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THE ROLE OF CHRONIC INFLAMMATION IN CARCINOGENESIS: MORPHOLOGICAL, CELLULAR, AND MOLECULAR MECHANISMS

Ruziyev Farxod Kurbanovich ¹
Tashkent State Medical University

Abstract

Chronic inflammation is considered one of the important factors involved in the development and progression of malignant neoplasms. Prolonged inflammatory stimuli are accompanied by structural tissue damage, disruption of cellular regulatory processes, accumulation of genetic and epigenetic alterations, and the formation of a specific tumor microenvironment. Unlike a short-term protective inflammatory response, chronic inflammation can create conditions that promote the survival of genetically damaged cells, enhance their proliferation, and contribute to subsequent malignant transformation. This article discusses the main pathomorphological changes associated with chronic inflammation, the role of cellular and molecular mechanisms of inflammation-induced carcinogenesis, and the significance of cytokines, oxidative stress, impaired apoptosis, and immune surveillance. Particular attention is paid to the relationship between chronic inflammatory diseases and the development of tumors of the stomach, liver, and intestine.

Keywords: Chronic inflammation, carcinogenesis, pathomorphology, tumor transformation, dysplasia, metaplasia, cytokines, oxidative stress, apoptosis, tumor microenvironment.

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INTRODUCTION

Malignant neoplasms represent a complex medical and biological problem, the development of which is determined by interactions among genetic, epigenetic, immunological, and environmental factors. In recent decades, particular attention has been paid to the role of chronic inflammation in tumor development. Numerous studies indicate that prolonged inflammatory reactions can not only accompany tumor growth but also directly participate in the mechanisms underlying the initiation and progression of malignant neoplasms.

Inflammation is a universal protective and adaptive response of the body aimed at eliminating damaging agents, limiting the spread of pathological processes, and restoring injured tissues. In acute inflammation, these mechanisms are usually limited in duration and end with the resolution of the inflammatory response or tissue repair. However, when the damaging factor persists, inflammation may become chronic.

Chronic inflammation is characterized by prolonged cellular infiltration, damage to parenchymal elements, activation of macrophages and lymphocytes, proliferation of connective tissue, and continuous stimulation of regenerative processes. As a result, a pathological microenvironment develops in which cell death, compensatory proliferation, and the accumulation of genetic alterations occur simultaneously.

Of particular importance is the fact that inflammatory mediators can alter the activity of genes responsible for cell-cycle regulation, apoptosis, differentiation, and immune responses. Thus, chronic inflammation may act not only as a response to tissue injury but also as an active participant in carcinogenesis.

The aim of this study is to summarize current concepts regarding the morphological and molecular mechanisms through which chronic inflammation contributes to carcinogenesis and to determine their pathomorphological and clinical significance.

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1. GENERAL CHARACTERISTICS OF CHRONIC INFLAMMATION AS A FACTOR IN CARCINOGENESIS

Chronic inflammation develops under the prolonged influence of infectious agents, physical and chemical factors, autoimmune reactions, and other damaging stimuli. Its morphological features are determined by the combination of alteration, cellular infiltration, and proliferative-reparative processes.

Unlike acute inflammation, which is characterized by vascular reactions and neutrophilic infiltration, chronic inflammation is associated with the accumulation of mononuclear cells. The main cellular components of the inflammatory infiltrate are macrophages, lymphocytes, and plasma cells.

Macrophages perform a central regulatory function. They participate in the phagocytosis of damaged cells, release pro-inflammatory cytokines, activate other immune cells, and regulate tissue repair. During prolonged activation, macrophages may contribute not only to tissue restoration but also to the maintenance of an inflammatory microenvironment favorable to tumor growth.

An important characteristic of chronic inflammation is the simultaneous occurrence of tissue destruction and repair. Repeated cycles of cell death stimulate compensatory proliferation of surviving cells. At the same time, an increased number of cell divisions raises the probability of genetic alterations becoming permanently established, particularly when DNA repair mechanisms are impaired.

In some organs, prolonged inflammation is accompanied by fibrosis, atrophy, and metaplasia. These processes alter normal tissue architecture and may create conditions that predispose tissues to precancerous changes.

2. MORPHOLOGICAL STAGES OF TUMOR TRANSFORMATION

From a pathological anatomical perspective, particular interest lies in the sequence of structural changes that may develop in tissues under prolonged inflammatory stimulation.

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2.1. Chronic inflammatory tissue injury

At the initial stage, the damaging factor persists and causes repeated destruction of cellular structures. In tissues, inflammatory infiltration, dystrophic changes, areas of necrosis, and disturbances of normal architecture may be observed.

In epithelial organs, tissue injury is accompanied by increased regenerative activity of epithelial cells. Enhanced proliferation is intended to restore tissue integrity; however, during prolonged inflammation, it may contribute to the accumulation of genetic alterations.

2.2. Atrophy and metaplasia

Atrophy is characterized by a reduction in tissue volume or cell size, accompanied by decreased functional activity of the organ. It may develop as a result of prolonged injury, impaired trophic support, and alterations in the regulation of cellular renewal.

Metaplasia is a reversible replacement of one differentiated cell type by another that is more resistant to a particular damaging stimulus. It represents an adaptive response; however, in the presence of persistent injury, metaplastic epithelium may undergo further pathological changes.

For example, intestinal metaplasia of the gastric mucosa may develop in patients with chronic gastritis associated with *Helicobacter pylori* infection.

2.3. Epithelial dysplasia

Dysplasia is characterized by impaired cellular differentiation, proliferation, and normal organization of the epithelial layer.

The main morphological features of dysplasia include:

- enlargement of nuclei and changes in their shape;
- nuclear hyperchromasia;
- an increased nuclear-to-cytoplasmic ratio;
- an increased number of mitotic figures;

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- the appearance of abnormal mitoses;
- loss of cellular polarity;
- disruption of normal epithelial maturation.

The degree of dysplasia is determined by the severity of cellular and architectural atypia. In severe dysplasia, these changes may involve almost the entire thickness of the epithelial layer.

It is important to distinguish dysplasia from carcinoma in situ. In carcinoma in situ, marked epithelial atypia extends throughout the entire epithelial thickness, but the basement membrane remains intact, meaning that invasive growth has not yet occurred.

2.4. Development of a malignant tumor

With the accumulation of additional genetic and epigenetic alterations, cells may acquire the ability to proliferate autonomously, evade apoptosis, invade surrounding tissues, and metastasize.

Morphologically, malignant transformation is accompanied by cellular and tissue atypia, impaired differentiation, invasive growth, and destruction of the normal architecture of the organ.

It should be emphasized that chronic inflammation does not necessarily progress through all the stages described above. The probability of malignant transformation depends on the combination of inflammatory duration, the nature of the damaging factor, genetic predisposition, and characteristics of the immune response.

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3. MOLECULAR MECHANISMS OF INFLAMMATION-INDUCED CARCINOGENESIS

3.1. Pro-inflammatory cytokines and intracellular signaling

One of the most important mechanisms of inflammation-induced carcinogenesis is the prolonged influence of pro-inflammatory cytokines on cells within damaged tissues.

The main mediators include interleukin-1 beta (IL-1 β), interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF- α).

IL-6 participates in the activation of the JAK/STAT3 signaling pathway. During prolonged stimulation, STAT3 promotes the expression of genes regulating cell proliferation, survival, and resistance to apoptosis.

TNF- α has complex effects on cellular processes. Depending on the cell type and intracellular signaling context, it may promote inflammation, activate apoptosis, or maintain survival signals through NF- κ B.

The transcription factor NF- κ B is one of the central regulators of the inflammatory response. Its prolonged activation promotes the production of cytokines, chemokines, adhesion molecules, and other mediators that maintain chronic inflammation.

Thus, persistent activation of NF- κ B and STAT3 establishes a sustained signaling environment that promotes cell survival and proliferation in damaged tissues.

3.2. Oxidative stress and genetic instability

During chronic inflammation, activated neutrophils and macrophages produce reactive oxygen and nitrogen species. Under normal conditions, these substances participate in the destruction of microorganisms and the regulation of cellular processes. However, their excessive production leads to oxidative and nitrosative stress.

Free radicals and other reactive compounds can damage cell membrane lipids, proteins, and nucleic acids.

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One of the well-known products of oxidative DNA damage is 8-oxoguanine. Its formation increases the likelihood of incorrect base pairing during DNA replication, which may result in mutations.

If the damage is not eliminated by DNA repair systems, genetic alterations may persist in daughter cells. The accumulation of such abnormalities contributes to genomic instability and disruption of the mechanisms controlling cell division.

3.3. Impaired apoptosis

Apoptosis is a regulated process of programmed cell death that ensures the elimination of cells with irreversible damage.

During chronic inflammation, the mechanisms regulating apoptosis may become altered. Certain inflammatory signals activate intracellular survival pathways, allowing damaged cells to avoid physiological cell death.

Proteins of the BCL-2 family are particularly important. Their anti-apoptotic members prevent the release of cytochrome c from mitochondria and inhibit the activation of the intrinsic apoptotic pathway.

The p53 protein plays a special role in cell-cycle control, cell-cycle arrest in response to DNA damage, and the activation of apoptosis when cellular alterations are irreversible.

Impaired TP53 function or disruption of other cell-cycle control mechanisms promotes the survival of genetically damaged cells and increases the probability of malignant transformation.

3.4. Epigenetic alterations

In addition to mutations, chronic inflammation may be accompanied by epigenetic changes that influence gene activity without altering the DNA sequence.

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The main mechanisms include:

- DNA methylation;
- histone modifications;
- changes in microRNA expression;
- disruption of the regulation of tumor suppressor genes.

For example, abnormal methylation of promoter regions of certain genes may reduce the expression of proteins involved in cell-cycle control and DNA repair. Thus, epigenetic abnormalities complement genetic alterations and contribute to the development of a stable pathological cellular phenotype.

4. THE ROLE OF THE TUMOR MICROENVIRONMENT

The tumor microenvironment is a combination of cellular and non-cellular components surrounding tumor cells and influencing their growth, invasion, and metastasis.

Its main components include:

- tumor-associated macrophages;
- lymphocytes;
- neutrophils;
- fibroblasts;
- endothelial cells;
- extracellular matrix;
- cytokines and growth factors.

Tumor-associated macrophages are particularly important. Depending on their functional state, they may exert either antitumor or tumor-promoting effects. When immunosuppressive and tissue-repair functions predominate, macrophages can stimulate angiogenesis, extracellular matrix remodeling, and tumor invasion. Fibroblasts also play an important role. Upon activation, they may acquire myofibroblast-like properties and develop into cancer-associated fibroblasts that produce collagen, growth factors, and various cytokines.

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Angiogenesis, the formation of new blood vessels, is another important process. Under hypoxic conditions, the HIF-1 α factor becomes activated and promotes increased expression of vascular endothelial growth factor (VEGF).

The newly formed vessels supply tumor tissue with oxygen and nutrients, although their structure often remains abnormal and is characterized by increased permeability.

Thus, chronic inflammation may contribute to the formation of a microenvironment that supports tumor growth and progression.

5. IMMUNE SURVEILLANCE AND IMMUNE EVASION BY TUMOR CELLS

The immune system plays an important role in identifying and eliminating cells that exhibit signs of malignant transformation. Cytotoxic T lymphocytes, natural killer (NK) cells, antigen-presenting cells, and other immune components participate in this process.

However, prolonged inflammation may lead to alterations in the immune response. Under certain conditions, an immunosuppressive microenvironment develops, allowing tumor cells to escape immune-mediated destruction.

One mechanism involves increased expression of immune checkpoint molecules, such as PD-L1, which interacts with the PD-1 receptor on T lymphocytes. This interaction reduces the activity of the antitumor immune response.

In addition, regulatory T lymphocytes and myeloid-derived suppressor cells may accumulate in the tumor microenvironment, suppressing the activity of cytotoxic immune cells.

Therefore, impaired immune surveillance is one of the mechanisms through which the inflammatory microenvironment promotes tumor cell survival and progression.

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6. EXAMPLES OF INFLAMMATION-INDUCED CARCINOGENESIS IN DIFFERENT ORGANS

6.1. *Helicobacter pylori*-associated chronic gastritis and gastric cancer

One of the most extensively studied examples is the association between *Helicobacter pylori* infection and the development of gastric adenocarcinoma. The bacterium colonizes the gastric mucosa and causes chronic active gastritis. The inflammatory infiltrate contains lymphocytes, plasma cells, and neutrophils. With prolonged disease progression, atrophy of the gastric glands, intestinal metaplasia, and epithelial dysplasia may develop.

The classical sequence of these changes is known as the Correa cascade:

Chronic gastritis → atrophic gastritis → intestinal metaplasia → dysplasia → gastric adenocarcinoma.

Virulence factors of *Helicobacter pylori*, including CagA, can influence intracellular signaling mechanisms in epithelial cells, disrupt cell polarity, and alter the regulation of proliferation.

Eradication of the infection reduces the risk of gastric cancer, particularly when treatment is provided before advanced precancerous changes develop.

6.2. Chronic viral hepatitis and hepatocellular carcinoma

Chronic infections caused by hepatitis B and hepatitis C viruses are important risk factors for the development of primary liver cancer.

In chronic viral hepatitis, the liver exhibits inflammatory infiltration of portal tracts, hepatocyte injury, focal necrosis, and regenerative changes.

Prolonged injury is accompanied by activation of hepatic stellate cells, which transform into myofibroblast-like cells and begin actively synthesizing extracellular matrix components.

As a result, fibrosis develops, which may progress to cirrhosis. Disruption of normal liver architecture, formation of regenerative nodules, and chronic

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regenerative stimulation create conditions that favor the development of hepatocellular carcinoma.

In HBV infection, integration of viral DNA into the hepatocyte genome is an additional factor. In HCV infection, carcinogenesis is predominantly associated with chronic inflammation, oxidative stress, and disturbances in cellular regulation.

6.3. Inflammatory bowel diseases and colorectal cancer

Ulcerative colitis and Crohn's disease are chronic inflammatory bowel diseases associated with an increased risk of colorectal neoplasia.

Prolonged intestinal mucosal inflammation leads to erosions, ulcerative lesions, inflammatory infiltration, and regenerative epithelial hyperplasia.

Repeated mucosal injury and repair are accompanied by the accumulation of genetic and epigenetic alterations. Subsequently, dysplastic lesions may develop in some patients and may progress to invasive carcinoma.

Inflammation-associated colorectal carcinogenesis is characterized by the sequence of inflammation, dysplasia, and carcinoma, which differs from the classical progression of sporadic colorectal cancer.

7. MODERN DIAGNOSTIC AND PREVENTIVE SIGNIFICANCE

Understanding the mechanisms of inflammation-induced carcinogenesis is important for improving the early diagnosis and prevention of malignant diseases. Morphological examination of biopsy or surgical specimens remains the principal method for assessing structural tissue alterations. Histological analysis makes it possible to identify chronic inflammatory infiltration, atrophy, metaplasia, dysplasia, and signs of invasive growth.

Immunohistochemical methods make it possible to assess the expression of specific proteins associated with proliferation, apoptosis, and tumor transformation. For example, the Ki-67 marker is used to evaluate cellular

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proliferative activity, while p53 is used to investigate the expression pattern of a protein involved in cell-cycle regulation.

Molecular genetic methods allow the identification of specific mutations and other abnormalities that may be relevant to diagnosis, prognosis, and treatment selection.

Important preventive measures include:

1. Timely detection and treatment of chronic infections.
2. Eradication of *Helicobacter pylori* when clinically indicated.
3. Monitoring of chronic inflammatory bowel diseases.
4. Prevention and treatment of chronic viral hepatitis.
5. Smoking cessation and limitation of exposure to carcinogenic factors.
6. Endoscopic and morphological surveillance in patients with precancerous lesions, according to clinical guidelines.

It should be noted that suppression of inflammation alone does not guarantee the prevention of tumor development. Effective prevention requires elimination or control of the underlying cause of inflammation, assessment of individual risk, and timely detection of morphological abnormalities.

8. FUTURE DIRECTIONS IN RESEARCH

Current research into inflammation-induced carcinogenesis focuses on a more detailed investigation of interactions among immune cells, tumor cells, and the stromal components of tissues.

Particular attention is being paid to the roles of specific macrophage subpopulations, neutrophils, regulatory T lymphocytes, and cancer-associated fibroblasts.

An important emerging direction is the investigation of the spatial organization of the tumor microenvironment using advanced morphological and molecular techniques. These studies help determine which cellular populations predominate in particular tumor regions and how they influence invasion and metastasis.

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Another area of interest is the study of neutrophil extracellular traps (NETs), which consist of extracellular DNA and neutrophil granule proteins. In certain tumor processes, they may contribute to inflammatory activation, thrombosis, and metastatic dissemination of tumor cells.

Investigation of these mechanisms may contribute to the development of new diagnostic biomarkers and therapeutic approaches targeting specific components of the tumor microenvironment.

CONCLUSION

Chronic inflammation is an important contributor to the multistep process of carcinogenesis. Its effects are mediated through prolonged tissue injury, disruption of regenerative processes, activation of intracellular signaling pathways, production of reactive oxygen species, and accumulation of genetic and epigenetic alterations.

From a pathomorphological perspective, atrophic, metaplastic, and dysplastic changes are particularly important because they reflect disturbances in normal tissue architecture and cellular differentiation. At the molecular level, major roles are played by pro-inflammatory cytokines, the NF- κ B and JAK/STAT3 signaling pathways, impaired p53 function, altered apoptosis regulation, and the formation of the tumor microenvironment.

Examples of chronic gastritis, viral hepatitis, and inflammatory bowel diseases demonstrate that prolonged inflammatory stimuli may increase the risk of malignant neoplasms in different organs.

Thus, the investigation of the relationship between chronic inflammation and carcinogenesis is of fundamental importance for pathological anatomy and modern oncology. A deeper understanding of the morphological and molecular mechanisms underlying this process provides a basis for improving early diagnosis, prevention, and the development of new approaches to the treatment of inflammation-associated tumors.

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