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Co-Expression of the TGF-β1 and TGF-β2 Isoforms in Nasal Polyps and in Healthy Mucosa

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Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

Summary

Background: The formation of nasal polyps is connected with a chronic inflammatory process with the activation of different cytokines. TGF-β induces fibrosis and acts as a chemoattractant and proliferation factor for fibroblasts. The aim of the study was to evaluate the expression profiles of the genes coding TGF-β isoforms in nasal polyps with predominately eosinophilic and neutrophilic infiltration and in healthy mucosa and to assess their mutual correlation with the levels of gene transcription.

Material/Methods: The study group consisted of 24 patients with nasal polyposis. On the basis of the histopathological evaluation there were 16 eosinophilic and 8 neutrophilic polyps. The control group constituted 9 healthy patients. The expression profiles of the genes coding the TGF-β isoforms were detected using real-time RT-QPCR.

Results: TGF-β1 and TGF-β2 mRNAs were revealed in 10 patients with eosinophilic polyps. TGF-β1 transcriptional activity was accompanied by TGF-β2 transcriptional activity in nasal polyps. TGF-β2 gene expression in tissues without mRNA for TGF-β1 was silenced. There was positive correlation between the expressions of the TGF-β1 and TGF-β2 isoforms in nasal polyps. TGF-β1 mRNA was present at higher levels in all control samples than in eosinophilic polyps. An increased TGF-β1 mRNA expression was accompanied by an increased TGF-β2 mRNA expression in healthy mucosa. TGF-β3 showed the most intensive transcriptional activity among the TGF-β isoforms in both nasal polyps and control tissues. There was no correlation between TGF-β3 and TGF-β1 nor between TGF-β3 and TGF-β2 transcriptional activity in nasal polyps and normal tissue.

Key words: gene expression • nasal polyps • real-time RT-QPCR • TGF-β isoforms

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Introduction

According to many authors, the formation of nasal polyps is connected with a chronic inflammatory process with the activation of different cytokines [1,3,23]. Transforming growth factor-β (TGF-β induces fibrotic processes and acts as a chemoattractant and proliferation factor for fibroblasts. Moreover, as revealed in recent studies, it plays an important role in cell regulation, migration, and survival in inflammation [20]. It also takes part in apoptosis through its influence on the Bcl-xL and Bcl-2 proteins [10].

Five TGF-β isoforms have been identified so far (TGF-β1 to -β5), but only TGF-β1, TGF-β2, and TGF-β3 occur in human tissue. Each isoform is coded by independent genes located on different chromosomes and they may play independent roles in immunoregulative processes. Their expression products have 64–85% homologous amino-acid sequences [14].

The potential role played by TGF-β in the development of nasal polyps has been reported. However, different results have been obtained using immunohistochemical techniques [1,20]. Some authors suspect that TGF-β may influence the structural changes of the polyps' background, such as fibrosis and thickening of the basal membrane [12,22]. The aim of this study was an evaluation of the expression profiles of the genes coding for the TGF-β1, TGF-β2, and TGF-β3 isoforms in both nasal polyps with predominately eosinophilic and neutrophilic infiltration and in healthy mucosa. Correlations between the levels of gene transcription were assessed as well.

Material and Methods

The study group consisted of 24 patients (16 males and 8 females, age range: 16–79 years). Nasal polyps were removed during standard polypectomy or FESS (functional endoscopic sinus surgery) at the ENT Department of Wroclaw Medical University. On the basis of histopathological evaluation there were 16 eosinophilic and 8 neutrophilic polyps. Ten patients (3 with neutrophilic and 7 with eosinophilic polyps) suffered from bronchial asthma, two of whom had an allergy to aspirin. Thirteen patients had polypectomy more than once (Table 1). The control group consisted of 9 healthy patients from whom normal nasal mucosa was taken during nasal septoplasty. All bioethical standards were adhered to. After surgery, the tissues were immediately frozen in liquid nitrogen and stored at –70°C before RNA extraction.

Table1. Characteristic of patient (n=24)

Characteristics	n
Males	16
Females	8
Mean age	52.6±16.1
Eosinophilic nasal polyps	16
Neutrophilic nasal polyps	8
Bronchial asthma	10
Aspirin intolerance	2
The number of polypectomy ≥2	13

RNA extraction

Total RNA was extracted from the nasal polyp tissue and normal mucosa with the use of TRIZOL® reagent (Invitrogen, Carlsbad, CA, USA) according to the manufacture's protocol. The concentration of RNA was measured spectrophotometrically (GeneQuant II, Pharmacia Biotech, USA).

Real-time RT-QPCR

The amounts of TGF-β1, TGF-β2, TGF-β3 isoform mRNA were evaluated using real time RT-QPCR with an Opticon™ DNA Engine Sequence Detector (MJ Research, USA). The reaction mixture consisted of 25 µl of 2× QuantiTect SYBR Green RT-PCR Master Mix (QIAGEN, Valencia, CA, USA), 0.5 µl of QuantiTect RT Mix, 100 ng RNA, and 0.5 µM of the forward and reverse primers (Table 2). The primers were designed using Primer Express™ Version 2.0 software (PE Applied Biosystems, USA). The thermal conditions of RT-QPCR were: reverse transcription at 50°C for 30 minutes, 95°C for 15 minutes, and then 45 cycles of amplification at 94°C for 15 seconds and at 60°C for 30 seconds. The transcriptional activities of β-actin and glyceraldehyde-3-phosphate dehydrogenase (GAPDH), used as endogenous controls, were evaluated in each sample. The specificity of the RT-PCR reaction was assessed on the basis of the melting temperature (TM) of each amplimer (Table 2).

A standard curve was drawn for the commercially accessible patterns of β-actin copies using the β-actin Control Reagent kit (Applied Biosystems, USA) to calculate the mRNA copy numbers of the genes tested. The results were recalculated per µg of total RNA.

Statistical analysis

Statistical analysis was performed using Statistica 5.0 software. The Mann-Whiteney *U*-test was applied to determine the differences between the transcriptional activities of the TGF-β isoforms in eosinophilic polyps, neutrophilic polyps, and the control group. The results were expressed as medians. Spearman's rank correlation test was applied to assess correlation between the TGF-β1, TGF-β2, and TGF-β3 transcriptional activities. Statistical significance was considered for differences with $p<0.05$.

Results

In the study group, TGF-β1 and TGF-β2 mRNAs were observed in 10 patients with eosinophilic polyps. TGF-β1 transcriptional activity was accompanied by TGF-β2 transcriptional activity in the nasal polyps. The expression of the TGF-β2 gene in tissues without mRNA for TGF-β1 was silenced. The average TGF-β1 transcriptional activity was 3.23×10^3 mRNA copies/µg of total RNA. TGF-β2 expression was 10-times less intensive, with 7.7×10^2 copies/µg of RNA. There was statistically significant positive correlation

Table 2. Characteristic of starters used for real-time RT-QPCR

Gene	Sequence of starters	Length of amplicon	TM
TGFβ-1	Forward 5'TGAACCGGCCTTTCCTGCTTCTCATG3'	151 bp	85°C
	Reverse: 5'GCGGAAGTCAATGTACAGCTGCCGC3'		
TGFβ-2	Forward: 5'TACTACGCCAAGGAGGTTTACAAA3'	201 bp	80°C
	Reverse: 5'TTGTTCAGGCACTCTGGCTTT3'		
TGFβ-3	Forward: 5'CTGGATTGTGGTTCCATGCA3'	121 bp	82°C
	Reverse: 5'TCCCCGAATGCCTCACAT3'		
GAPDH	Forward 5'GAAGGTGAAGGTCGGAGTC3'	226 bp	80°C
	Reverse 5'GAAGATGGTGATGGGATTC3'		
β-actin	Forward 5'TCACCCACACTGTGCCCATCTACGA3'	295 bp	85°C
	Reverse 5'CAGCGGAACCGCTCATTGCCAATGG3'		

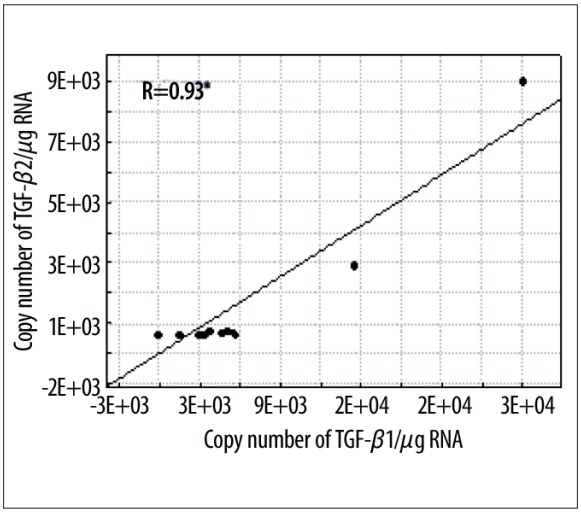

Figure 1. Correlation between TGF-β1 and TGF-β2 genes expression in eosinophilic nasal polyps (*p<0.05)

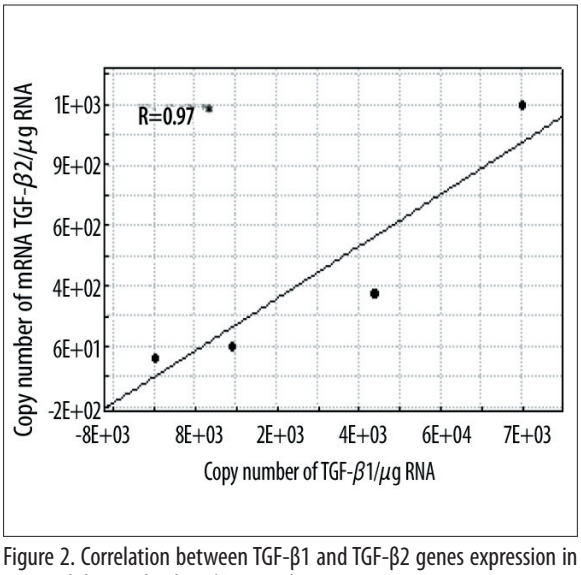

Figure 2. Correlation between TGF-β1 and TGF-β2 genes expression in neutrophilic nasal polyps (*p<0.05)

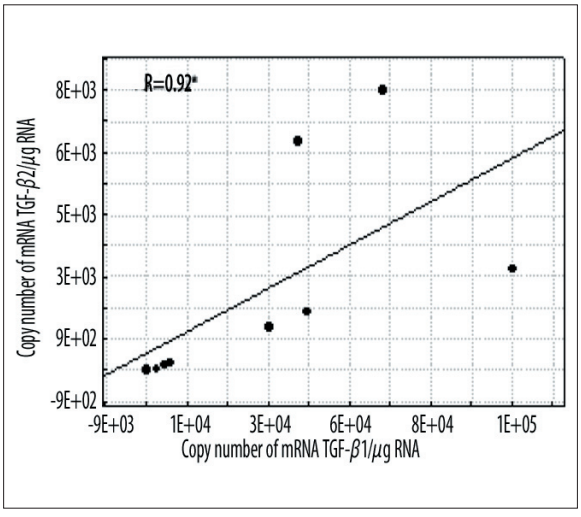

Figure 3. Correlation between TGF-β1 and TGF-β2 genes expression in normal mucosa (*p<0.05)

between the expressions of TGF-β1 and TGF-β2 (R=0.93, p=0.0000) in eosinophilic nasal polyps (Figure 1).

There was no TGF-β1 mRNA in 3 samples of neutrophilic polyps (n=8) and no TGF-β2 mRNA in two samples. TGF-β1 and TGF-β2 expression levels were 1.54×10^3 and 3.2×10^2 copies/μg of total RNA, respectively. Very strong correlation between TGF-β1 and TGF-β2 transcriptional activities (R=0.98, p=0.0048) was found in neutrophilic polyps (Figure 2).

TGF-β1 mRNA was present in all control group samples, with the average amount of 3.5×10^4 copies/μg of total RNA, and was significantly higher than in both eosinophilic polyps (p=0.0017) and in neutrophilic polyps (p=0.0119). The mean level of TGF-β2 mRNA in normal mucosa was 1.32×10^3 copies/μg total RNA and was significantly higher only compared with eosinophilic polyps (p=0.0022), but not with neutrophilic nasal polyps (p=0.0829). Strong positive correlation between the expressions of the TGF-β1 and TGF-β2 genes in the healthy mucosa (R=0.92, p=0.0005) was revealed as well (Figure 3).

Table 3. TGF-β mRNAs levels in nasal polyps and normal nasal mucosa (copy number $\times 10^3$ per 1 μg RNA; median, range)

Type of Tissue	TGF-β1		TGF-β2		TGF-β3	
Normal mucosa	3.23	(0–27.19)	1.54	(0–7.23)	35.1	(1.86–251.99)
Eosinophilic polyps	0.77	(0–9.45)	0.32	(0–1.22)	1.32	(0.02–8.24)
Neutrophilic polyps	69.65	(0.24–330.99)	4.23	(2.17–94.10)	64.08	(0.36–125.83)

TGF-β3 mRNA was detected in all the examined tissues of nasal polyps and in control tissues. Moreover, the transcriptional activity of TGF-β3 was the most intensive of all the TGF-β isoforms, with a value of 10^4 TGF-β3 mRNA copies/μg of total RNA (Table 3). The expressions of TGF-β3 gene in normal mucosa and in both eosinophilic (p=0.7602) and neutrophilic polyps (p=0.4376) were at the same level. There was no correlation between the transcriptional activities of TGF-β3 and TGF-β1 nor between TGF-β3 and TGF-β2 in nasal polyps and in healthy tissues.

Discussion

The spectrum of TGF-β activity is broad and diverse. Its immunosuppressive properties are the most important. TGF-β inhibits proliferation, differentiation, and activity of T and B lymphocytes and of NK and LAK cells [26]. It is a potential inhibitor of many cells, e.g. epithelial cells, endothelial cells, and fibroblasts [17]. As TGF-β affects the inflammatory process, it is a chemoattractant for monocytes, T lymphocytes, neutrophils, and fibroblasts. TGF-β also possesses immunomodulative activity through its regulative influence on the generation of other cytokines, such as interleukins (IL-1, IL-6), TNFα, and PDGF [8]. TGF-β is produced by all the cell types (platelets, lymphocytes, monocytes, and fibroblasts) in a latent form bound with LAP (latency-associated peptide) or with LTBP (latent TGF-beta-binding protein). It may bind to a receptor after release from its initial binding [24,25]. Specific protein receptor types I and II (containing serine-tyrosine kinase) and type III (betaglycan) are essential for the biological activity of TGF-β [5,13].

According to Wang et al., TGF-β1 is the most active TGF-β isoform of all the three found in humans [29]. TGF-β2 is structurally similar to TGF-β1, but the biological responses to these cytokines differ according to the cell type. The promoter sequences of the genes coding the different TGF-β isoforms are not homologous. Analysis of the TGF-β1 and TGF-β3 promoters revealed the presence of a few binding sites for the transcriptional factors Sp-1 and AP-1. Fragments of the TGF-β1 and TGF-β3 promoters may compete for binding of Sp-1 to DNA. The TGF-β2 promoter does not contain binding sites for the Sp-1 transcriptional factor [15]. The lack of correlation we observed between TGF-β1 and TGF-β3 transcriptional activity may result from the similar regulation of the expressions of these genes and the competition for binding Sp-1. Further investigations are necessary.

Autocrine native mRNA induction is an important property of TGF-β. TGF-β1 and TGF-β3 mRNAs were proved to be present in both healthy and fibrotic pulmonary tissue with equal distribution [7]. Coker et al. [7] suggested that co-localization TGF-β1 and TGF-β3 mRNAs may indicate simultaneous expression activation of both genes. As it was showed in our study, an increase in transcriptional activity of TGF-β1 gene highly correlated with an increase in TGF-β2 activity, which may suggest similar ways of regulating the transcriptional activity for these genes.

The transcription factor AP-1 plays a key role in the regulation of TGF-β1 expression. Three elements binding AP-1 responsible for TGF-β1 auto-induction have been identified so far. Two of them are recognized as the complements c-jun and c-fos that block TGF-β1 autocrine expression. Ventura et al. [28] explained the role of c-Jun N-terminal kinase (JNK) in TGF-β1 expression regulation. They noted significant expression of TGF-β1 in fibroblasts deprived of JNK. Additional studies revealed JNK to be the repressor of TGF-β1 gene. All these data suggest that JNK takes part in the signaling pathway regulating TGF-β1 expression. The different control of the individual isoforms has numerous biological consequences. Almost all cell types synthesize TGF-β spontaneously or in response to stimulation. Moreover, co-expression of TGF-β isoforms is observed in most cases and the lack of one type may be compensated by another. Nilsson et al. [21] used RT-PCR to show low TGF-β3 mRNA isoform expression with simultaneous high TGF-β1 expression during primary ovarian vesicle growing. However, there are cell types that synthesize only one TGF-β isoform. Platelets, the richest source of TGF-β1, seem to be the best example [4]. Other studies showed that retinol acid inhibited TGF-β3 expression in pulmonary cancer cells with simultaneous stimulation of TGF-β2 expression [18]. The present study revealed the presence of all isoforms in healthy mucosa with a lack of TGF-β1 and TGF-β2 mRNA in the same eosinophilic and neutrophilic nasal polyps.

In studies performed by Balzar et al. [2] in patients with bronchial asthma, only TGF-β2 was significantly more concentrated in comparison with healthy mucosa. According to the authors this was connected with a higher amount of eosinophils presenting more intensive TGF-β2 expression.

The studies on TGF-β isoform expression in nasal polyps performed so far have yielded very different results. Coste et al. [9], evaluated the expressions of TGF-β1–3 isoforms using immunohistochemical methods in healthy and inflamed mucosa and in nasal polyps. The expressions of the TGF-β isoforms were more intensive in nasal polyps and inflamed mucosa than in normal mucosa. TGF-β1 was the most concentrated isoform present, also in macrophages and eosinophils. A higher expression of the TGF-β2 isoform in nasal polyps than in healthy mu-

cosa was proved immunohistochemically by Eisma et al. [11]. TGF-β1 was less concentrated in nasal polyp tissue than in healthy mucosa, which is consistent with our results. Hirschberg et al. [16] used ELISA to determine the TGF-β1 concentration in atopic and non-atopic patients and in healthy mucosa and revealed a much higher concentration of this isoform in healthy tissue than in nasal polyps. However, there were no differences between atopic and non-atopic polyps. As the authors suggested, this may result from the activation of mechanisms that promote a short incubation time of TGF-β1. An evaluation of TGF-β expression using RT-PCR was performed by Lee et al. [19]. There was TGF-β mRNA expression in all the polyp tissue samples (n=14), but only in 3 of the 6 samples of healthy mucosa. Moreover, Bradley and Kountakis [6] used real-time RT-PCR to estimate TGF-β transcriptional activity in tissue sampled from patients with chronic rhinosinusitis and with chronic rhinosinusitis and nasal polyps. The expression turned out to be more intensive in the patients with nasal polyps. Similarly significantly higher expression of TGF-β1 mRNA in healthy mucosa compared with nasal polyps was also revealed in the present study both for eosinophilic and neutrophilic polyps. According to Sharma and Ziyadeh [27], TGF-β1 strongly inhibits epithelial and endothelial cell proliferation, whereas its influence on cells of mesenchymal tissue (fibroblasts) is ambiguous: a low concentration of TGF-β1 promotes proliferation of these cells and a high concentration inhibits it. This could explain the low TGF-β1 expression in nasal polyps obtain here. Such a low TGF-β1 expression perhaps promotes fibroblast proliferation in nasal polyps. Additionally, the lower TGF-β1 concentration in nasal polyps may be connected with the presence other TGF-β isoforms. Our results confirmed that the expression of TGF-β3 was significantly more intensive in eosinophilic polyps than in health tissue and neutrophilic polyps. Eisma et al. [11], using immunohistochemical methods, revealed a higher TGF-β2 isoform concentration in nasal polyps than in healthy mucosa. The TGF-β1 isoform was less concentrated in nasal polyps, which is in agreement with our data.

Due to the fact that none of the currently discussed theories seem adequate to account for all the known facts related to nasal polyps, further investigations are necessary.

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