**Teaching unit 12**

**INFLAMMATION AND ONCOGENESIS**

**Introduction**

**Inflammation** is the host's physiological response to tissue damage. One of the causes of tissue damage is infection caused by bacteria, viruses, fungi and parasites. Classic signs and symptoms of acute inflammation are redness (rubor), swelling (tumor), heat (calor), pain (dolor) and loss of function (functio laesa). All of the above signs and symptoms reflect vascular, cellular, and molecular changes that result from the host's response to tissue damage. In addition to infection, the inflammatory process can be caused by other factors: trauma, heat (burns and frostbite), exotoxins, endotoxins, chemical agents, hypersensitivity reactions, etc. Therefore, inflammation is the body's response to endogenous and exogenous noxes, and is characterized by:

* changes in local tissue and blood vessels
* creating mediators of inflammation
* activating endothelial cells
* adhesive interactions of vascular endothelium and leukocytes
* mobilization and activation of inflammatory cells
* activating the complement system, coagulation and fibrinolytic system.

The activation of different mechanisms of inflammation depends on the cause of the tissue damage, the type and localization of the affected tissue, as well as on the genotype of the host. In the early stage of inflammation, neutrophils are the first cells to migrate to the site of inflammation under the control of molecules released by resident macrophages and mast cells. As inflammation progresses, under the influence of a large amount of growth factors, cytokines and chemokines, various types of leukocytes, lymphocytes and other cells are activated and attracted to the site of inflammation.

The main goal of the inflammatory reaction is to restore damaged tissue and establish homeostasis. Every pro-inflammatory response is followed by an anti-inflammatory response. The optimal balance between pro-inflammatory and anti-inflammatory mechanisms determines the elimination of the initial cause of tissue damage, as well as tissue repair and the establishment of tissue homeostasis. One of the important events that enables the transition from tissue remodeling (induced by inflammation) to tissue repair is the increased production of anti-inflammatory lipoxin and, at the same time, decreased production of pro-inflammatory prostaglandin. Lipoxin stimulates the recruitment of monocytes that differentiate into macrophages that then remove local debris and coordinate repair. The resolution of inflammation also requires a rapid and programmed clearance of cells at the site of inflammation by neighboring macrophages by inducing their apoptosis and subsequent phagocytosis. Phagocytosis of apoptotic cells also promotes an anti-inflammatory response with increased production of TGF-β. However, if this resolution of inflammation is dysregulated, the cellular response is altered and results in chronic inflammation. In some situations, imbalance is also possible, i.e. predominance of pro-inflammatory mediators, which results in chronic inflammation that persists for a longer period of time (months and years) and induces significant tissue damage. Chronic inflammation is dominated by macrophages with different morphology, as well as lymphocytes. Macrophages and other inflammatory cells generate large amounts of growth factors and cytokines, as well as reactive oxygen and nitrogen radicals that can cause DNA damage.

Inflammatory processes are closely related to malignancies. In early carcinogenesis, it is believed that cells of the immune system are optimally activated during acute inflammation, which results in the elimination of tumor cells. However, chronic inflammation, induced by infection or altered response to microflora microorganisms, as well as pathological processes unrelated to infection, may favor early genetic, epigenetic, tissue or cellular changes involved in the initiation of carcinogenesis. In addition to the above, in most cases, the tumor microenvironment by chronic activation, primarily cells of innate immunity, polarizes chronic inflammation, which in various ways encourages tumor progression (Figure 1). It is believed that the cells of innate immunity, which infiltrate the incipient tumor, induce oxidative stress by releasing free oxygen radicals and nitrogen monoxide, which results in DNA damage of the cells. Also, by producing various cytokines, growth factors, chemokines and matrix metalloproteinases, these cells stimulate angiogenesis and tissue remodeling, which significantly increases tumor growth and progression. It is obvious that with the development of chronic inflammation by various mechanisms, the cells of the immune system in the tumor microenvironment gradually lose their effector abilities and enable or even encourage tumor progression instead of eliminating it.



**Picture 1.**Inflammation and cancer

**Immune surveillance**

More than 1 century ago, it was shown that iatrogenic induction of bacterial infection establishes acute inflammation, which is responsible for the remission of people suffering from incurable cancers. Proinflation therapy (eg live BCG vaccine) used for local treatment of bladder cancer is based on this principle.

Paul Ehrlich hypothesized that the immune system could prevent new tumors from forming and slow the growth of existing tumors. In 1950, this hypothesis was confirmed by Burnet and Thomas. They established the concept of immune surveillance and hypothesized that one of the physiological roles of the immune system is to recognize clones of malignantly transformed cells and remove them before a malignant tumor is established, as well as to kill malignant cells after their development. The theory of immune surveillance is still controversial to this day. Contrary to the evidence that the immune system is important and effective in controlling the formation and development of tumors, there is an irrefutable fact that malignant tumors also develop in immunocompetent individuals.

There is also the concept of tumor-immune editing, which is divided into three phases: the elimination phase, the equilibrium phase, and the avoidance phase. When malignantly transformed cells escape "intrinsic" non-immune tumor-suppressor mechanisms, these malignant cells can be recognized by cells of the innate and acquired immunity which then eliminate them (elimination phase). However, if the immune system fails to completely eliminate the malignantly transformed cells, a transient phase of equilibrium between the immune system and the tumor is established. It is likely that this equilibrium phase is partly responsible for the long latency phase of tumors registered in clinical and experimental studies. During this phase, the tumor is assumed to be dormant or continue to develop by accumulating gene mutations (DNA mutations or changes in gene expression). If this process continues, the immune system is responsible for selective pressure on tumor cells by removing only sensitive variants of tumor cells and giving selective advantage to those variants characterized by genetic instability, acquisition of new gene mutations and modulation of their immunogenicity. If tumor cells are resistant to effector immune mechanisms (by inducing immunosuppressive mechanisms or becoming non-immunogenic), numerous interactions with the tumor microenvironment and stroma are established that favor tumor progression and dissemination (avoidance phase). Thus, during the avoidance phase, the immune system is no longer able to control tumor growth resulting in progressive tumor growth.

**INFLAMMATION AND CANCEROGENESIS**

Numerous data from the literature indicate the association of inflammation with tumor initiation and progression. Inflammatory processes affecting different organs (eg liver, pancreas, colon, stomach and prostate) are associated with an increased risk of developing cancer. Thus, it has been observed that many types of malignant tumors develop at the site of persistent (chronic) inflammation, and at least about 15% of human tumors are of infectious origin. Table 1 lists examples of tumors associated with chronic inflammation of non-infectious origin, while Table 2 shows malignant tumors associated with chronic inflammation caused by infection. The earliest evidence suggesting a close relationship between tumors and inflammation is the finding of a reduced incidence of tumors (eg, colon cancer) in affected individuals after administration of nonsteroidal anti-inflammatory drugs.

**Table 1.**

|  |  |  |
| --- | --- | --- |
| **Chronic inflammatory conditions associated with tumor development** | | |
| **Pathological conditions** | **Tumors** | **Etiological agents** |
|  |  |  |
| Sunburn, burn scars | Basal cell carcinoma, squamous cell carcinoma, melanoma | Ultraviolet rays |
| Epidermolysis bullosa | Squamous cell carcinoma | Genetically and mechanically |
| Gingivitis | Squamous cell carcinoma of the oral cavity |  |
| Sialodenitis | Salivary gland carcinoma |  |
| Sjogren's syndrome, Hashimoto's thyroiditis | Lymphomas of lymphatic tissue associated with mucous membranes |  |
| Asbestosis, silicosis | Mesothelioma, lung cancer | Asbestos fibers, silicate dust |
| Bronchitis (caused by nitrosamine and peroxides) | Lung cancer | Asbestos, smoking |
| Reflux esophagitis, Barrett's esophagus | Carcinoma of the esophagus | Stomach acid, alcoholism, smoking |
| Liver cirrhosis | Hepatocellular carcinoma | Alcoholism |
| Chronic pancreatitis | Pancreatic cancer | Genetic (mutations of the trypsinogen gene), alcoholism, smoking |
| Inflammatory bowel diseases (Crohn's disease and chronic ulcerative colitis) | Colorectal cancer, Small intestine cancer |  |
| Bladder inflammation | Bladder cancer | Catheters |

Aangular inflammation prevents tumor development, while chronic "smoldering" inflammation is often associated with tumor initiation and progression. In general, factors with antiapoptotic, proangiogenic, prometastatic, and immunosuppressive effects favor tumor development and progression. Often, factors and genes responsible for the development of the Th2 immune response play a protumor role in tumor development. Conversely, factors with proapoptotic, antiangiogenic, and immunostimulatory effects, as well as factors favoring the Th1 immune response, suppress tumor progression. However, this division is not absolute and the same factors can have both pro- and anti-tumor effects depending on the stage of the disease. Thus, it is believed that TNF, which is mainly produced by activated macrophages, plays an important effector role in innate and acquired immune mechanisms and has the ability to cause apoptosis of tumor and endothelial cells. Administration of high doses of TNF can induce the destruction of tumor blood vessels. However, this cytokine can have an antiapoptotic effect by activating the transcription factor NF-κB, and it is also important in tumor initiation. TNF, along with other cytokines, is expressed in many human tumors (eg, ovarian, breast, and prostate cancer). One of the possible mechanisms of these protumor effects of TNF is the induction of the synthesis of matrix metalloproteinase-9 (MMP-9) and the chemokine MCP-1 (monocyte chemotactic protein-1), which regulates the infiltration of monocytes into tumor tissue. TNF promotes angiogenesis and induces DNA damage, inhibits DNA repair, and functions as a growth factor for tumor cells.

**Table 2.**

|  |  |  |
| --- | --- | --- |
| **Tumors associated with inflammation resulting from infection** | | |
| **Pathological conditions** | **Tumors** | **Microorganisms** |
|  |  |  |
| Hepatitis | Hepatocellular carcinoma | *Hepatitis B Virus, Hepatitis C Virus* |
| Mononucleosis | V-cell non-Hodgkin's lymphoma, Burkitt's lymphoma | *Epstein-Barr Virus* |
| AIDS | non-Hodgkin's lymphoma, squamous cell carcinoma, Kaposi's sarcoma | *HIV, HHV8* |
| Pelvic inflammatory disease | Ovarian cancer, cervical cancer | *N. gonorrhoeae, Chlamydia spp, Papillomavirus* |
| Osteomyelitiss | Skin cancer in the region of the draining sinus | Bacteria |
| Chronic prostatitis | Prostate cancer | Gram-negative bacteria |
| Chronic cystitis | Bladder and liver cancer | *Schystosoma spp* |

It was still in 1863. Virchow first suggested the connection between inflammation and tumors based on the finding of inflammatory cells in the tumor stroma. The results of epidemiological studies indicate that colorectal cancer develops more often in patients with long-term chronic inflammatory bowel disease. It has been observed that the incidence of colon cancer, and especially small intestine cancer, is increased in patients with Crohn's disease, while the incidence of colon and rectal cancer is increased in patients with ulcerative colitis. Clear evidence of the link between chronic inflammation and tumors is the finding that the use of non-steroidal anti-inflammatory drugs reduces the incidence of cancer. Nonsteroidal anti-inflammatory drugs have been used in experimental animals and in humans, and these drugs have been observed to prevent the development of colon cancer. The enzyme COX-2 (cyclooxygenase-2) is overexpressed in intestinal epithelial cells and colorectal cancer. By increasing the synthesis of prostaglandins, this enzyme controls inflammation (acting as a vasodilator) and angiogenesis and also increases the homing of hematopoietic cells into the tumor tissue. In addition to the above, COX-2 affects the adhesion and apoptosis of epithelial cells and regulates the functions of the immune system. Long-term treatment with non-specific cyclooxygenase inhibitors, such as aspirin, has been shown to reduce the risk of colon cancer by about 50%. Conversely, the use of specific COX-2 inhibitors has been registered to have a smaller effect. A specific COX-2 inhibitor does not prevent cancer but increases survival after surgical resection in those patients diagnosed with colon cancer with increased expression of COX-2 or with mutated forms of the gene. This specific inhibitor reduces the number of already established polyps in patients with familial adenomatous polyposis.

Some microorganisms, especially viruses (eg Epstein-Barr virus and Human papillomavirus), can directly induce the malignant transformation of cells. Additionally, these infections induce chronic inflammation in the microenvironment that favors malignant transformation or promotes tumor progression. For example, infection caused by the Hepatitis C Virus in the liver predisposes to hepatocellular carcinoma, while infection caused by Schystosoma mansoni induces inflammation and mechanical damage in the bladder resulting in an increased incidence of bladder cancer. Apart from carcinogenesis, it is believed that inflammatory processes can promote tumor invasion and metastasis. Thus, a polymorphism of the IL-1 gene that causes increased production of this cytokine is associated with an increased risk for the progression of hepatocellular carcinoma in people with chronic HCV infection. Also, the infection caused by Helicobacter pylori is believed to be responsible for chronic inflammation of the stomach, which results in atrophy, metaplasia, dysplasia and eventually gastric cancer. The risk of gastric cancer in patients with H. pylori infection is significantly increased by polymorphism of those genes encoding pro-inflammatory cytokines, such as IL-1β, IL-8, TNF and IL-10. In humans and mice, co-infection with H. pylori and an extracellular parasite induces a shift in the direction of a Th2 immune response that reduces gastric atrophy and the risk of cancer.

**MECHANISMS OF MALIGNANT TRANSFORMATION OF CELLS AND TUMOR DEVELOPMENT IN THE INFLAMMATORY MICROENVIRONMENT**

Malignant transformation of cells is a complex process that implies a disturbance in the activation of oncogenes and anti-oncogenes. Thus, the development of a malignant tumor is the result of the accumulation of genetic mutations, which results in the "unplanned" proliferation of cells that also become immortalized and capable of invading and metastasizing into other tissues. An inflammatory microenvironment can create conditions characterized by gene instability that favors or induces initial gene mutations. In most tumors, the mutation of a single gene is not sufficient for the development of a tumor, but several successive inherited mutations need to occur to establish a cancer.

Carcinoma can be induced in tissue, at the site of chronic inflammation. In cancer-associated inflammation, two molecular pathways linking inflammation and cancer have been identified. Infection and various irritants induce the extrinsic pathway by stimulating the migration of inflammatory hematopoietic cells, resulting in chronic inflammation that significantly increases the risk of various types of tumors. Genetic events (eg, oncogene mutations) induce malignant cell transformation and often trigger an inflammatory cascade that stimulates the synthesis of pro-inflammatory cytokines, chemokines, as well as metalloproteinases (which remodel the stroma), which represents the internal pathway. Both the external (induced by inflammatory processes that predispose to tumor development) and the internal pathway (induced by genetic events that cause carcinogenesis) contribute to the development of an inflammatory milieu in the tumor microenvironment that greatly promotes tumor growth and progression.

Chronic inflammation contributes to the increased frequency of DNA mutations and genetic instability in several ways. Tissue damage and repair increase the degree of proliferation in the affected tissue, which consequently increases the likelihood of mutations or chromosomal translocations during mitosis. Additionally, during inflammation, free oxygen and nitrogen radicals can reduce the expression and enzymatic activity of products of the DNA repair system, such as MLH-1, MSH-2, and MSH-6, resulting in increased genetic instability and an increased rate of errors during replication. Genes that control the cell cycle or survival, which contain unstable short repetitive DNA sequences known as microsatellites in their coding region, are particularly affected. Direct interaction of mucosal epithelial cells with H. pylori and enteropathogenic E. coli rapidly reduces the expression of MLH-1 and MSH-2. In response to inflammation or interaction with bacteria, the expression of methyltransferases is increased with the switching off of many genes, including genes of the DNA repair system and tumor-suppressor genes (anti-oncogenes), all of which contribute to carcinogenesis. Aberrant expression of activation-induced cytidine deaminase, the initiator of somatic hypermutations in V lymphocytes and mucosal cells, is induced by inflammation and is partly mediated by TNF, IL-4 and IL-13, which is probably related to mutations in human colorectal cancer. These mechanisms suggest that genomic instability, epigenetic changes, and modifications of functional genes are involved in the initial events of carcinogenesis, all of which are induced by inflammation.

**Reactive oxygen and nitrogen radicals** significantly contribute to the damage found in inflamed tissue. The pro-oxidant state can induce tumor development and growth. Reactive oxygen and nitrogen radicals, produced by inflammatory cells, induce a series of cellular damages including DNA single base breaks and mutations, epigenetic modifications, and post-translational modification of proteins that control apoptosis, survival, DNA repair, and the cell cycle. One of the nitrogen radicals is nitrogen monoxide (NO, English Nitric Oxide), which plays a contradictory role in the tumor. Thus, the anti-inflammatory role of NO is reflected in the fact that it can induce DNA damage, increase angiogenesis (increasing the production of VEGF), and stimulate the proliferation and invasion of malignant cells. However, when present in high concentrations, NO can inhibit proliferation and induce apoptosis of tumor cells. These different effects of NO can be partially explained by the status of the p53 gene (anti-oncogene) in the tumor. In the absence of p53 or in the presence of its mutated form in tumor cells, NO fails to induce apoptosis but stimulates cell proliferation and contributes to genotoxic stress. By activating the MAPK signaling pathway, NO increases the migration, invasion and metastasis of breast and colon cancer tumor cells.

**COXs** are enzymes responsible for the synthesis of prostaglandins, especially prostaglandin E2 (PGE2, English prostaglandin E2). Although increased COX-2 expression was first identified in colorectal cancer, this enzyme is overexpressed in almost all tumors at a very early stage of their development. COX-2 expression in human lung fibroblasts can be induced by cigarette smoking, suggesting that smoking increases the risk of tumor development by inducing lung inflammation. PGE2 affects the degree of DNA mutations and promotes tumor progression by modulating angiogenesis, apoptosis and metastasis formation.

Several transcription factors activated in the inflamed microenvironment significantly influence tumor initiation and progression, with NF-κB and STAT3 taking center stage.

In the cytoplasm, NF-κB is in an inactive form and is bound to IκB with which it forms a complex. In response to extracellular stimuli, IκB degradation occurs, NF-κB is released and translocated to the nucleus where it binds near the promoters of target genes. NF-κB activation is regulated by other transcription factors such as Notch-1, STAT-3, β-catenin and p53. NF-kB, since it regulates the synthesis of numerous gene products, plays an important role in carcinogenesis in several ways. This transcription factor is thought to play a key role in the establishment of chronic inflammation. NF-κB acts as a critical mediator of inflammatory processes by regulating the expression of many molecules, such as cytokines and adhesion molecules. It promotes the production of reactive oxygen radicals that can cause genetic mutations. NF-κB is activated in response to cigarette smoking, stress, food additives, obesity, alcohol, infectious agents, radiation, and other stimuli. NF-kB is constitutively active in most tumors. This transcription factor is associated with the survival of tumor stem cells and early precursor cells that acquire the ability to self-renew. NF-kB regulates the expression of most antiapoptotic gene products (bcl-2, bcl-xl, c-FLIP...) which results in the survival of tumor cells. In addition, NF-κB contributes to tumor development by activating the expression of genes for growth factors, the oncogene c-Myc, and the cell cycle regulator, cyclin D1, thereby stimulating cell proliferation. NF-κB is also important in the later stages of tumor development. This transcription factor controls the expression of genes whose products (MMP, adhesion molecules, VEGF, TWIST and CXCR4) participate in tumor invasion, angiogenesis and metastasis. NF-κB is activated by inflammatory stimuli and is constitutively activated in the tumor suggesting that it is a critical promoter of tumor development at the site of inflammation. Constitutive activation of NF-κB is registered in leukemia, lymphoma, pancreatic, breast, liver, ovarian and colon cancer. NF-κB activation is thought to be associated with metastasis of prostate cancer to the lymph nodes. In addition, the activation of this transcription factor is related to the resistance of tumor cells to chemotherapy and radiation.

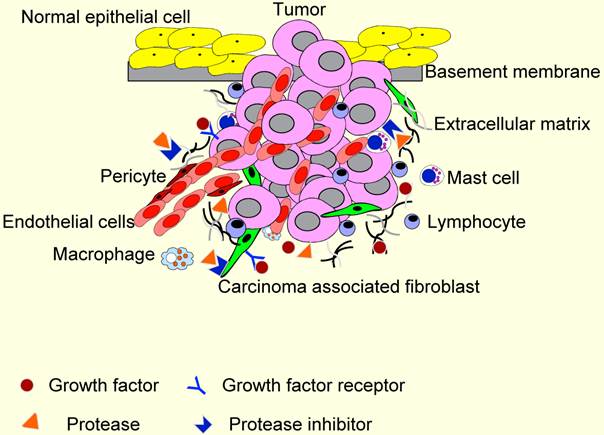
In most malignancies, STAT3 is overexpressed, and is present in the nucleus in a phosphorylated form, in tumor cells, stromal cells, and infiltrating hematopoietic cells. When overexpressed in tumor cells, STAT3 contributes to their survival, proliferation and dissemination by controlling the expression of several genes involved in the cell cycle, as well as the oncogene c-Myc. Many factors released in tumor cells but also in stromal cells are VEGF, IL-6 and IL-10 which contribute to the activation of STAT3. STAT3 in tumor cells also contributes to the recruitment of hematopoietic cells into tumor tissue by controlling the production of chemotactic factors and their receptors in infiltrating cells. Activation of STAT3 in tumor-associated macrophages has an anti-inflammatory effect, while in dendritic cells it prevents their complete maturation. In addition, it inhibits the synthesis of pro-inflammatory cytokines (eg IL-12) and at the same time favors the alternative activation of macrophages. These effects of STAT3 are favorable for tumor growth.

**HIF-1** (Hypoxia-Inducible Factor-1) is a heterodimeric transcription factor that regulates oxygen homeostasis. HIF-1α is stabilized under hypoxic conditions while HIF-1β is constitutively expressed. Hypoxia is an important characteristic of inflammatory processes. HIF-1 is involved in inflammatory processes by inducing leukocyte adhesion and maintaining the physiological functions of myeloid cells recruited to the site of inflammation. HIF-1 can also promote chronic inflammation by preventing apoptosis of neutrophils and T lymphocytes under hypoxic conditions. Its persistent presence may be the result of activation of NF-κB and/or COX-2 in the tumor microenvironment under the influence of proinflammatory cytokines.

Epithelial cells can produce various inflammatory cytokines and chemokines, metalloproteinases, as well as angiogenetic factors that participate in the migration and activation of infiltrating hematopoietic cells. Oncogene products such as RAS, RET, BRAF and MYC can induce an intrinsic inflammatory pathway in malignantly transformed epithelial cells, suggesting that these "feedback" mechanisms contribute both to the malignant transformation of epithelial cells and to the formation of an inflammatory microenvironment that promotes progression tumors.

**INFLAMMATORY CELLS AND STROM CELLS IN TUMOR INITIATION AND IN THE TUMOR MICROENVIRONMENT**

Initial events in tumor development also affect epithelial cells, fibroblasts, endothelial and inflammatory cells, as well as other stromal cells. In lesions of both acute and chronic inflammation, infiltrates of hematopoietic cells are registered, with phagocytes (neutrophils) dominating at the beginning, which are later replaced by macrophages and other cells, including lymphocytes, when the inflammation becomes chronic. In an established tumor, the type and level of cellular infiltrate is variable but always present. Not only hematopoietic cells participate in the regulation of inflammation in the tumor microenvironment, but every type of cell (tumor cells, fibroblasts, endothelial and epithelial cells, macrophages, etc.) produces and responds to products that regulate inflammation (Figure 3). It is believed that inflammation in the tumor microenvironment facilitates the disruption of the basement membrane, which is necessary for the invasion and migration of malignant cells.

**[](http://www.google.rs/url?sa=i&rct=j&q=&esrc=s&frm=1&source=images&cd=&cad=rja&docid=sYFBp1rLKvqBFM&tbnid=2ZYjgwAggf56yM:&ved=0CAUQjRw&url=http://www.jcancer.org/v04p0066.htm&ei=00UZUcD8EJHgtQbR1YC4Cw&psig=AFQjCNHFV3qIGMMByG6WWOhTLtSBNdHDhA&ust=1360696375339754)**

**Figure 2.**Tumor microenvironment

*Cancer-associated fibroblasts*

Cancer-associated fibroblasts (CAFs) acquire stable characteristics that enable them to better support tumor progression compared to fibroblasts in normal tissue. By expressing alpha-smooth muscle actin, CAFs acquire the characteristics of myofibroblasts. These cells are not immortalized and their phenotype is likely due mainly to epigenetic modifications induced by tumor-promoting conditions related to infection, inflammation, or radiation. CAFs can differentiate from already existing normal fibroblasts, from stem cells present in the tissue, and possibly from circulating cells originating from the bone marrow. CAFs achieve their protumor effect by secreting soluble factors that induce angiogenesis, attract inflammatory cells and directly support the growth and dissemination of malignant cells. One of the most important protumor factors secreted by CAFs are chemokines SDF-1/CXCL12, TGF-β and matrix metalloproteinases.

*Mast cells*

In the cervical and cancerous lesions, mast cells are present in large numbers and are associated with increased non-angiogenesis. Factors produced by mast cells directly act on endothelial cells and their precursors, as well as on other cells in the tumor stroma. Many of these factors secreted by mast cells during the inflammatory response are preformed in secretory granules, while others are synthesized de novo. Heparin and histamine affect angiogenesis, and MMP-2 and MMP-9, as well as serine proteases released by mast cells, have a particularly important proangiogenic effect. The ability of these proteases to degrade the extracellular matrix contributes to both angiogenesis and the invasion and dissemination of malignant cells. In addition to the above, mast cells also release several cytokines such as FGF-2, VEGF, TGF-β, TNF and IL-8 that not only affect angiogenesis but also recruit and activate cells originating from the bone marrow into the tumor tissue.

*Dendritic cells*

Dendritic cells (DCs) are cells originating from the bone marrow and are present in the lymphatic organs as well as in any other peripheral tissue. These cells are classified into two main groups: conventional DCs and plasmacytoid DCs.

*Conventional dendritic cells*

Conventional DCs are characterized by secreting proinflammatory cytokines, such as IL-12, TNF, IL-6, IL-1 and type I IFNs. By producing IL-12 and type I IFNs, as well as other cytokines, DCs activate effector cells of innate immunity such as NK and NKT cells that then produce proinflammatory IFN-γ.

In chronically infected tissue or in a tumor, DCs are present, but the phenotype of these cells is altered due to interactions with other cells in the inflamed tissue or with tumor cells. In general, DCs are reactive to stimuli that normally activate and induce the maturation of DCs under physiological conditions. One of the factors produced by tumor cells or stromal cells, that contribute to this state of reactivity of DCs in the tumor microenvironment, are IL-10, TGF-β, VEGF, and prostaglandins. VEGF is thought to interfere with the maturation of DCs. In human breast cancer, it has been observed that immature DCs are in close contact with malignant cells, while mature DCs are present at the periphery of the tumor often in groups of infiltrating cells (T lymphocytes and cells of bone marrow origin). Melanoma-derived interleukin-10 stimulates the development of tolerogenic dendritic cells and thus induces tumor-specific anergy. Arachidonic acid metabolites, such as prostaglandins and thromboxanes, have a direct inhibitory effect on dendritic cells.

*Plasmacytoid dendritic cells*

Plasmacytoid DCs are functionally different from conventional DCs. These cells are the main source of type I IFN during viral infections in vivo and play a central role in the regulation of cell resistance to the virus. It has been shown that plasmacytoid DCs are capable of inducing immune tolerance in vivo and in vitro by expressing the immunosuppressive enzyme IDO (eng. indolamine 2,3-dioxygenase) and by inducible costimulatory ligand (ICOS-L ) activate T lymphocytes that produce IL-10. Plasmacytoid DCs isolated from human tumors have been reported to have immunosuppressive properties.

*Granulocytes*

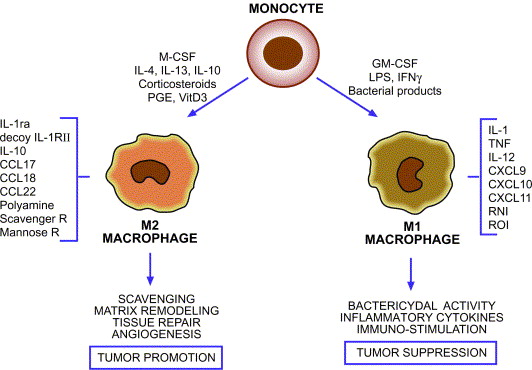
Neutrophils are the first cells to infiltrate a site of infection or tissue damage. Also, these cells are present in the tumor stroma, where they exert a strong angiogenic effect by expressing MMP-9, as well as various cytokines. Additionally, neutrophils may represent a link between inflammation and carcinogenesis by inducing DNA damage through the release of oxygen free radicals and myeloperoxidase.

Eosinophilia in peripheral blood and an increased number of eosinophils in tumor tissue have been registered in various types of human malignancies. In some types of tumors, including tumors of the digestive system, tumor-associated eosinophilia has a favorable prognostic significance, while in other tumors such as squamous cell carcinoma of the oral cavity it has an unfavorable prognostic significance. Tumor-associated eosinophils can have a cytotoxic effect on tumor cells and can also recruit and activate other hematopoietic cells. Conversely, these cells can induce immunosuppression in the tumor microenvironment and thus contribute to tumor progression. These cells are a source of free oxygen radicals, as well as leukotrienes and prostaglandins. It is clear that eosinophils are important participants in the regulation of the inflammatory response, especially in the recruitment and activation of other inflammatory cells, as well as in tissue repair and remodeling.

*Tumor-associated macrophages*

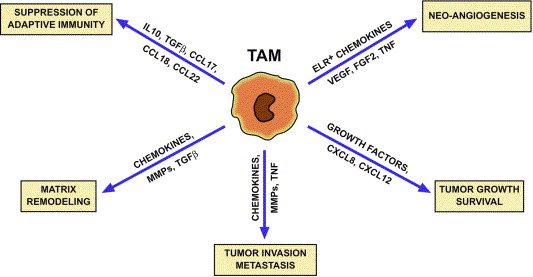
Tumor-Associated Macrophages (TAMs) represent one of the main cellular components in the tumor tissue. These cells are attracted to tumor tissue by chemokines produced by malignant cells or stromal cells. MCP-1 is the main chemokine responsible for this recruitment of TAMs. TAMs affect tumor growth in two ways: regressive and progressive. Activated macrophages can be cytotoxic to tumor cells and massive tumor infiltration by activated macrophages with increased synthesis of MCP-1 results in tumor destruction.

The ability of TAMs to express different functional programs, either cytotoxic and antitumor or protumor and proangiogenic, is a consequence of the plasticity of macrophage activation in response to various stimuli from the microenvironment. There are classically activated (M1) macrophages and alternatively activated (M2) macrophages (Figure 3). M1 macrophages produce a high level of proinflammatory cytokines, especially IL-12, which polarizes the Th1 immune response. These cells also synthesize reactive oxygen and nitrogen radicals. Although M1 macrophages have a cytotoxic effect on an established tumor, the products of these cells can participate in tumor progression by inducing chronic inflammation. In most tumors, TAMs have an M2 macrophage phenotype. In general, M2 macrophages promote angiogenesis, remodeling and tumor progression. These cells produce much lower levels of IL-12 and proinflammatory cytokines compared to M1 macrophages. IL-4, IL-13 and IL-10, engagement of TLRs in the presence of immune complexes are all together stimuli that induce alternative activation of macrophages. Although Th1 lymphocytes participate in the maintenance of the M1 phenotype by producing IFN-γ, during chronic infection, extensively activated Th1 lymphocytes begin to produce both IFN-γ and IL-10, which results in a weakening of the immune response. In chronic infection and in the tumor, IL-10, originating from regulatory T lymphocytes, and in some cases from tumor cells, favors the differentiation of M2 macrophages.

[](http://www.sciencedirect.com/science/article/pii/S0959804906000402#gr2)

**Figure 3.**Classically activated M1 and alternatively activated M2 macrophages

TAM2 have an antitumor effect. These cells express a low level of pro-inflammatory cytokines, synthesize little NO and free oxygen radicals, and by releasing IL-10 and TGF-β achieve an immunosuppressive function. TAM2 favor tumor growth and metastasis in several ways: 1) by producing pro-angiogenic cytokines, VEGF, TNF and FGF2 induce angiogenesis; 2) by producing growth factors and chemokines, they induce the growth and survival of malignant cells; 3) through the expression of MMPs, TGF-β, TNF and chemokines, they induce matrix remodeling, which results in tumor invasion and the formation of metastases (Figure 4).

**[](http://www.sciencedirect.com/science/article/pii/S0959804906000402#gr3)**

**Figure 4.**Antitumor functions of TAMs