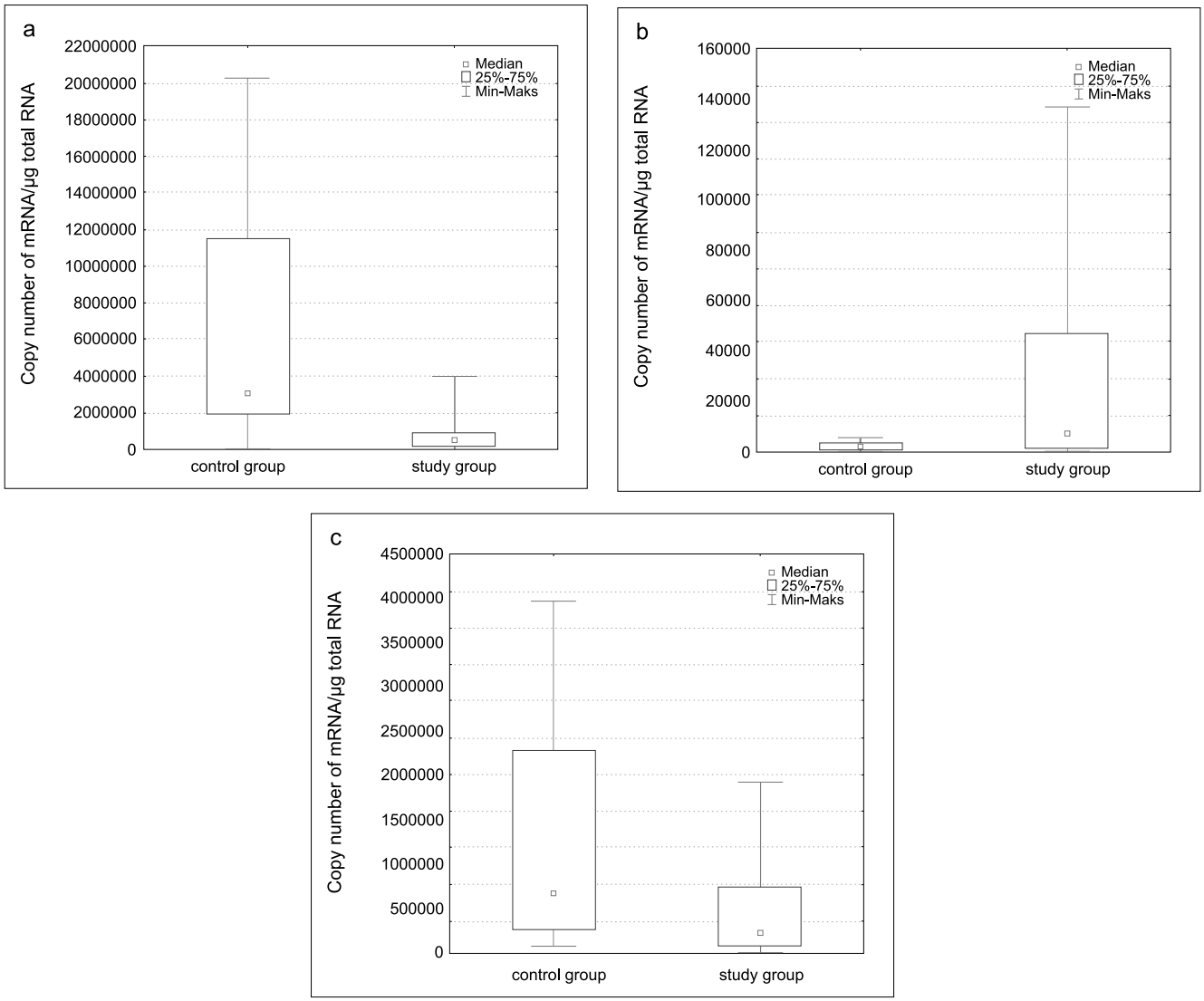

Fig. 1a-c. mRNA expression profile of the genes: *TGF-β1* (a), *TGF-β2* (b), *TGF-β3* (c) in the sample and control groups

The opposite situation occurred in case of *TGF-β2*, which show overexpression in psoriatic patients when compared with the healthy volunteers from the control group.

The statistical analysis performed with the use of the Mann-Whitney U test ($p < 0.05$) showed three statistically significant differences in expressions of the individual TGF-β isoforms between the sample and control groups. Statistically significant differences for gene expression between the two analysed groups were observed for *TGF-β1* ($p = 0.00005$), *TGF-β2* ($p = 0.007$), *TGF-β3* ($p = 0.007$).

DISCUSSION

Psoriasis is a dermatosis, with complex pathophysiology, involving interdependencies and interactions between keratinocytes of epidermis, T lymphocytes and endothelial cells. With regards to etiopathogenesis, it is classified as a proinflammatory disease through a strong and inseparable relationship with the immunological system, which involves increased concentration of pro-inflammatory cytokines, including: interleukins (IL) – IL-17, IL-6, IL-1β, IL-6, IL-22, IL-23, tumour necrosis factor (TNF-α), gamma interferon (IFN-γ), beta transforming growth factor (TGF-β) (6, 15-23).

Beta transforming growth factor (TGF-β) is one of the most known and characterised pleiotropic peptides, taking part in many metabolic processes, among others, in: cellular proliferation, their differentiation, apoptosis and is generated in response to pending inflammations (24, 25). Beta transforming growth factor is a natural and strong growth inhibitor of various types of cells, including: epithelial cells, endothelial cells and hematopoietic cells (26, 27). An important role is played by TGF-β in the course of various skin diseases, e.g. in psoriasis, wound healing disorders, formation of hypertrophic scars and skin cancer. Moreover, the cytokine is classified as an inhibitor of keratinocyte proliferation in psoriasis (24). Litvinov states that the process of TGF-β signalling deregulation can be observed in psoriasis, during which psoriatic keratinocytes undergo hyperproliferation due to decreased expression of *TGF-β* (1). On the basis of the mentioned publications, it may be inferred that *TGF-β* plays an important role in psoriasis, which translates into the idea to consider determination of the changes in the isoform transcription activity of the cytokine as the complementary molecular markers in diagnostics of the dermatosis.

Patients with severe psoriasis vulgaris processes show lower concentrations of TGF-β1 in their serum, which implies intensified migration of neutrophils, macrophages and lymphocytes T into the skin, increased production and secretion of cytokines and epidermal keratosis. Reduced concentration of TGF-β1 may be treated as the marker of psoriasis intensification, disease severity clinical assessment index and may become a potential new therapeutic objective (31).

Our study was conducted to determine changes in the expression profiles of the individual *TGF-β* isoforms in the group of psoriatic patients when compared with a group of healthy volunteers. We also tried to assess the possibilities to make use of determined transcription activity of mRNA of *TGF-β1-3* genes as the complementary diagnostic markers in psoriasis. Such studies seem to be extremely important and essential, not only because of the possibility to broaden knowledge of the dermatosis and the participation of the said cytokine in it, but also from the patient's perspective. The situation results from the fact that molecular changes precede phenotypic changes, thus molecular markers would make it possible to diagnose psoriasis earlier, when the changes are not very intensive or when they have not occurred yet. Consequently, the molecular marker system would also enable to monitor those persons who have family history of psoriasis and to implement a relevant therapy on time, preventing further exacerbation of the disease. Such conclusion seems to be reasonable, since psoriasis is a disease, in which genetic background plays an important role. It has been demonstrated that when both parents have psoriasis, the probability of its occurrence in their offspring is 40%, when only one of the parents has psoriasis, the risk is 14%, in case of siblings it amounts to around 6% (29, 30).

Doi et al. assessed changes in the level of expression of *TGF-β1-3* isoforms in psoriatic patients, when compared with healthy persons, the material under study being skin bioptats. They demonstrated that mRNA transcription activity of *TGF-β2* and *TGF-β3* was lower in psoriatic patients in comparison with the monitored control group (31). Results achieved by the mentioned team are to great extent identical with the observations made during our analysis of changes in *TGF-β1-3*, the material for the tests being the whole blood. *TGF-β3* expression could be observed in psoriatic patients, when compared with the control group. Different results were achieved for *TGF-β2* isoform, which may result, e.g. from various materials used to test transcriptome, variances in the inclusion and exclusion criteria used to qualify the persons to the individual groups (the sample and control groups). Nevertheless, the observation of the occurrence of all three isoforms in both the sample and control groups and changes in their expressions between the groups covered by the study indicates the possibility to consider determination of *TGF-β* isoforms expression as a complementary diagnostic marker. Statistically significant differences verified with the use of the Mann-Whitney U test ($p < 0.05$), occurring between the sample and control groups, show that the changes in *TGF-β1-3* isoforms expression profile are great, consequently, this molecular marker could be a reliable index to be used in the dermatosis. Moreover, the possibility to determine changes in *TGF-β1-3*, transcription activity, with the material used for the tests being peripheral blood, indicates that the procedure would not be very burdensome for patients and the blood could be sampled simultaneously with blood samples taken in order to determine routine parameters, e.g. exacerbation of an inflammatory process.

CONCLUSIONS

Results of the observed changes in *TGF-β1-3* expression profile in the group of psoriatic patients, when compared with the control group indicate the possibility to make use of changes in the said cytokine expressions as a complementary diagnostic marker. Searching for new markers of the disease, including those based on molecular biology techniques, is an extremely important and needed task, which could contribute to monitoring exposure to the disease occurrence, its early diagnostics, thus increasing the changes of an optimum and efficient therapy. Molecular analysis is an answer to medicine personalisation, therapeutic strategies and individual approach towards patients.

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