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INFLAMMATION AND CANCER

The link between inflammation and cell malignant transformation was observed as far back as in the XIXth century by R.Virchow based on the facts that tumors often arise at sites of chronic inflammation and that inflammatory cells are present in tumors. But only in recent years has it become a generally accepted phenomenon. Currently begins a new stage of investigation of this problem, based on molecular biological, cellular and biochemical studies.

Epidemiological data accumulated during the last two decades have proved that chronic infection and inflammation, induced by biological, chemical and physical factors contribute to the development of at least 15% of all forms of cancer. Association of cancers linked to chronic inflammation has been described, in particular, for the digestive system (Barrett esophagus, *Helicobacter pylori* infection of stomach, chronic hepatitis B, C and, especially, mixed-hepatitis B + C, chronic pancreatitis, ulcerative colitis, Crohn disease), respiratory system (asbestosis, tuberculosis, chronic bronchitis and pneumonia, associated with the impact of wood and fur dust), urogenital system (chronic cervicitis, prostatitis, particularly those associated with sexually transmitted infections).

The material basis for the relationship of inflammation processes and carcinogenesis is in the expression, from one hand, of the receptors for cytokines, chemokines, immunoregulatory and growth factors by normal epithelial cells. From other hand, these cells constitutively express (or secrete upon activation) cytokines, eicosanoids, endotelins, defensins, molecules of intercellular interactions, and nitric oxide. Thus, epithelial cells cooperate with the "professional" inductors and effectors of inflammation and immunity, actively take part in cascade and network interactions, which determine the development of these processes.

In turn, the mediators and products of inflammation may contribute to the initiation of carcinogenesis, and act as a powerful factor in the promotion, stimulation of the the tumor progression, and subsequently intensify the proliferation, increase survival and invasion of malignant cells, facilitate the migration of tumor cells, influence on growth of primary tumor and on ability of cells to colonize the metastatic niche. Inflammation affects the tumor microenvironment (both cellular and metabolic), may alter neoangiogenesis processes, and modify the tumor response to therapeutic substances and hormones.

At the molecular level the reactive species of oxygen and nitrogen, and aldehydes, produced during chronic infection by inflammation effectors, can induce DNA damage in epithelial cells, gene mutations and posttranslational modifications of key cancer-related proteins. Other products of inflammation (cytokines, phlogogenic mediators, growth factors) control the expression of some tumor suppressor genes and oncogenes as well as increase the expression and activity of signaling molecules, involved in inflammation and cancer. Primarily, these include the nuclear transcription factors — NF-κB; signal transductor and transcription activator STAT3, and hypoxia-inducible factor 1α (HIF-1α). Significant activation of NF-κB system can promote malignant transformation, providing anti-apoptotic and pro-proliferative signals. The genes coding cytokines, acute phase proteins, enzymes of inflammation (nitric oxide synthases iNOS, cyclooxygenase COX2) could be the targets of mentioned transcription factors. Thus, transformed cells in turn produce inflammatory mediators and enzymes, generating inflammatory microenvironment, and forming a typical vicious circle of mutual reinforcement of inflammatory and neoplastic processes.

There are still large gaps in our knowledge on the activity, expression patterns and involvement of mentioned (as well as other) molecules at different stages of neoplastic disease. Despite considerable progress, many important questions await their solution, including the identification of the components of inflammation, which may be particularly important in carcinogenesis in various tissues, as well as evaluation of the relationship of these components with different types of human tumors. Future studies would also provide the new information concerning the potential benefits of targeting these molecules and their signaling complexes. Understanding the pathways involved in inflammation and tumor growth can help to develop synergistic therapies, directed on the inflammatory components of the microenvironment. Some anti-inflammatory agents have been already tested in clinical trials as tumor preventive drugs. These drugs act by inhibiting specific signaling pathways, for example, NF-κB, or inhibiting nitric-generating enzymes (iNOS) and inflammatory mediators (for instance, COX2) by removing the reactive oxygen and nitrogen and modulating xenobiotic metabolizing enzymes. The function of NF-κB is critical in the inflammation-associated carcinogenesis. Therefore, the inhibitors of NF-κB pathway are expected to be developed and tested in clinical trials in the near future. However, the use of such inhibitors may have unintended adverse effects on various cellular signaling pathways. So, it is necessary to carefully examine the fundamental aspects of the critical issues in order to take into account all the possible side effects and minimize the risk of complications.

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