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THE BIOCHEMICAL ROLE OF DIFFERENT CLASSES OF CYTOKINE IN CANCER

Abstract. *Cytokines play a prominent role in facilitating not only growth but also metastatic spread.The cytokines are a diverse group of peptide molecules that regulate cell and tissue functions. Some cytokines have also been used to treat cancer.*
Keywords: *Cytokines, cancer, role.*

Introduction. The cytokines are a very diverse group of soluble glycoproteins and low-molecular weight peptides. Cytokines are involved in regulating the growth and spread of cancers.Cancer cells are capable of producing cytokines constitutively. These cytokines may act on the cancer cells in an autocrine manner or on the supporting tissues such as fibroblasts and blood vessels to produce an environment conducive to cancer growth. 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[1]. 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. Cytokines primarily regulate the development of local defense

reactions in tissues with the participation of different types of blood cells, endothelium, connective tissue and epithelium[2].

Cytokine production is an integral part of the cellular response associated with cell recognition of the myelomonocytic series of similar structural components of different pathogens, called molecular patterns associated with pathogens.

Leukocytes express the corresponding pattern recognition receptors, also called Toll-like receptors (TLRs) and specific to certain structural patterns of microorganisms. Following the interaction of microorganisms or their components with TLR, a cascade of intracellular signal transduction is triggered, leading to an increase in the functional activity of leukocytes and the expression of cytokine genes[3]

Activation of TLR leads to the synthesis of two main groups of cytokines: proinflammatory cytokines and type I interferons, mainly IFNα / β. The key event is the synthesis of a complex of proinflammatory cytokines families from developing an inflammatory reaction and ensuring a ventilatory expansion of activation of different cell types involved in maintaining and regulating inflammation, including all types of leukocytes, dendritic cells, T and B lymphocytes, cells NK, endothelial and epithelial cells, fibroblasts and others. It provides consistent stages in the development of the inflammatory response, which is the main mechanism for the implementation of innate immunity[4].

Results :The multitude of cytokines that are produced in the tumor microenvironment have an important role in the pathogenesis of the cancer itself. Cytokines that are released in response to infection or inflammation can inhibit the development and progression of cancer. But at the same time cancer cells can respond to host cytokines, thus promoting growth, attenuating apoptosis and facilitating invasion and metastasis. Depending on the tumor microenvironment, cytokines can modulate an antitumor response, but during chronic inflammation, they can also induce cell transformation and malignancy, conditioned by the balance of pro and anti-inflammatory cytokines, their relative concentrations, cytokine receptor expression content, and the activation state of the surrounding cells. As mentioned, unresolved inflammation can lead to malignancy[5].

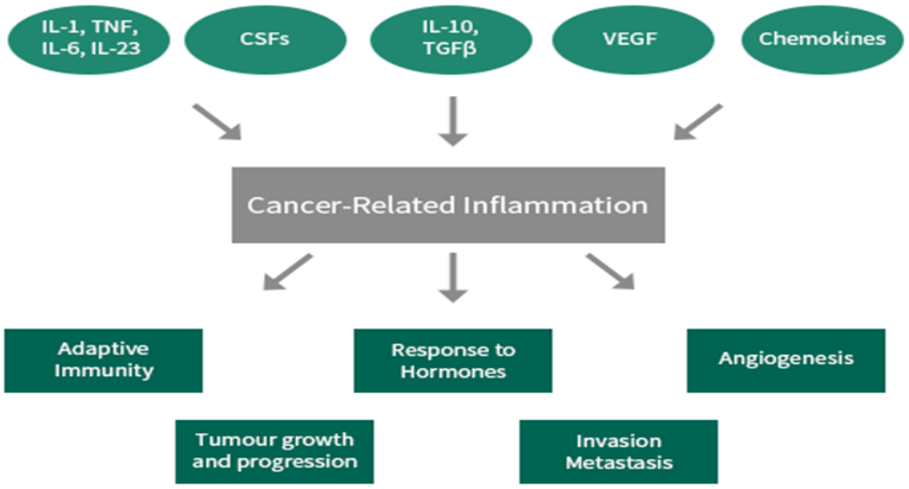

Fig. 1. **Cytokines as a key component in cancer associated with inflammation**

Tumor necrosis factor (TNF-α) is an inflammatory mediator that has been implicated in carcinogenesis due to its participation in chronic inflammatory diseases. The effect of TNF-α appears to be more significant in the early stages of carcinogenesis, including angiogenesis and invasion, than in the progression of carcinogenesis.

While TNF-α is a prototypical proinflammatory cytokine, the evidence suggests a dual role in carcinogenesis. This cytokine is recognized by two receptors: the TNF-α-1 receptor (TNF-αR-1), expressed ubiquitously and TNF-αR-2, expressed mainly in immune cells . Trimerization occurs at TNF-α binding to TNF-α-Rs, leading to the activation of at least four signaling pathways: a proapoptotic pathway induced by the caspase-8 interaction with the Fas-associated death domain (FADD); an antiapoptotic platform activated by the cellular inhibitor of apoptosis-1 protein (cIAP-1) and which interacts with TNF-αR-associated factor 2 (TRAF2); an AP-1 signaling pathway mediated by TRAF2 and JNK; and an NF-κB-induced protein-interacting receptor (RIP). According to these findings, the pro- or antitumor response of TNF-α in the tumor microenvironment depends not only on the local concentration, but also on its place of expression in the tumor. Patients with elevated TNF-α levels in tumor cells from small cell lung cancer, mainly restricted to macrophages and mast cells, had the highest survival rates, while patients with high stromal TNF-α content had lower survival rates [6].

Another proinflammatory cytokine with a typical protumorigenic effect is IL-6. Elevated serum IL-6 levels have been detected in patients with systemic cancer compared to healthy controls or in patients with benign disease. IL-6 has been proposed as a predictor of malignancy, with sensitivity and specificity of approximately 60-70% and 58-90%, respectively . However, there are limited studies available that could be used to define limit values for IL-6 as a diagnostic tool.

IL-6 plays a key role in promoting the proliferation and inhibition of apoptosis, by binding to its receptor (IL-6Rα) and the gp130 coreceptor (glycoprotein 130), thus activating the JAK / STAT signaling pathway of Janus kinases (JAK) and the signal translators and transcription activators (STAT) STAT1 and STAT3.

Interleukin 10 (IL-10) is known to be a potent anti-inflammatory cytokine. Almost all immune cells, including T cells, B cells, monocytes, macrophages, mast cells, granulocytes, dendritic cells and keratinocytes, produce IL-10. Tumor cells can also secrete IL-10, as can macrophages that infiltrate tumors.

When IL-10 binds to its receptor, tyrosine kinases Jak1 and Tyk2 phosphorylate an intracellular IL-10R domain, allowing it to interact with STAT1, STAT3, and STAT5, promoting STAT translocation in the nucleus and induction of target gene expression. Several studies have shown that IL-10 has both pro and antitumor effects. IL-10 inhibits NF-κB signaling; therefore, it can down-regulate the expression of proinflammatory cytokines and act as an antitumor cytokine. Consistent with this finding, Berg et al. demonstrated that IL-10-deficient murine models are prone to bacterial-induced carcinogenesis, while adoptive transfer of IL-10-expressing CD4 + CD25 + T cells in Rag2 - / - (lymphocyte-deficient) mice inhibits inflammation colorectal and carcinomas.

Mechanisms of immune defense evasion in cancer

Tumor formations have the property of being tolerated by the immune system by expressing factors that negatively influence the body's immune response.

There are a number of reasons for the lack of an effective immune response in tumors. Each autologous protein is degraded in the cytoplasm to peptides of 9-12 amino acids. These peptides are transported by a system called "tranporter

associated with antigen processing (TAP)" to the endoplasmic reticulum where they are bound to MCH class I molecules and presented to CD8 + T cells.

Some tumor cells are also able to stop the production of tumor antigens thus preventing the immune response. Tumors can also produce immunosuppressive substances such as IL-10, TGFβ (transforming growth factor beta), prostaglandins, and in some cases tumor cells can express MCH I-like molecules that interact with inhibitory ligands on T cells, leading to T cell apoptosis[8].

Cytokines in the diagnosis and prognosis of cancer

Methods for determining cytokines have evolved very rapidly over 20 years of intensive study and today represent a whole area of scientific knowledge. Researchers in cytokineology at the beginning of their activity face the problem of choosing a method.

A new method of evaluating the prognosis of cancer was to highlight the concentration of certain cytokines in certain types of tumors. An eloquent example is in the case of colorectal cancer and IL-8. Colorectal cancer, one of the most common malignancies, is a problematic pathology in public health systems.

Interleukin 8 values were measured using the Sandwich ELISA technique using the Human IL-8 ELISA kit produced by Krishgen BioSystem in Spain, in the presence of standard concentrations. For the interpretation of the results was used the specialized software for ELISA technique, Magellan IVD in version 5.4 produced by DIGIREAD Software which determined the average absorption for each set of standards and duplicate samples. Interleukin 8 values in tumor tissue.

The minimum value of interleukin 8 in the tumor supernatant for patients with stage II TNM of colorectal cancer was 9,200 picograms / milliliter and the maximum value was 60,100 picograms / milliliter. In the case of patients in stage III TNM, the minimum value was 5,300 picograms / milliliter and the maximum value 150,000 picograms / milliliter. For patients with stage IV TNM, minimum values of 15,900 picograms / milliliter and maximum values of 320,000 picograms / milliliter were measured. A progressive upward trend can be observed depending on the stage of TNM[7].

Conclusion: With increasing evidence linking inflammation with cancer development, more critical mediators within cancer-related inflammation can be revealed. Inflammatory cytokines are involved in multiple cancer development processes, which makes them ideal antitumor targets. Given that much research has been conducted evaluating the safety and efficacy of different therapies regarding inflammatory cytokines, no significant progress has been demonstrated in terms of clinical values.

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