Comparison of interleukin 17 family protein expression in neutrophils of patients with oral inflammation and patients with cancer disease of the same location

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Abstract

Current data indicate the involvement of the interleukin 17 (IL-17) family of cytokines both in the inflammatory and neoplastic processes. Among the family members, IL-17A and IL-17E seem to play a special role, showing different biological activities via their specific receptors IL-17R and IL-17BR. The comparison of the expression of IL-17 cytokines between leukocytes of patients with inflammation and leukocytes of those with neoplasia of the same location may elucidate their involvement in these two pathologies. The study was conducted in a group of 30 patients with perimaxillary inflammation and 32 patients with oral squamous cell carcinoma. The control group consisted of 15 healthy subjects. The expressions of IL-17E, IL-17A, IL-17BR and IL-17R in PMN and PBMC lysates were assessed by Western blot. The levels of IL-17E and IL-17A in cell supernatants and in serum were determined using the ELISA method. The expression and secretion of IL-17E, IL-17A and the expression of their receptors IL-17BR and IL-17R were higher in the leukocytes of patients with inflammation than in carcinoma patients. In the inflammatory patients, the expressions and secretion of IL-17E and IL-17A were higher in newtrophils (PMN) than in peripheral blood mononuclear cell (PBMC). The expressions of IL-17A and IL-17R were increased as compared to IL-17E and IL-17BR in the cells studied. A correlation was found between the levels of IL-17A in PMN supernatants and in the serum of patients with inflammation. The changes observed in the expression of the IL-17 family of cytokines and receptors are more characteristic of the inflammatory process and of neutrophils, which indicates greater involvement of these cells and the cytokines in the inflammatory process than in the neoplastic process occurring at the same location.

Key words: *neutrophils, IL-17, oral inflammation, squamous cell carcinoma of oral mucosa.*

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Introduction

The interleukin 17 (IL-17) family of cytokines has been identified as a separate system of intercellular signalling covering a group of ligands and receptors, among which IL-17A and IL-17E and their specific receptors IL-17R and IL-17BR play a special role [1-3].

Interleukin 17A induces various biological effects, such as the production of inflammatory mediators and growth factors, granulopoiesis or adhesion molecule expression [4-6]. Recent studies have revealed the involvement of IL-17A in the neoplastic process, e.g. via T cell stimulation and pro-angiogenic cytokine expression [7, 8].

Interleukin 17E takes part mainly in the development of Th2-dependent response, first of all by initiating the synthesis of many cytokines that exhibit different activities compared to IL-17A [9, 10]. Moreover, it regulates prolif-

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eration of bone marrow progenitor cells by controlling the number of mature leukocytes, affects recruitment of B cells to tumour microenvironment and enhances production of antibodies [1, 11].

The secretion of IL-17A and IL-17E by immunocompetent cells may thus affect a variety of reactions, involved in both inflammatory and neoplastic processes. Neutrophils (PMN), able to synthesize and release many cytokines, including IL-1β, IL-6, IL-8, IL-15, IL-18, TNF-α, G-CSF, TRAIL, APRIL and BAFF play a special role in the early phase of both inflammatory and neoplastic response [12-18]. These cells also release cytokine-regulating proteins, e.g. sIL-1RII, IL-1Ra, sIL-6Rα and sgp130, sTNFRp55 and sTNFRp75 [14, 15, 19, 20]. The capacity of human neutrophils to produce and release IL-17A and IL-17E, and to express their specific receptors, IL-17R and IL-17BR, has also been demonstrated [8, 21].

There is some evidence indicating that the production and activity of cytokines can be altered both by inflammation and neoplasia, as these proteins have been implicated in these two processes. A significant role of inflammatory mediators and effector cells has been observed in the promotion and progression of the neoplastic process and in the formation of secondary foci [22, 23]. On the other hand, the inflammatory components in tumour microenvironment may play a key role in cancer growth inhibition by stimulating the cytokine-controlled immune antineoplastic mechanisms [22].

As demonstrated in our earlier studies, both PMN and peripheral blood mononuclear cells (PBMC) of patients with oral inflammatory condition and squamous cell carcinoma of oral mucosa show altered ability to release IL-17 family proteins [24, 25].

The comparison of the expression of IL-17 family cytokines between leukocytes of patients with inflammation and leukocytes in neoplasia of the same location may contribute to better understanding of their involvement in these two pathologies. Moreover, the results obtained would allow precise determination of the role of mononuclear cells and neutrophils associated with the cytokine activity. In the current study, IL-17E secretion by neutrophils and mononuclear cells of patients with perimaxillary inflammation and with squamous cell carcinoma of oral mucosa was compared with IL-17A secretion. Moreover, the expressions of the cytokine specific receptors, IL-17BR and IL-17R, in the leukocytes studied were compared.

Material and methods

Tissue samples and patient characteristics

The study involved a group of 30 patients with perimaxillary inflammation, aged 23-54 years, and group of 32 patients with squamous cell carcinoma of oral mucosa, aged 42-73 years, hospitalized in the Maxillofacial and Plastic Surgery Clinic, Medical University of Bialystok. Assays were performed in patients before the treatment. Study results, in patients with cancer, were analyzed taking into account a clinical stage of the disease according to TNM classification. Characteristic of patients was presented in the Table 1.

The control group constituted 15 healthy people, aged from 20 to 50 years, volunteer blood donors.

Cells were isolated from whole blood collected for heparin (10 IU/ml-Heparin, Polfa-Łódź, Poland) using Gradisol G (1.115 g/ml, Polfa-Łódź, Poland) according to

Table 1. Clinicopathological characteristics of patients

Patients with oral inflammation											
Sex	**Total (*n*)**	**Mean age**	**Site of inflammation**								
			intraoral inflammatory infiltration	**submandibular inflammatory infiltration**	**inflammatory infiltration of cheek**	**intraoral abscess**	**submandibular abscess**	**cheek abscess**	**Ludwig's angina**	**submandibular phlegmon**	
F	12	40	1	3	1	2	2	–	1	2	
M	18	32	3	2	1	2	3	2	2	3	
Patients with oral cancer											
Sex	**Total (*n*)**	**Mean age**	**Site of cancer**						**TNM classification**		
			oral cavity fundus	**oral cavity fundus + inferior gingival**	**inferior gingival**	**cheek mucosa**	**palate mucosa**	**lower lip**	**I°**	**II°**	**III°**	**IV°**
F	11	60	3	1	2	2	1	2	3	5	1	2
M	21	64	5	3	4	3	3	3	5	3	7	6

Zeman *et al.* [26]. Sera were obtained from blood samples collected without anticoagulant agents.

The two leukocyte fractions obtained, i.e. polynuclear cells (containing 94% neutrophils) and mononuclear cells (containing 96% lymphocytes), were suspended in a culture medium containing RPMI-1640 or Hanks' fluid (BIOMED-Lublin, Poland), subjects' own serum, 100U/ml penicillin and 50ng streptomycin (Polfa Trachomin S.A., Poland), reaching the concentration of 5×10^6 cells/ml. The purity of isolated PMN and PBMC were determined by May-Grunwald-Giemsa-staining (Aqua-med, Poland) Then, the cells were incubated in microplatelets (Microtest III-Falcon, BD Biosciences, Bedford, USA) at 37°C, in an incubator with a flow of 5% CO_2 (NUAIRE™ US AUTOFLOW CO_2 Water-Jacketed Incubator). Following culture, the viability of PMN and PBMC were > 95% as determined by trypan blue exclusion (Lachema, Praga, Czech Republic).

After 20 hours, the supernatant was collected from each well and stored at –20°C.

Informed written consent was obtained from all participants and the Ethics Committee of the Medical University of Bialystok approved the study.

Expressions of proteins IL-17A, IL-17E both receptors IL-17R and IL-17BR assessed by the Western blot method

PMN and PBMC were subjected to lysis by means of sonification (SONICS Vibra Cell) in the presence of protease inhibitors (Sigma-Aldrich, Steinheim, Germany). The lysate was suspended in Laemli's buffer (Bio-Rad Laboratories, Herkules CA, USA). The cytoplasmic fraction of proteins underwent electrophoresis on SDS-PAGE (Bio-Rad Laboratories, Herkules CA, USA). The protein fractions were transferred onto nitrocellulose (Bio-Rad Laboratories, Herkules CA, USA). Then, nitrocellulose was incubated with suitable polyclonal anti-IL-17A, anti-IL-17E, anti-IL-17R and anti-IL-17BR antibodies (R&D Systems, Minneapolis, USA). After rinsing with 0.1% TBS-T, nitrocellulose was incubated with alkaline phosphatase-labelled antibody against IgG (Victor Laboratories, Burlingame, CA, USA). Immunoreactive protein bands were obtained by adding the BCIP/NBT Liquid Substrate System (Sigma-Aldrich, Steinheim, Germany).

Interleukin 17A and interleukin 17E levels assessed using ELISA method

Interleukin 17A levels in the serum and cell supernatants were measured by ELISA method using R&D Systems kits (Minneapolis, USA) according to the instructions given. Human recombinant IL-17A was used as a standard.

Interleukin 17E concentrations in blood serum and cell supernatants were determined by ELISA method using a PeproTech kit (Rocky Hill, USA) according to the instructions enclosed. Human recombinant IL-17E was used as a standard.

Statistical analysis

The data obtained were subjected to statistical analysis using Microsoft Excel calculation sheet and the Statistica 8 package. Data are presented as the mean ± standard deviation (SD).

Normality of data distribution was assessed by the Kołomogorov-Smirnov test. Since the data were not consistent with normal distribution, the non-parametric Mann-Whitney test was used to compare differences between the groups.

The Pearson's linear correlation was used for the analysis of parameter correlation, whereas *t*-Student test for correlation coefficient was applied to assess the correlation significance. The threshold p-value < 0.05 was considered to be the level of statistical significance.

Results

Interleukin 17A and interleukin 17E expressions assessed by Western blot

The expressions of IL-17A (35 kDa) and IL-17E (34 kDa) in PMN and PBMC of patients with inflammatory condition were more pronounced as compared to the control group and carcinoma patients. In PMN, the expressions of IL-17A and IL-17E were found to be higher than in PBMC (Fig. 1). No differences were observed in the expressions of these cytokines between the cells of patients with various forms of inflammation (data not presented).

In cancer patients, no changes were noted in the expressions of IL-17A and IL-17E in PMN and PBMC in comparison with the control group. No differences were found in the expression of both cytokines in PMN and PBMC in relation to disease advancement (Fig. 1), and location (data not presented).

Both PMN and PBMC showed higher expression of IL-17A as compared to IL-17E (Fig. 1).

The expressions of interleukin 17R and interleukin 17BR assessed by Western blot

The study showed higher expressions of IL-17R (110 kDa) and IL-17BR (56 kDa) in PMN and PBMC of patients with inflammatory condition and cancer patients as compared to healthy subjects (Fig. 1).

Patients with inflammation showed significantly increased expressions of IL-17BR and IL-17R in PMN and PBMC in comparison with cancer patients (Fig. 1).

No differences were noted in the expressions of IL-17R and IL-17BR between PMN and PBMC in the two groups of patients (Fig. 1). The expression of the receptor IL-17R in PMN and PBMC in the study groups was significantly higher than that of the receptor IL-17BR (Fig. 1).

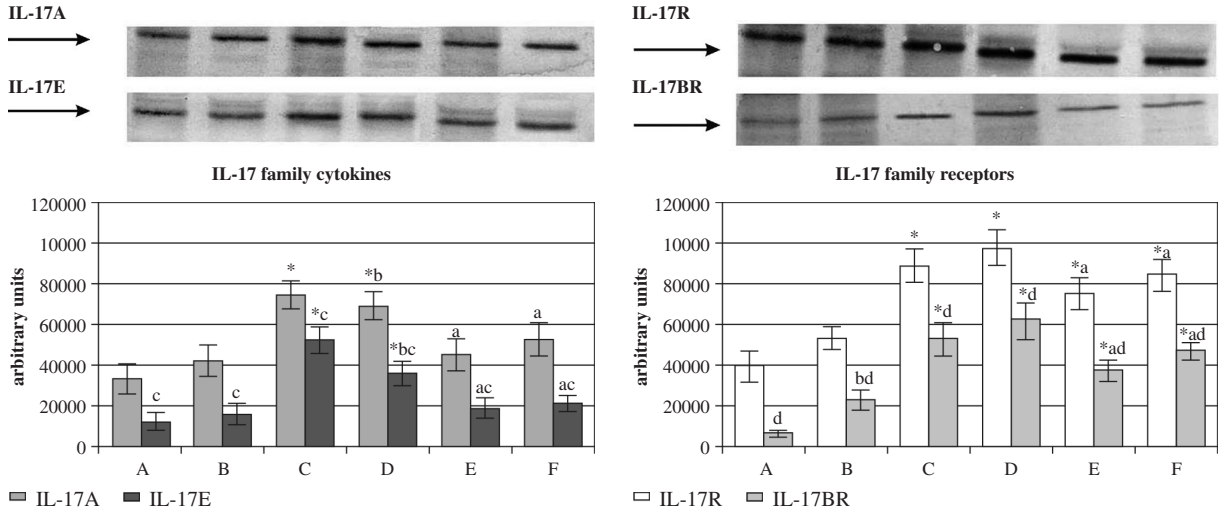

Fig. 1. Expressions of IL-17A, IL-17E, IL-17R and IL-17BR in PMN and PBMC in healthy subjects and patients using Western blot method. A – PMN of healthy subjects, B – PBMC of healthy subjects; C – PMN of patients with oral inflammation; D: PBMC of patients with oral inflammation; E – PMN of patients with oral cancer; F: PBMC of patients with oral cancer. Statistically significant difference ($p < 0.05$): * – between healthy subject and patients, [a] – between patients with inflammation and cancer, [b] – between PMN and PBMC, [c] – between IL-17A and IL-17E, [d] – between IL-17R and IL-17BR

No significant differences were found in the receptor expressions in PMN and PBMC with respect to disease advancement (Fig. 1) and location (data not presented), in inflammation and neoplasia.

The levels of interleukin 17A and interleukin 17E in cell supernatants and in blood serum as assessed by ELISA

The study demonstrated significantly higher levels of IL-17A and IL-17E in PMN and PBMC supernatants and in blood serum of patients with inflammation and cancer as compared to the control group (Table 2, 3).

In all the study groups, the levels of IL-17A in PMN and PBMC supernatants and blood serum were significantly higher in comparison with IL-17E (data not presented).

The levels of IL-17A and IL-17E were significantly increased in PMN and PBMC supernatants and in blood serum of patients with inflammation as compared to oral carcinoma patients (Table 2, 3).

Table 2. Interleukin 17A concentrations in blood serum and cell supernatants of PMN and PBMC in healthy subjects and patients using ELISA method

IL-17A [pg/ml]							
	Cells	Control (n = 15)	Patients with oral inflammation (n = 30)	Patients with oral cancer			
				TNM classification			
				I° (n = 8)	II° (n = 8)	III° (n = 8)	IV° (n = 8)
PMN	$\bar{x}$	9.18	40.59*	25.62*[a]	26.32*[ac]	25.69*[a]	25.10*[ad]
	± SD	±2.36	±9.74	±3.48	±3.05	±2.63	±2.33
PBMC	$\bar{x}$	10.52	34.89*[b]	26.29*[a]	30.90*[ac]	28.08*[a]	26.22*[ad]
	± SD	±2.49	±8.94	±2.01	±4.23	±2.78	±2.26
serum	$\bar{x}$	15.27	70.57*	31.33*[a]	35.47*[a]	29.24*[af]	27.09*[ade]
	± SD	±3.53	±25.79	±4.68	±5.97	±4.23	±4.55

** – a statistically significant difference between healthy subject and patients ($p < 0.001$), [a] – a statistically significant difference between patients with inflammation and patients with cancer ($p < 0.05$), [b] – a statistically significant difference between PMN and PBMC patients with inflammation ($p < 0.05$), [c] – a statistically significant difference between I° and II° ($p < 0.05$), [d] – a statistically significant difference between II° and IV° ($p < 0.05$), [e] – a statistically significant difference between I° and IV° ($p < 0.05$), [f] – a statistically significant difference between II° and III° ($p < 0.05$)*

Table 3. Interleukin 17E concentrations in blood serum and cell supernatants of PMN and PBMC in healthy subjects and patients using ELISA method

IL-17E [pg/ml]							
	Cells	Control (n = 15)	Patients with oral inflammation (n = 30)	Patients with oral cancer			
				TNM classification			
				I° (n = 8)	II° (n = 8)	III° (n = 8)	IV° (n = 8)
PMN	$\bar{x}$	8.04	26.05*	13.36*[a]	14.33*[a]	15.54*[ac]	17.75*[ade]
	± SD	±1.69	±5.75	±2.94	±3.05	±1.08	±2.89
PBMC	$\bar{x}$	9.03	23.27*[b]	14.92*[a]	15.05*[a]	17.13*[ac]	18.46*[ade]
	± SD	±1.46	±4.36	±2.20	±1.80	±2.42	±2.79
serum	$\bar{x}$	10.10	33.47*	17.53*[a]	17.87*[a]	17.95*[a]	18.87*[a]
	± SD	±1.82	±11.05	±3.36	±2.04	±2.76	±3.10

** – a statistically significant difference between healthy subject and patients ($p < 0.05$), [a] – a statistically significant difference between patients with inflammation and patients with cancer ($p < 0.05$), [b] – a statistically significant difference between PMN and PBMC patients with inflammation ($p < 0.05$), [c] – a statistically significant difference between I° and III° ($p < 0.05$), [d] – a statistically significant difference between I° and IV° ($p < 0.05$), [e] – a statistically significant difference between II° and IV° ($p < 0.05$)*

In patients with inflammation, the levels of IL-17A and IL-17E in PMN supernatants were higher than in PBMC (Table 2, 3).

No significant differences were noted in the levels of IL-17A and IL-17E between PMN and PBMC supernatants in the control group and cancer patients (Table 2, 3).

The analysis of the results, with respect to carcinoma advancement, showed a significant rise in the level of IL-17A in PBMC supernatants in stage II patients as compared to stage I and IV patients. The serum level of IL-17A was the highest in stage II patients, being significantly higher as compared to stage III and IV (Table 2).

Elevated levels of IL-17E were observed in PMN and PBMC supernatants in patients at stage III and IV in comparison with stage I. Moreover, the levels of IL-17E in PMN and PBMC of stage IV patients were significantly higher than in stage II patients. Stage-dependent changes in the serum levels of IL-17E were not significant (Table 3).

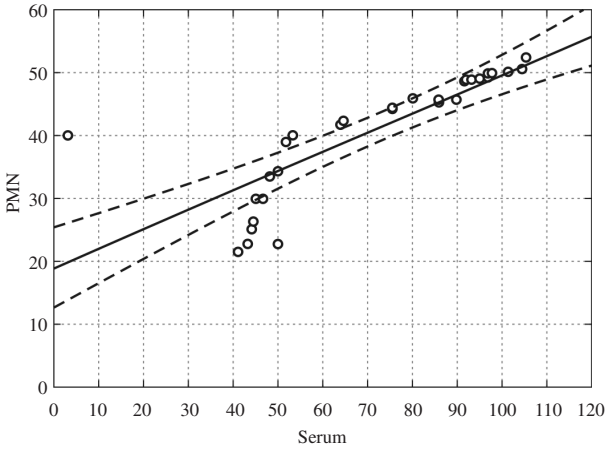

Fig. 2. A correlation between the levels of IL-17A in PMN supernatants and in the serum of patients with inflammation ($r = 0.81$, $p < 0.001$)

No differences were observed in the levels of IL-17A and IL-17E in cell supernatants and sera of patients with cancer in relation to location, as well as in patients with various forms of inflammation (data not presented).

A correlation was found between the levels of IL-17A in PMN supernatants and in the serum of patients with inflammation ($r = 0.81$, $p < 0.001$) (Fig. 2).

Discussion

Considering the great variety of biological effects of the IL-17 family of cytokines, the knowledge of their cellular origin may contribute to a better definition of the bases for immunoregulation with the involvement of these proteins in various pathologies.

In the current study conducted in patients with inflammation or neoplasia of the same location, neutrophils and mononuclear cells showed varied capacity to produce the IL-17 cytokines and to express their specific receptors. In the inflammation patients, the rise in IL-17A and IL-17E secretion was accompanied by increased expression of the receptors IL-17R and IL-17BR on these cells. At the same time, higher expression and secretion of IL-17A and IL-17E by neutrophils as compared to mononuclear cells in this group of patients seem to indicate a special role of neutrophils in inflammatory reactions controlled by both cytokines.

High secretion of IL-17A by the two groups of leukocytes may induce the synthesis of the proteins responsible

for both the development and maintenance of inflammatory reaction as well as affect cancer growth [27-29]. The elevated level of IL-17A may enhance the production of GM-CSF or ENA-78, by stimulating granulopoiesis as well as recruitment and activation of neutrophils by inducing the production of such chemotactic factors as IL-8, GRO-α and GCP-2 [4, 7, 30, 31]. Yu *et al*., studying the role of IL-17A and IL-17R in maxillitis induced by bacteria Porphyromonas gingivalis in mice, observed enhanced recruitment of neutrophils [32]. High level of IL-17A may also lead to the increased class I and II MHC molecule expression, thus enhancing the process of antigen presentation [8, 33]. Moreover, substantial amounts of IL-17A may stimulate the *in vitro* production of proangiogenic factors, such as FGF, HGF, VEGF and TGF-β by macrophages and fibroblasts [34, 35]. These actions in the course of inflammation may exert a beneficial effect on the processes of repair and by reducing inflammation. However, in carcinoma patients, they may have an unfavourable effect associated with enhanced neoangiogenesis, tumor growth and formation of secondary foci.

In both groups of patients, the enhanced secretion of IL-17A was accompanied by the increased expression of the specific receptor IL-17R in PMN and PBMC, the expression being the highest in patients with inflammation. This suggests potentially higher sensitivity and activity of the cells studied to the effect of IL-17A in this group of patients.

The role of IL-17A in the inflammatory process affecting the oral cavity was confirmed by Johnson *et al.,* who showed the increasing levels of IL-17A in the inflamed gingival tissue with the disease progression [36]. Moreover, Čolić *et al.* observed a correlation between the level of IL-17A in PBMC supernatants and enhancement of gingival tissue inflammation [37].

The changes observed in the secretion of IL-17A may result in its increased serum levels in both groups of patients. The correlation observed between the levels of IL-17A in PMN supernatants and sera of patients with inflammation seem to confirm the role of PMN in IL-17A secretion. The patients with oral squamous cell carcinoma also showed elevated levels of this cytokine, although lower than in the case of inflammation. Linkov *et al.* in their study conducted on a large group of patients with squamous cell carcinoma of the head and neck (SCCHN) found no significant increase in the serum levels of IL-17A. These discrepancies may be due to different group selection. Our study was limited to a narrow group of patients with squamous cell carcinoma of oral mucosa belonging to a large group of head and neck carcinomas, whereas Linkov *et al*. investigated patients with SCCHN, not taking into account the precise location [38].

High activity of PMN and PBMC, associated with IL-17A release observed in the two groups of patients can be at least partly counterbalanced by the increased IL-17E secretion by these cells.

The enhanced production of IL-17E may augment the synthesis and release of IL-13, which inhibits Th17 cell response, thus reducing the level of IL-17A [39]. Moreover, the presence of increased amounts of IL-17E may inhibit proliferation of CFU-GM, which decreases the number of mature leukocytes in the blood [11]. High concentrations of IL-17E, leading to an increase in the synthesis and release of IL-4 and IL-10 exert an anti-inflammatory and suppressive effects, thus affecting both the inflammatory and the neoplastic process [40-42]. On the other hand, IL-17E by inducing IL-5 production may aid the synthesis of IgM antibodies and recruitment of eosinophils, and thus lead to reaction enhancement in patients with inflammation. However, in cancer patients the increased recruitment of B cells to tumour microenvironment by IL-17E may promote enhanced production of cancer-specific antibodies [43].

The level of IL-17E in PMN and PBMC, increasing as the cancer stage advances and being the highest in stage IV patients, suggests a potential role of IL-17E secretion by these cells as a factor associated with oral squamous cell carcinoma progression.

Like in the case of the specific receptor for IL-17A (IL-17R), the increase in the specific receptor for IL-17E (IL-17BR) both in PMN and PBMC in the two groups of patients, suggests potential readiness of these cells for the para- and/or autocrine action of this cytokine.

The lower expressions of IL-17E and IL-17BR as compared to IL-17A and IL-17R in PMN and PBMC in the control group and in patients indicate a less substantial role of these two groups of cells in the reactions with the involvement of IL-17E, as compared to IL-17A.

These observations seem to indicate a novel role of the IL-17 family of proteins, not only as inflammatory markers, but also as leukocyte activity indices in IL-17E and IL-17A-dependent reactions in the neoplastic process. The changes observed in the expression of the IL-17 family of cytokines and receptors are more characteristic of the inflammatory process and of neutrophils, which indicates greater involvement of these cells and cytokines in the inflammatory process than in the neoplastic process occurring at the same location.

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