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The role of pro-inflammatory cytokines in the pathogenesis and progression of neoplasms

Rola cytokin prozapalnych w patogenezie i progresji nowotworów

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Summary

Cytokines play an important role in the functioning of the immune system. Studies have reported an increased secretion of inflammatory cytokines by the neoplasms. Inflammation plays a role in the pathogenesis of various diseases; it is also a risk factor for the development and progression of a neoplasm, as exemplified by the development of cancer in the region of the head and neck in response to chronic inflammation caused by irritants present, e.g. in cigarette smoke. Cytokines (IL-1 beta, IL-6, TNF, IL-8, IL-17), which take part in the inflammatory response and are, therefore, strongly involved in the development of cancer. The combined action of cytokines produced by the neoplastic cells via multiple mechanisms, modulates cell response of the host immune system. Clinical observations suggest that cancer patients show a progressive disorder of the immune system, resulting in tumor progression. The mechanisms conducive to the weakening or lack of an immune response to neoplastic antigens contribute to the severity of the invasion of cancerous lesions. Although mechanisms that occur between tumor cells, the micro-environment of the tumor and immune cells of the host are not thoroughly known, previous research point to the importance of this interaction in oncogenesis, which may ultimately affect the prognosis.

Keywords: **IL-1beta • IL-6 • IL-8 • IL-17 • TNF**

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INTRODUCTION

Cytokines play an important role in the functioning of the immune system. After binding to specific receptors these proteins are involved in all stages of the cell cycle, i.e. in the processes of cell proliferation, growth, differentiation and apoptosis. They play a role in the course of inflammation, and they regulate every part of the immune response. The cytokines exhibit pleiotropic and redundancy action and can also interact in a synergistic, additive, or antagonistic way. They have high activity at low concentrations. Over 100 cytokines produced by different cell types have been described. The cytokines include: interleukins, interferons, chemokines, grow factors, tumor necrosis factor family. Due to the nature of the action, the following can be distinguished among them, e.g. pro- and anti-inflammatory cytokines. The first group includes: IL-1 beta, IL-6, IL-8, IL-15, IL-17, TNF. Anti-inflammatory cytokines are: IL-4, IL-10, IL-13, TGF-β. Specific cytokines often have the opposite effect, depending on the cells producing them, the target cells, and the surrounding microenvironment.

Many researchers point to the participation of these proteins in the development of a neoplasm. Cytokines play a role at all stages of carcinogenesis, induce changes in the tumor microenvironment allowing its further development, and they regulate the immune response. On the one hand, many studies have shown the significant role of cytokines in inhibiting cancer; on the other hand, its promotion and spread. A progressive disorder of creation and operation of cytokines occurs during the development of neoplastic disease. The individual elements of the neoplasm have the capacity to secrete numerous cytokines, which allow an autocrine growth of cancer cells and further development of cancer (Fig.1).

Tumors are a heterogeneous structure. Apart from tumor cells, the neoplastic infiltration includes: carcinoma-associated fibroblasts (CAFs), smooth muscle cells, endothelial cells, adipocytes, immune cells infiltrating the tumor (macrophages, B and T lymphocytes) [38]. The phenomena, observed during inflammation occur in the environment of the tumor, are aimed to repair damaged tissues. Inflammation plays a role in the pathogenesis of various diseases; it is also a risk factor for the development and progression of the neoplasm [8].

Exposure to irritants present, e.g. in cigarette smoke, can cause chronic inflammation, which is associated with head and neck cancer [18]. The relationship between a viral infection and the development of cancer has been confirmed in animal models and in epidemiological studies. There are reports that the formation and progression of cancer is accompanied by chronic inflammation [60], e.g. pancreatitis is associated with pancreatic cancer, chronic cholecystitis with gallbladder cancer, ulcerative colitis with colorectal cancer, viral hepatitis (HBV, HCV) with liver cancer, chronic HPV infection with cervical cancer and cancer of the oropharynx, Helicobacter pylori infection with gastric cancer.

Kressner et al. found in their study that the occurrence of infectious postoperative complications predisposes to a higher incidence of local recurrence [39]. One of the mechanisms in which the chronic bacterial infection predisposes to cancer is the DNA damage caused by reactive forms of oxygen which are formed during the inflammatory response, resulting in the mutation and development of cancer [69].

PRO-INFLAMMATORY CYTOKINES

The network of cytokines formed during the inflammatory response consists of a number of cytokines which are mediators of the immune response. They stimulate the processes necessary for tissue healing (anti-inflammatory cytokines) and cause their degradation (pro-inflammatory cytokines).

A strong correlation exists between pro- and anti--inflammatory cytokines secreted in the tumor microenvironment both by the immunocompetent cells and tumor cells. Their combined effect, via multiple mechanisms, modulates the response of the host immune cells. Cytokines produced by tumor cells may influence the functioning of immune cells, e.g. by inducing secretion of pro-inflammatory (IL-1, IL-6,IL-8, TNF), inflammatory and angiogenic cytokines, and, as a result of this the further development of cancer may occur. The studies suggest that an excess of inflammatory cytokines promotes tumor growth and survival [28].

A number of studies have reported an increased secretion of particular pro-inflammatory cytokines by the tumor: IL-1 in gastric and ovarian cancer, IL-6 in prostatic, kidney, cervix, ovary, colon carcinoma, melanoma, lymphoma B-cell disease, multiple myeloma, lymphoma, Hodgkin's lymphoma, TNF in ovarian cancer, IL-8 in pancreatic cancer, prostate cancer, colon cancer, stomach, liver, ovarian, squamous cell carcinomas of the head and neck, melanoma. Cytokines that are involved in the inflammatory response are, therefore, strongly involved in the development of cancer [5, 7]. Chronic inflammation may play a significant role in the formation and the further development of cancer, and some cytokines, e.g. IL-6, IL-8, TNF, modify the immune response and are associated with angiogenesis and metastasis [32].

Pro-inflammatory cytokines such as IL-6 and TNF are mediators of immune response. Research has shown that they take part in the development and progression of cancer and may affect the prognosis [8]. In the case of head and neck tumors, cancer cells and endothelial cells in the tumor microenvironment secrete IL-6, which is involved in tumor invasion and metastasis [1, 68]. This study showed an increased risk of recurrence and death in the case of TNF [75].

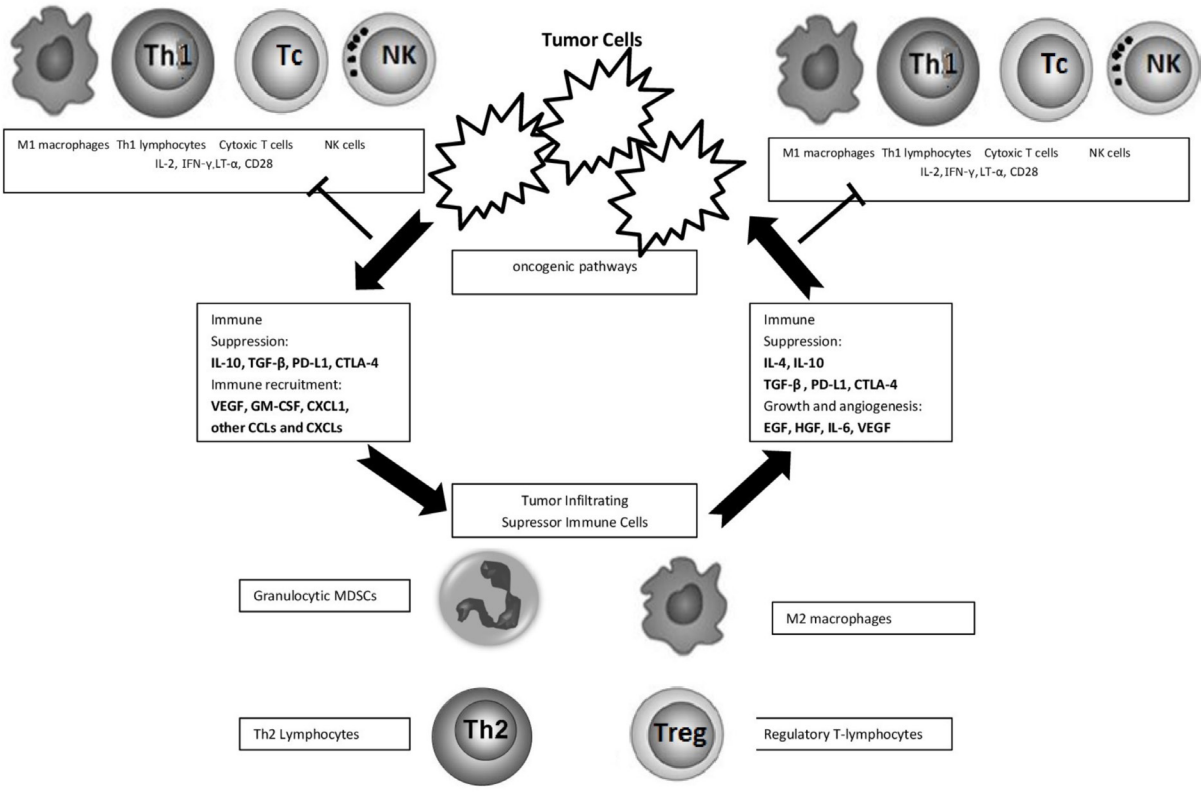

Fig. 1. The role of inflammatory cytokines in the pathogenesis of neoplasms

Clinical observations suggest that a progressive disorder of the immune system occurs in cancer patients resulting in tumor progression. This is related to the synthesis of cytokines by the individual elements neoplastic infiltration, for example Tumor Associated Fibroblasts (TAF) are the source of IL-6, IL-10, TGF beta, M-CSF [42].

Piers and Wollenber demonstrated in their review that the cells of head and neck squamous cell carcinoma (HNSCC) produce a variety of immunosuppressive cytokines promoting tumor growth causing a disorder of the immune response [58].

The local chronic inflammation can lead to the secretion of cytokines by the tumor environment, which influences the secretion of Myeloid-derived suppressor cells (MDSC) in the bone marrow. MDSC cells suppress the function of T-lymphocytes via an arginine depletion and nitric oxide production. This is one of the immunodeficiency mechanisms accompanying neoplastic processes. Cytokines that stimulate the formation of MDSC may include IL-6 and IL-1 beta.

The mechanisms conducive to the weakening or lack of an immune response to tumor antigens contribute to the severity of the invasion of cancerous lesions. The tumors of the head and neck revealed the presence of various tumor-infiltrating lymphocytes (TIL) [74], which, due to the development of numerous escape immune mechanisms by tumor cells, are not able to successfully fight cancer.

Suppressive activity of inflammatory cytokines (IL-6, IL-8) regulating the immune response in the stroma of cancers of the head and neck was confirmed in a paper by Pries et al. [57]. The study of laryngeal squamous cell carcinoma showed that cancer cells in the mixed cultures affect the activity of T lymphocytes in peripheral blood and modify the release of the cytokines IL-6 and IL-8. In vitro studies of normal epithelium cells indicated that larynx tumor showed capability of interleukin 8 secretion [68]. In addition, tumor cells stimulated the secretion in vitro of IL-10 and TNF by the T cells (but not by the cells of the larynx carcinoma) [67].

The role of cytokines in the pathogenesis and progression of cancer and suppression of the immune system has been proven in several studies that were conducted on cell lines of a given tumor, homogenates of tumors, primary cell cultures, in saliva and serum of patients.

INTERLEUKIN 1 BETA

The major pro-inflammatory cytokine, which alone or in combination with other cytokines induces acute

and chronic inflammatory conditions is IL-1 beta. This cytokine stimulates chemotaxis in monocytes and neutrophils, activates lymphocytes and osteoclasts and stimulates host cells (fibroblasts, epithelial cells, neutrophils) to produce more enzymes which are destructive to tissue. The increase in concentration occurs in response to an infection, damage to cells, activation of relevant antigens. It is secreted by various cell types, mainly by macrophages. IL-1 beta is involved in local and general inflammatory response, together with IL-6 and TNF. IL-1 beta may activate NF-kB in a manner similar to TNF. IL-1 beta belongs to the family of IL-1 which induces the genes supporting tumor growth and metastasis. IL-1 beta strongly promotes carcinogenesis. It is responsible for the expression of adhesion molecules, increased production of prostaglandins, the release of chemokines [29], whereby there is cell chemotaxis, blood vessel formation and an increase in cellular adhesion, and thus further development of the tumor. There are some studies suggesting that it can contribute to cell proliferation, angiogenesis, and metastasis of various tumors occurring in humans [47].

Overexpression of IL-1 beta contributes to gallbladder cancer tumorigenesis via Twist activation [23].

Its elevated concentrations are found in various tumor types. The increase in IL-1 concentration has been shown in oral cancers, lung, colon, breast, and skin cancers and melanoma [3, 6]. It has been shown that tumors that secrete IL-1 beta are characterized by poor prognosis [78]. The increase in IL-1 beta correlated with tumor progression [6]. The expression of IL-1 beta was observed in 90% of cases in invasive breast cancer and a high concentration of the cytokine in the tumor microenvironment is associated with higher malignancy and more aggressive phenotype [20]. Changes caused by IL-1 beta (from macrophages or from breast cancer cells) produce osteoprotegerin that contributes to increased invasion [12].

INTERLEUKIN-6

IL-6 is produced by fibroblasts, osteoblasts and osteoclasts, as well as immunocompetent cells, endothelial cells and renal tubules. IL-6 regulates the inflammatory response and hematopoiesis, and plays a significant role in the immunological mechanisms. It is not secreted by the cells constitutively, but its synthesis is induced by other cytokines, lipopolysaccharide and viral infections. IL-6 plays a role in processes involved in the destruction of the bone [53]. This cytokine is produced by osteoblasts influenced by various osteotropic factors, e.g. IL-1. The low concentration of IL-6 stimulates osteoclastogenesis, whereas an increase in the concentration activates osteoclasts which begin to produce IL-6, thereby intensifying the effect of resorption [59]. Sonis reported in their study proinflammatory cytokines (TNF, IL-1 beta, IL-6) which played a part in the development of stomatitis [65]. IL-6, together with other cytokines, regulate the immune response induced by oral bacteria, such as Aggregatibacter actinomycetemcomitans and Lactobacillus casei. Excessive IL-6 response may contribute to the development of chronic inflammation. IL-6 is one of the factors inhibiting the growth of cancer cells, but its effect changes during tumor progression from anti- into proliferative.

Many studies have shown that the presence of high levels of IL-6 in sera of patients is associated with poor prognosis [11, 49, 54]. Studies have shown that IL-6 stimulates the growth of tumor cells and its presence is associated with increased risk of metastasis [52]. Multivariate analysis shows that the elevated serum level of IL-6 is an independent risk factor for progression to extensive hepatic metastasis inclusive people with pancreatic ductal adenocarcinoma. At the same time, an increased level of IL-6 did not correlate with shorter time of living [34]. Overexpression of IL-6 can enhance the invasion and migration of breast and gallbladder cancer cells by stimulating epithelial-mesenchymal transition (EMT) [72, 84]. Its action, which is inhibitory or stimulating, differs depending on the cell population, e.g. it induces tumor growth in cervical cancer, inhibits the proliferation of normal melanocytes, melanoma at an early stage, as well as the epithelial cells of lung and liver, and stimulates the growth of cells in advanced stages of melanoma, non-small cell lung cancer and liver cancer.

In addition, IL-6 participates in the development of tumors by the inhibition of apoptosis or programmed cell death, resulting in the activation of the signal transducer and activator of transcription 3 (STAT3) [82]. IL-6 inhibits apoptosis in kidney cancer, prostate cells and multiple myeloma [49].

The study has demonstrated that IL-6 expression at both the mRNA and protein level in the tissues of the oral squamous cell carcinoma (OSCC) was significantly higher than in the normal mucous membrane [63]. Both the mRNA of IL-6 and IL-6R (IL-6 receptor) are increased in OSCC cell lines as compared to human keratinocyte cell line (HaCaT). This data suggests that IL-6 can contribute to carcinogenesis and/or the progression of OSCC.

The study has shown that levels of IL-6 in the saliva of patients with oral cancer were higher than in healthy controls [17]. Studies have confirmed the the secretion of proinflammatory cytokines such as IL-1, IL-6, IL-8 and lack of TNF secretion by cell lines in cancer of the head and neck [10]. The level of cytokines expression in the serum of patients with squamous cell carcinoma of head and neck depends on the clinical severity: overexpression of IL-6 was found in advanced disease and correlated with both the T (tumor) and N (nodus) characteristics [66]. Higher levels of IL-6 in patients with laryngeal cancer was demonstrated in the study by Pignataro et al. [56] and in a study by Chen et al. [10]

conducted on head and neck cancer patients in whom overexpression of the cytokines IL-6, IL-8 was observed. Preliminary studies of patients with squamous cell carcinoma of the larynx showed the coexistence of high concentrations of IL-6 and IL-8 with metastases to the lymph nodes [68].

In the study, assessing IL-6 concentration, higher levels of this cytokine as compared with the control group was found in the serum of patients with esophageal squamous cell carcinoma [54]. The study of patients with cervical cancer confirmed a significant association of IL-6, IL-8 and TNF in serum with the clinical level of severity [11]. Higher concentrations of IL-6 and IL-1 beta, IL-8 and TNF have been reported in patients with colorectal cancer and metastases to the liver [73]. The research results shows that IL-6 makes a progress of colitis-associated colorectal cancer in early period of disease progression throughout control of activity of HIF-1α [25]. There are also studies in which there was no association between cytokines and the clinical and morphological features of HNSCC. An example of this is the study by Lathers et al., where no significant correlation of IL-6 and IL-8 in the blood serum with morphological parameters of TNM classification were observed [44].

IL-6 also acts as an angiogenic factor and is involved in many of the same processes as TNF. Proinflammatory cytokines IL-6 and TNF are mediators of the immune response involved in the formation and progressions tumor and are associated with an increased risk of recurrence and death.

In a study of lung cancer, an increased production of proinflammatory cytokines (IL-6 was produced in 55% and IL-8 in 94% of the cell lines of lung cancer) was also found, and there was no production of TNF by tumor cells [19].

TUMOR NECROSIS FACTOR TNF

One of the main inflammatory mediators is TNF. A study conducted by Curiel et al. demonstrated that the pro-angiogenic cytokines TNF and IL-8 are produced by immature lymphoid dendritic cells in the tumor microenvironment [14]. TNF is produced early in the cascade of the inflammatory process. Its actions include the activation of macrophages, monocytes, lymphocytes and neutrophils, stimulation of fibroblast growth. The antitumor effect of this cytokine is mainly due to the activation of apoptosis. The progression of a cancer is accompanied with a change in TNF action, which begins to function as anti-apoptotic factor [43]. In tumors which are resistant to the cytotoxicity, TNF stimulates proliferation, survival, migration, and angiogenesis, resulting in the further growth of the tumor [27].

TNF is involved in various stages of OSCC neoplastic transformation [46]. It plays an important role in the formation of a tumor effect on the development of local blood vessels and stimulates tissue remodeling. Distant metastasis of cancer is also dependent on the migration of these cells and it is also engaged in the process. Operation of cytokines allows passage of tumor cells through the walls of blood vessels and lymph vessels to facilitate the process of metastasis. Pro-inflammatory cytokine TNF by inducing the expression of proteases contributes to the degradation of the basement membrane and extracellular matrix participating in metastasis.

High levels of TNF in tumor tissue are associated with the degradation of the tumor vasculature. However, if TNF is chronically produced, it promotes tumor growth.

The study confirmed that a low concentration of TNF stimulates and its high concentration inhibits the proliferation of cervical cancer cells, stimulates the growth of ovarian cancer cells in advanced stage and inhibits the growth of these cells in the early stage of ovarian cancer [2].

TNF was detected in tumor cells and stroma of the breast, colon, ovarian, prostate, bladder tumors and lymphomas and leukemias. It coexisted frequently with IL-1 and IL-6.

A study conducted by Juretić et al. have demonstrated that TNF and IL-6 have a higher concentration in OSCC patients' saliva as compared to healthy controls [30]. In a study by Krishnan et al., published in 2014, as in the studies of other authors, it has been demonstrated that the level of the local production of TNF (levels measured in saliva) is higher than the systemic (TNF in serum) [40]. Higher concentrations were observed in clinical stage IV oral cancer. Apart from increased concentration of TNF, IL-1, IL-6 and IL-8 were also found in samples of saliva in patients with oral cancer (OSCC) in comparison to the control group [62]. Severe biosynthesis TNF is one of the pathogenetic elements leading to the growth of SCC [55].

INTERLEUKIN-8

IL-8 produced by the tumor cells increases the influx of neutrophils around the tumor, which in turn produce the compounds that contribute to tumor growth and progression [36] and include respiratory bursts, associated with neutrophil, and the formation of excess reactive oxygen species in the environment of the tumor that can increase the number of secondary mutations of tumor cells [16]. IL-8 can directly stimulate cell proliferation, differentiation of endothelial cells [48]. This cytokine is able to provoke tumor cell proliferation by activating downstream signals of epidermal growth factor receptor. IL-8 can regulate tumor metastasis through the cyclin D1 signaling pathway [64]. In addition, TNF as IL-1, IL-6 can stimulate the secretion of angiogenic cytokines by other cells [24].

IL-8 induces the expression of metalloproteinases associated with the extracellular matrix, as shown in respect

of melanoma, hilar cholangiocarcinoma and prostate cancer [70, 76]. Tumor-associated endothelial cells (TEC) may be an important source of IL-8 in HCC microenvironment. In the study, they postulated that IL-8 secreted by TEC may facilitate the transendothelial migration of tumor cells [81].

IL-8/IL-8R (interleukin-8/interleukin-8 receptors) can modulate tumor cells by activating a epithelial-mesenchymal transition (EMT). EMT can increase stemness, metastatic dissemination and intrinsic resistance. IL-8/IL-8R can change leukocyte infiltration into the tumor that can provoke the dysfunction of cytotoxic antitumor immune cells [15].

A study of pancreatic cancer confirmed the role of pro-inflammatory cytokines such as IL-6, IL-8 in cancer progression and metastasis [4]. Results of preliminary tests in patients with squamous cell carcinoma of the larynx or with colorectal cancer showed the relationship of IL-8 serum level with the stage of severity [35, 68].

INTERLEUKIN-17

Pro-inflammatory cytokine IL-17 may play a significant role in the pathogenesis of various diseases and carcinogenesis, but its impact on the development of disease progression is unknown. IL-17 was first described in 1993. This is an inflammatory cytokine, mainly secreted by Th-17 (secondary cells T17). Due to the secretion of large amounts of IL-17 byTh-17, most activities of Th-17 are attributable to this cytokine. In addition to Th-17, IL-17 is also secreted by a subpopulation of T lymphocytes CD8+, gamma-delta cells, mast cells and NK cells [37].

A meta-analysis found that the increase in IL-17 can be correlated with poor overall survival (OS) and disease free survival (DFS) in gastrointestinal tumors [83]. The presence of IL-17 is considered a negative factor in patients with hepatocellular carcinoma and non-small cell lung cancer, the preferred agent for esophageal squamous cell carcinoma and ovarian cancer [3, 41, 77, 83].

The study indicated that IL-17 can induce the production of IL-6, VEGF, prostaglandin E1 and E2, matrix metalloproteinase MMP in the cells of surrounding tissues [83], leading to inflammation and recruitment of neutrophils and macrophages [50], which act as pro-angiogenic factors in the tumor, promoting cancer growth and progression [26]. IL-17 produced by the transformed enterocytes affect the development of colon cancer by activating ERK, p38 MAPK and NF-kappa B signaling. On the other hand, IL-17 inhibits regulatory T cells (Treg) in the tumor microenvironment and affects the effector activity of the cytotoxic lymphocytes (CTLs) by demonstrating antitumor activity [80].

In ovarian cancer, where elevated levels correlated with a better prognosis, it was found that IL-17 in association with interferon gamma (IFN-gamma) induced more chemokine TH-1 type CXCL9/10, which was associated with the inhibition of angiogenesis and progression [41]. The researchers suggest that the effect of IL-17 may depend on the immune status of the patient, the severity of cancer, immunogenicity of the tumor and its microenvironment [26]. Th-17 cells are involved in inflammation due to the induction of IL-6, IL-8, COX-2 inhibitors, MMP-1, MMP-3, CXCL1 NOS-2, the epithelial cells, endothelial cells, macrophages and fibroblasts [22]. These compounds are responsible for angiogenesis, tumor growth and metastasis [48]. A study by Kesselring et al. [33] demonstrated that Th-17 cells are always present in a higher concentration in HNSCC tumors regardless of the stage of the disease. A release by the tumor cells and the TILs, IL-6 and IL-23, and IL-1 beta by immune cells infiltrating the tumor occurs in the HNSCC tumor microenvironment. IL-1 beta and IL-6 induce Th-17, and IL-23 results in the proliferation of Th-17.

Kesselring et al. studied the presence of Th-17 cells in patients with squamous cell carcinoma of the head and neck. Increased number of cells producing IL-17 in the peripheral blood, tumor tissue and the regional lymph nodes and proliferative HNSCC angiogenesis disorder in the presence of Th-17 cells has been demonstrated in these patients, which suggests that Th-17 cells (producing a pro-inflammatory cytokine IL-17) may have a significant impact on the development and progression of HNSCC [33].

Anti-apoptotic and pro-angiogenic activities of IL-17 can promote tumor growth, but can also support the functioning of effector cytotoxic T lymphocytes (CTL), thereby enhancing the anti-tumor response [51]. Many studies have assessed IL-17 in solid tumors for its prognostic value. Some studies indicate its association with tumor progression and poor prognosis [9, 21]. However, there are also papers which indicated that there is no relationship of this cytokine with prognosis or it was suggested that a high level of IL-17 in the blood of patients or in tumor tissue had a relation with improved OS and DFS [13].

The study by Wang et al. demonstrated that mast cells are the predominant cell type secreting IL-17 in esophageal squamous cell carcinoma [77]. The density of cells secreting IL-17 in muscle layer (the muscularis propria) was inversely proportional to tumor invasion and was a factor of a favorable prognosis. This may suggest that mast cells may play a significant role in the immune response to the tumor (tumor immunity) by release of IL-17 in squamous cell carcinoma of the esophagus. However, Sun et al., in a study of juvenile nasopharyngeal angiofibroma (JNA), found that patients who have numerous cells producing IL-17 had significantly higher rates of recurrence [71]. Large infiltration of cells producing IL-17 in JNA microenvironment is an independent negative factor for shorter disease free survival (DFS). The IL-17 function in the development and pro-

gression is not completely understood.

CONCLUSIONS

Many studies in the literature assess the levels of chosen pro-inflammatory cytokines produced by immunocompetent and tumor cells in serum or in saliva of patients with cancer present in the microenvironment of the tumor in the primary cultures of tumor cells and in experimental systems for tumor cell lines [45].

A review of the literature suggests that pro-inflammatory cytokines are a poor prognostic factor in the majority of clinically occurring cancers, while it is a good prognostic factor in a decided minority (Tab. 1). The conclusions of the study on the significance of cytokines in the development of cancer are not clear. Analysis was carried out on different biological material.

Determining cytokine levels would have a positive impact on the planning and management of treatment as well as the monitoring of the effectiveness of applied therapy. It could serve as a predictor of cancer and determine the susceptibility of a person to the disease.

Researchers suggest the possibility of testing cytokine

Table 1. The role of pro-inflammatory cytokines in neoplasms

	Good prognostic factor	Poor prognostic factor
IL-1 beta		breast cancer [47] colorectal cancer with metastases to the liver [73] OSCC [6] lung cancer [6] colon cancer [6] skin cancer [6] melanoma [6]
IL-6	breast cancer [31] melanoma at an early stage [49]	esophageal squamous cell carcinoma [54] cervical cancer [11] colorectal cancer with metastases to the liver [73] lung cancer [19, 49] OSCC [30, 63, 79] squamous cell carcinoma of the head and neck [10, 58, 79] advanced stages of melanoma [49] liver cancer [49] kidney cancer [49] prostate cancer [49] multiple myeloma [49] pancreatic cancer [4]
IL-8		squamous cell carcinoma of the head and neck [10, 57, 58, 79] squamous cell carcinoma of the larynx [68] cervical cancer [11] colorectal cancer with metastases to the liver [72] lung cancer [19] OSCC [79] melanoma [76] prostate cancer [19]
IL-17	esophageal squamous cell carcinoma [77] ovarian cancer [41, 83]	hepatocellular carcinoma [83] non-small cell lung cancer [83] squamous cell carcinoma of the head and neck [33] juvenile nasopharyngeal angiofibroma [71]
TNF	cervical cancer (high concentration of TNF) [30] ovarian cancer in the early stage [2]	squamous cell carcinoma of the head and neck [75] cervical cancer (low concentration of TNF) [30] colorectal cancer with metastases to the liver [73] advanced stages of OSCC [30] advanced stages of ovarian cancer [2]

levels in the saliva of patients with oral cancer. OSCC cells produced certain interleukins, e.g. IL-1, IL-6, IL-8, TNF. It was suggested that in patients with OSCC, the level of IL-6 in saliva has an impact on the survival and prognosis of these patients. Current studies suggest that IL-6 and IL-8 can be also suitable for use in the diagnosis and monitoring of treatment [61]. However, further studies to confirm and verify the diagnostic accuracy (sensitivity and specificity) measurements of inflammatory cytokines in the case of OSCC in the population at increased risk for this cancer are necessary. The possibility of using tests of cytokine concentrations in the saliva would be further non-invasive diagnostic tool to monitor patients during and after treatment, which would consequently improve the results of treatment and prognosis.

Although mechanisms that occur between tumor cells, their microenvironment and immunocompetent cells of the host are not thoroughly understood, previous research and clinical observations point to the importance of this interaction in tumorigenesis, progression of the disease, response to therapy, which may ultimately affect the prognosis [68].

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