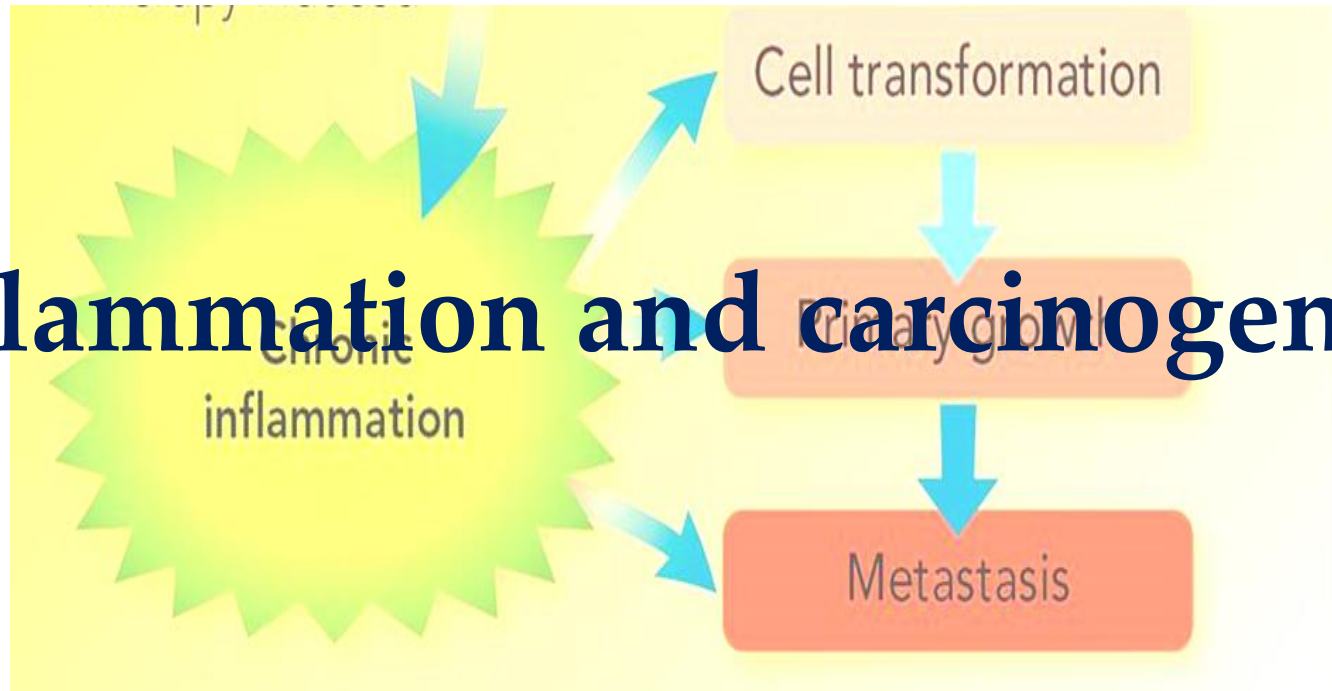


TEACHING UNIT 12

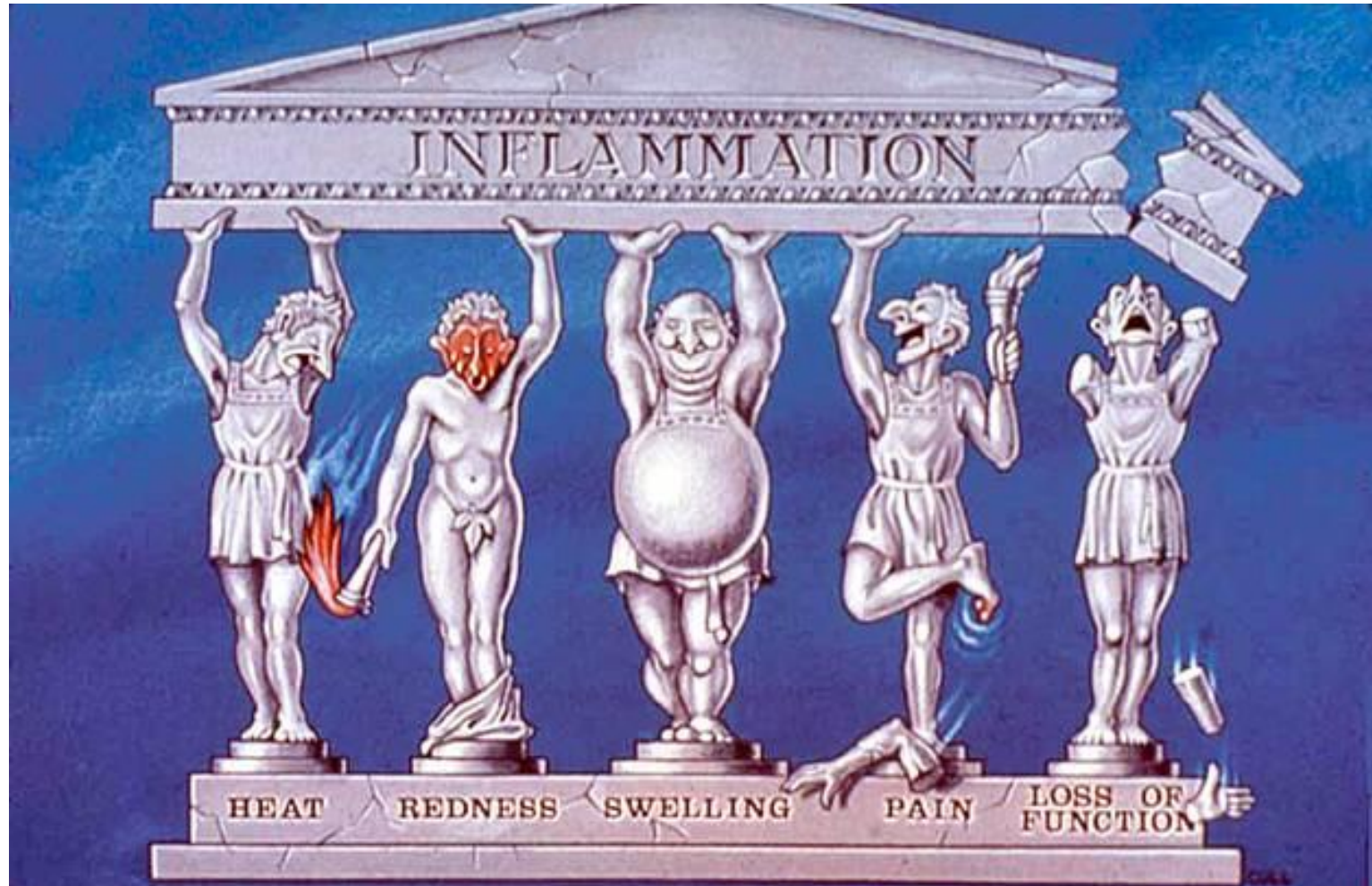
Inflammation and carcinogenesis



Mechanisms of malignant cell transformation and tumor development in the inflammatory microenvironment

Inflammatory and stromal cells in initiation and tumor progression

Inflammation is the host's physiological response to damaged tissues...

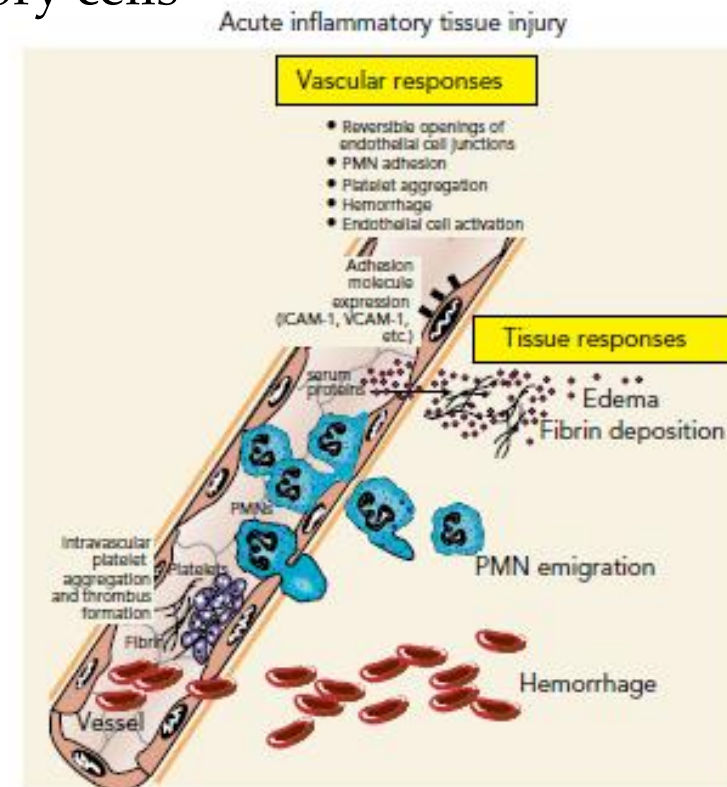


In addition to infection, other factors may also be involved in the inflammatory process:

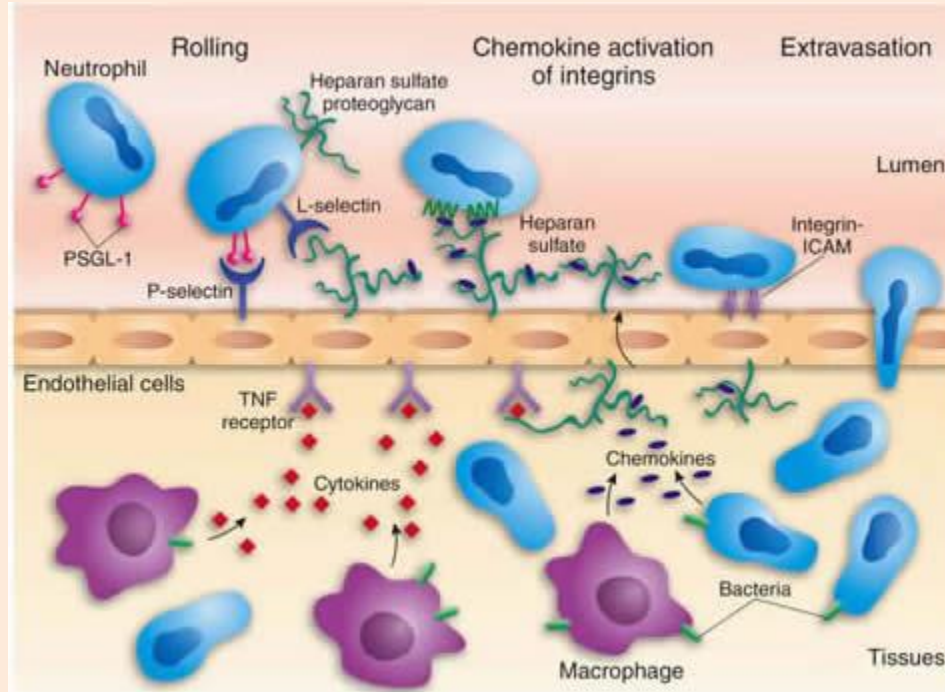
- ✖ trauma
- ✖ heat (burns and frostbite)
- ✖ chemical agents
- ✖ hypersensitivity reactions...

... 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



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**, different types of leukocytes, lymphocytes and other inflammatory cells are activated and attracted to the site of inflammation under the influence of a large number of growth factors, cytokines and chemokines.

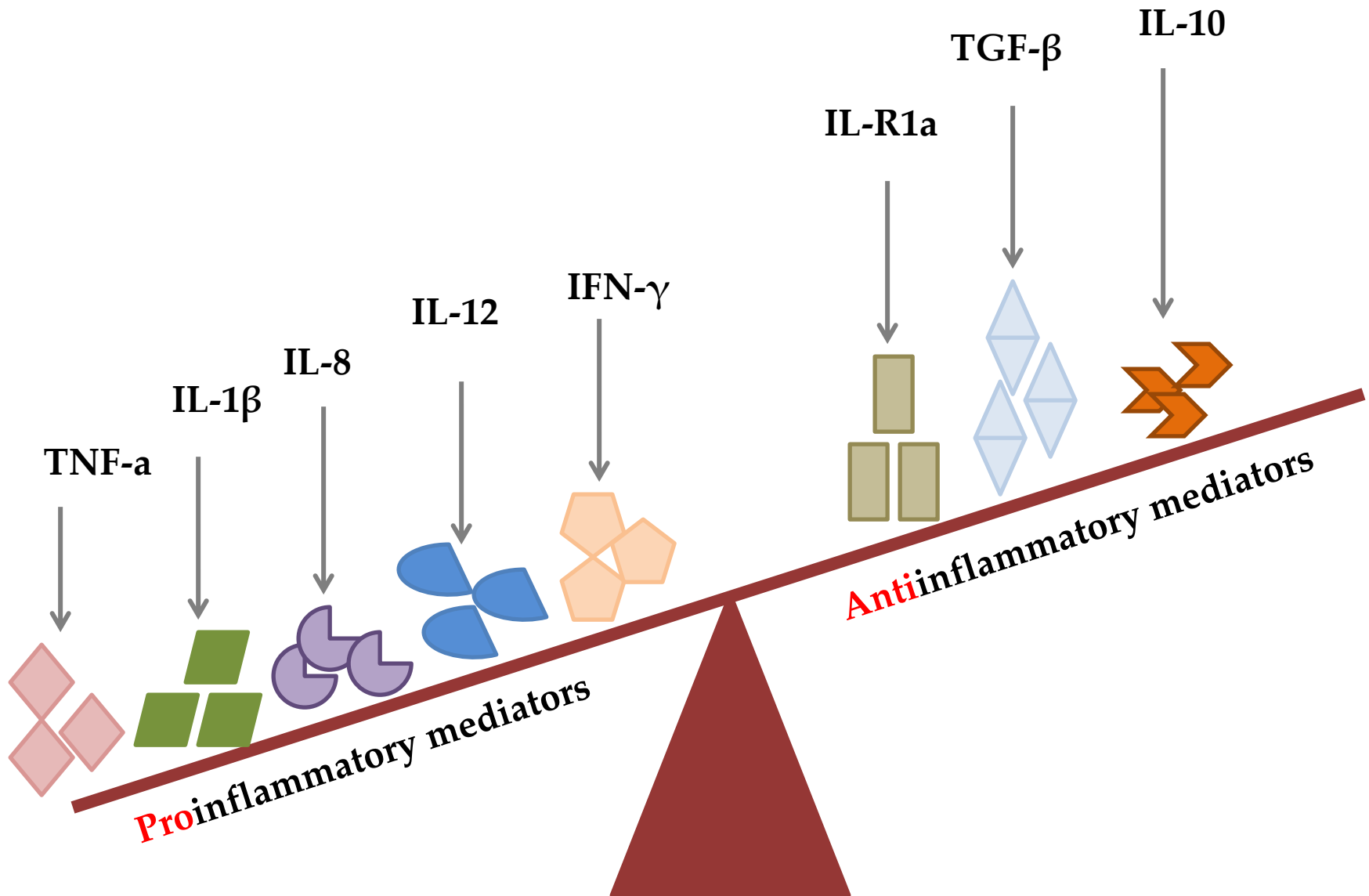
The goal of inflammatory reactions is to **restore damaged tissue** and **establish homeostasis...**



... The **optimal balance between pro-inflammatory** and **anti-inflammatory** mechanisms determines the elimination of infection, as well as the resolution of damaged tissue and the establishment of tissue homeostasis.

Chronic inflammation

imbalance between mediators



Neurodegenerative diseases
Alzheimer's
Parkinson's

Metabolic disorders
Type 2 diabetes
Fatty liver disease
Sleep apnea

Cardiovascular diseases
Cardiomyopathy
Atherosclerosis
Stroke

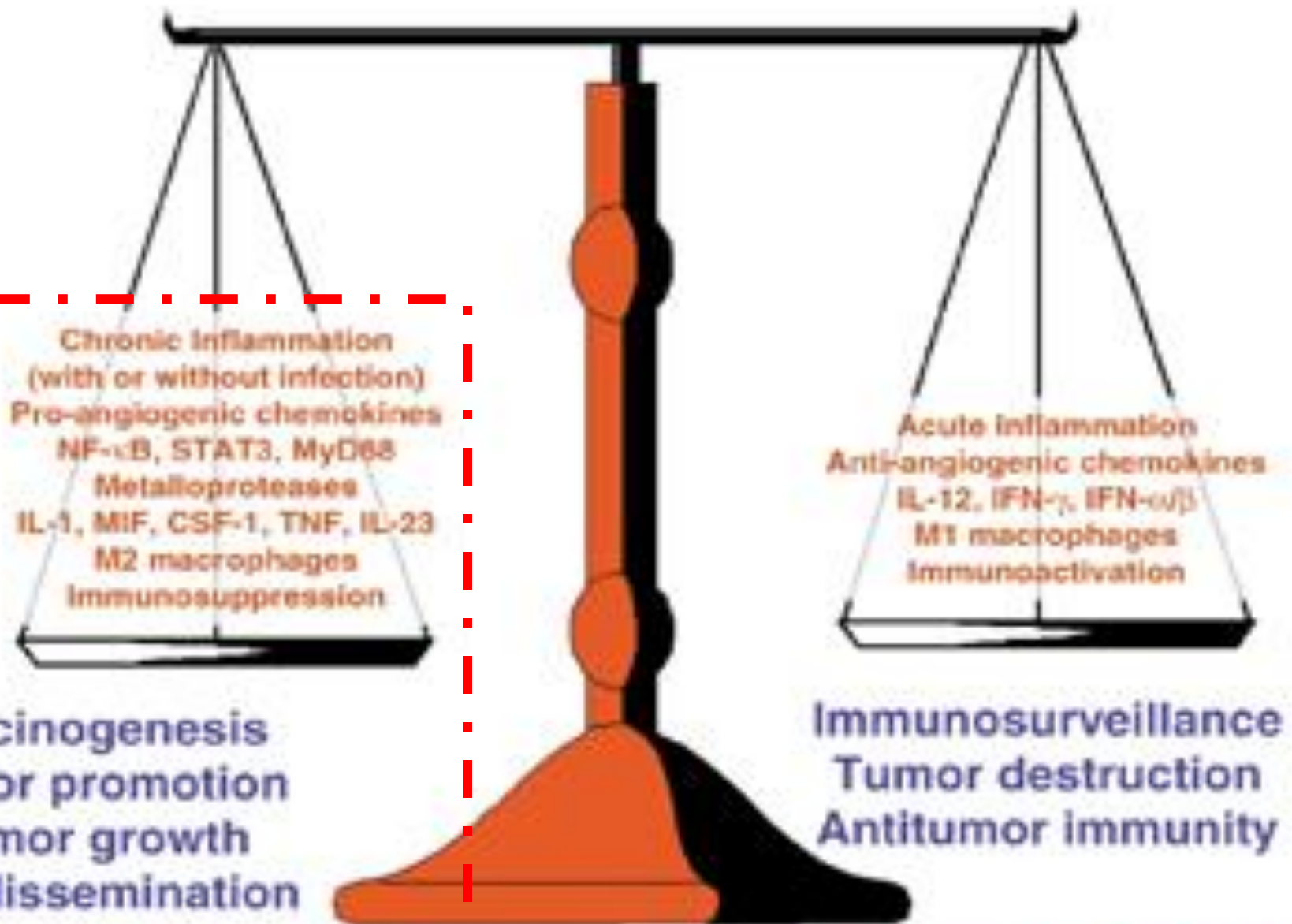
***Chronic
Inflammation***

Musculoskeletal disorders
Osteoarthritis
Osteoporosis
Sarcopenia

Cancer
Gastric, Liver, Lung,
Gall bladder, Colon,
Rectal, Pancreatic,
Prostate, etc



Cancer and Inflammation



CHRONIC INFLAMMATION

In chronic inflammation, macrophages dominate, as well as lymphocytes. Macrophages generate a large amount of growth factors and cytokines, as well as reactive oxygen and nitrogen radicals that can cause DNA damage.

Chronic inflammation favors genetic, epigenetic, tissue or cellular changes involved in the initiation of carcinogenesis.

With the development of chronic inflammation by various mechanisms, 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.

Immune surveillance...

In 1950, Burnet and Thomas proposed 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.



Cancer immunoediting

Normal

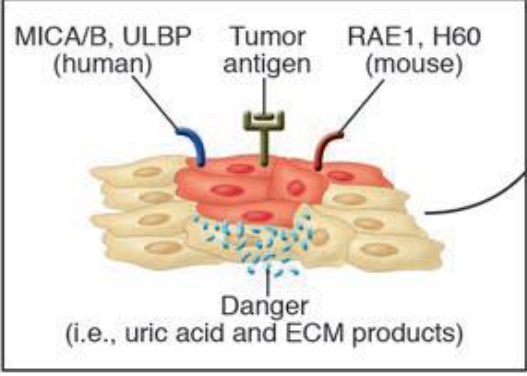


Carcinogens
Chronic inflammation
Inherited genetic mutations
Radiation
Viral infection

Repair, senescence, and/or apoptosis: intrinsic tumor suppression

Loss of polarity
Loss of ECM contact

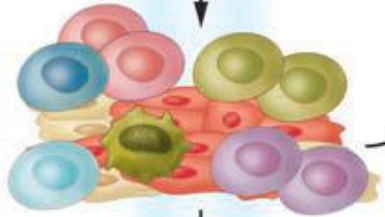
Transformed



Elimination (Cancer immune surveillance)



Innate and adaptive immunity



IFN- γ
Perforin
TRAIL
IFN- α/β
NKG2D

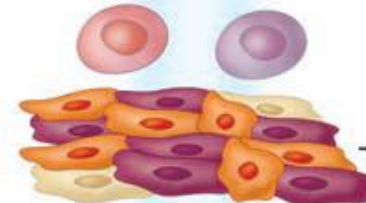


Protection (i.e., extrinsic tumor suppression)

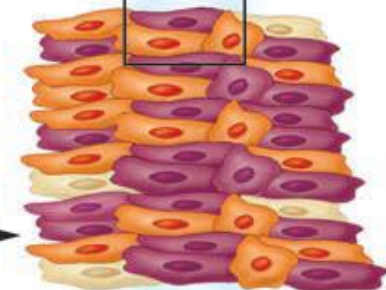
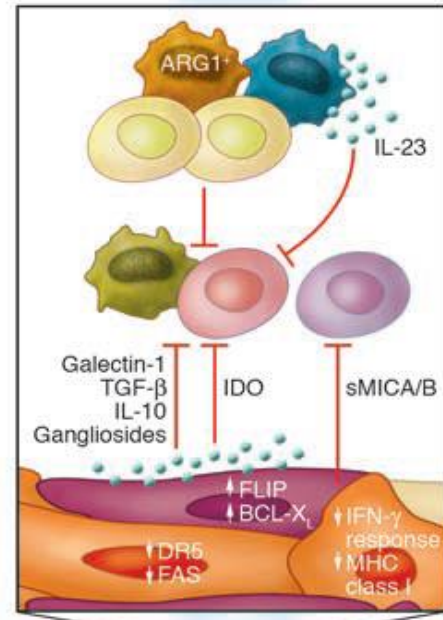
Equilibrium (Cancer persistence)



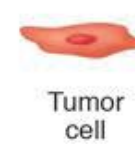
Genetic instability and/or immune selection



Escape (Cancer progression)



Chronic inflammation

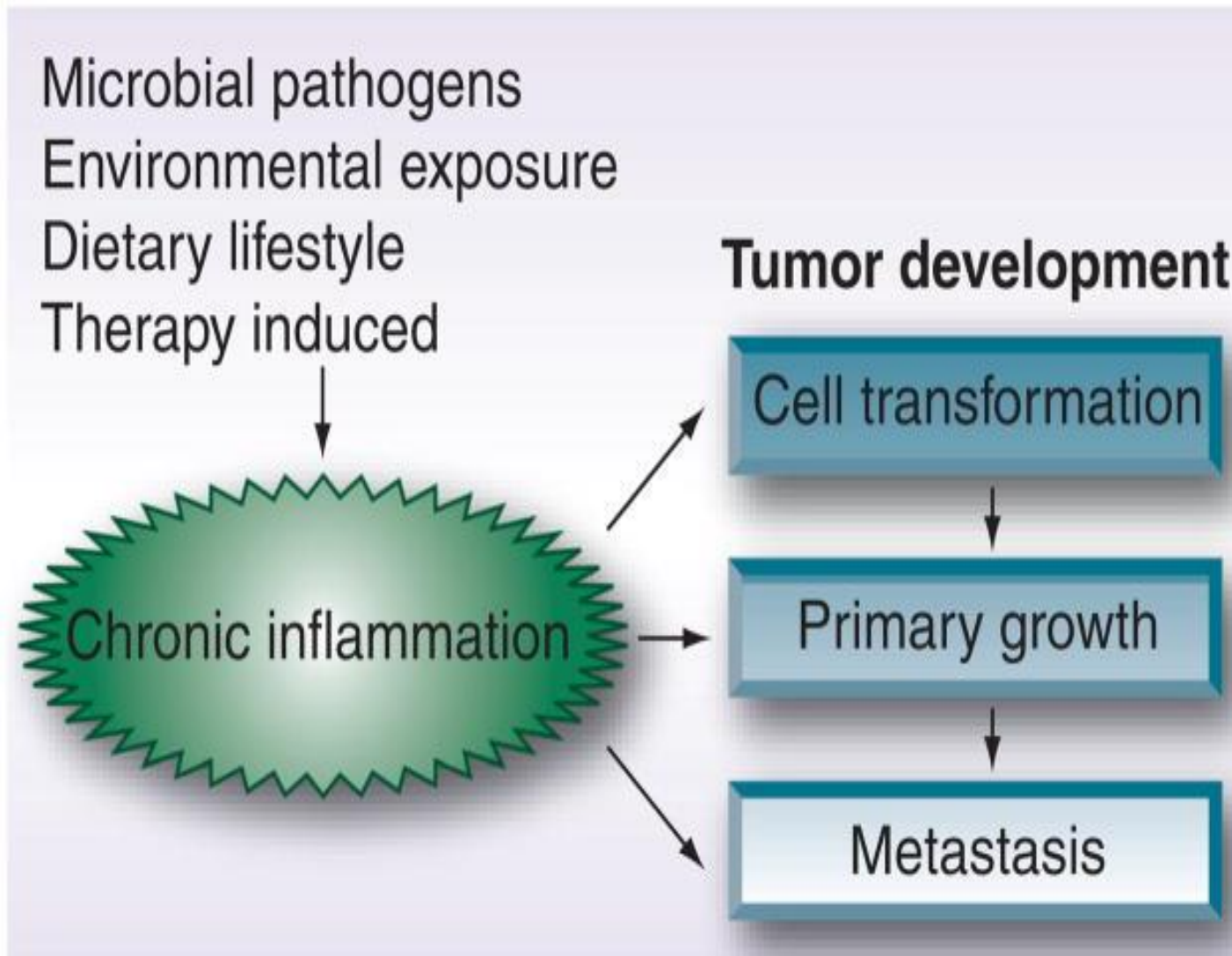




In 1863, Virchow was the first to notice the connection between inflammation and tumors.

**Rudolph Virchow
(1821-1902)**

Chronic "smoldering" inflammation is often associated with tumor **initiation** and **progression**.



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	
Sialadenitis	Salivary gland carcinoma	
Sjogren's syndrome,	Lymphomas of lymphatic tissue associated	
Hashimoto's thyroiditis	with mucous membranes	
Asbestosis, silicosis	Mesothelioma, lung cancer	Asbestos fibers, silicate dust
Bronchitis (caused by nitrosamine, 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 intestinal diseases (Cron's disease and chronic ulcerative colitis)	Colorectal cancer, Small intestine cancer	

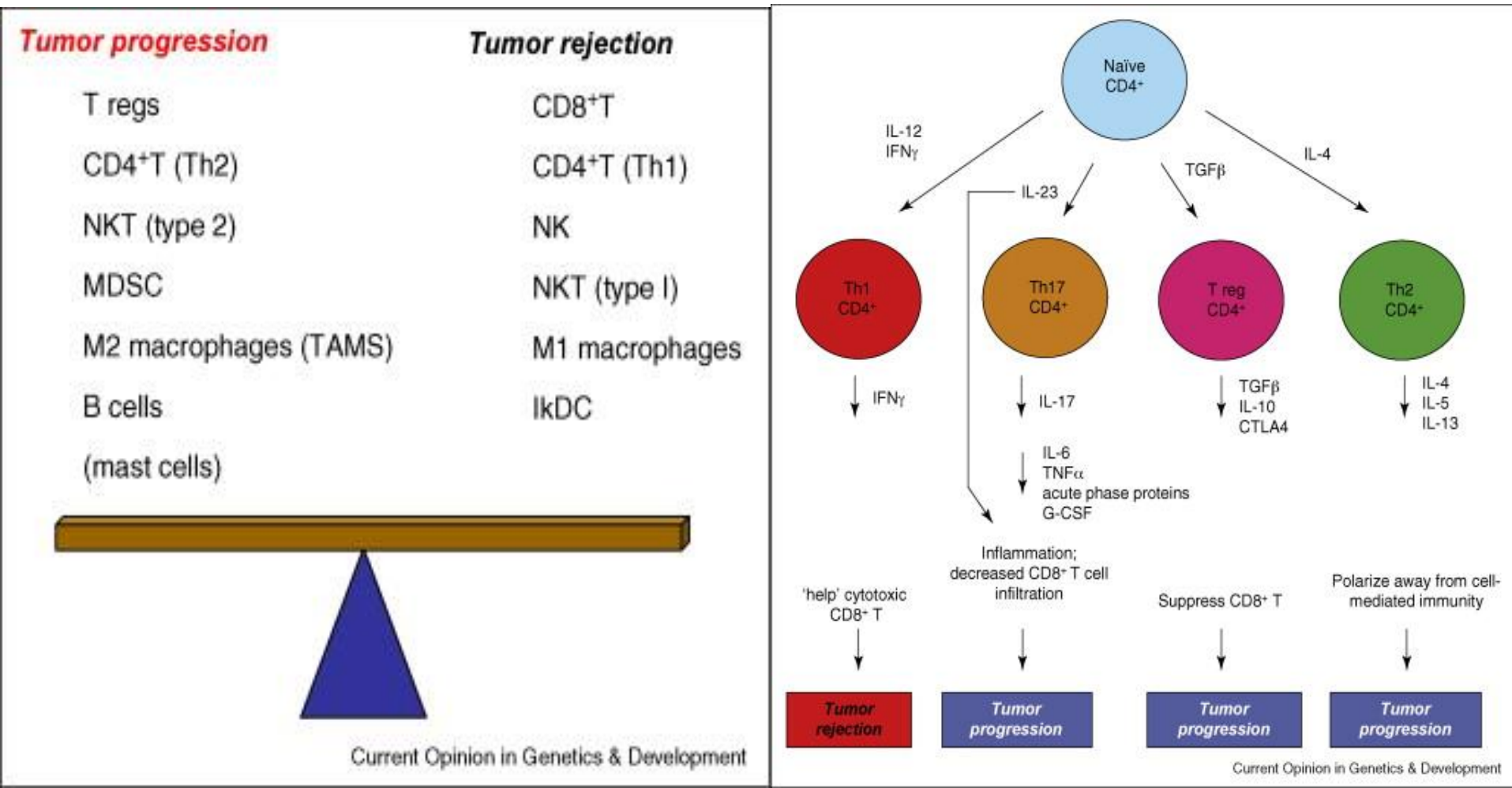
Tumors associated with inflammation resulting from infections

Pathological conditions	Tumors	Microorganisms
Hepatitis	Hepatocellular carcinoma	<i>Hepatitis B Virus</i> , <i>Hepatitis C Virus</i>
Mononucleosis	V-cell non-Hodgkin's lymphoma, Burkitt's lymphoma	<i>Epstein-Barr Virus</i>
AIDS	non-Hodgkin's lymphoma, squamous cell carcinoma, Kaposi's sarcoma	<i>HIV</i> , <i>HHV8</i>
Pelvic inflammatory disease	Ovarian cancer, cervical cancer	<i>N. gonorrhoeae</i> , <i>Chlamydia spp</i> , <i>Papillomavirus</i>
Osteomyelitis	Skin cancer in the region of the draining sinus	Bacteria
Chronic prostatitis	Prostate cancer	Gram-negative bacteria
Chronic cystitis	Bladder cancer, liver cancer	<i>Schistosoma</i> <i>haematobium</i> , <i>S.</i> <i>japonicum</i> ,

Factors with proapoptotic, antiangiogenic and immunostimulatory effects **suppress tumor progression.**

Factors with antiapoptotic, proangiogenic, prometastatic and immunosuppressive effects **favor tumors development and progression.**

This division is not absolute and the same factors can have both pro- and anti-tumor effects depending on the stage of the disease.

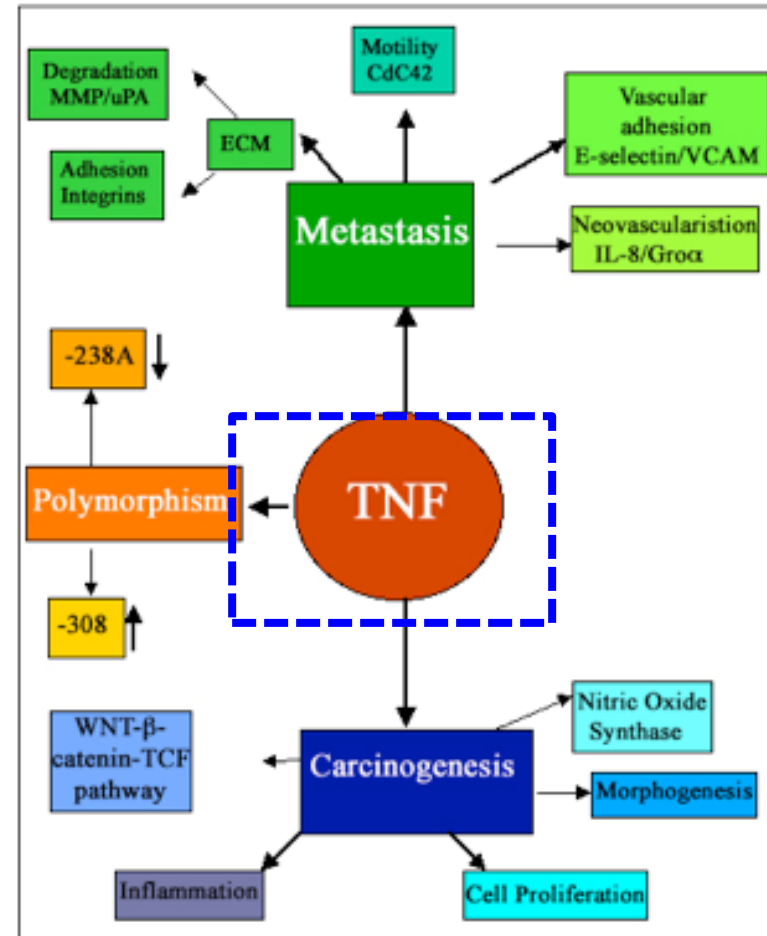


Antitumor effect of TNF:

It is mainly produced by activated macrophages and plays an important effector role in immune response. It has the ability to induce apoptosis of tumor and endothelial cells. Administration of high doses of TNF can induce destruction of tumor blood vessels.

Protumor effect of TNF:

It activates NF- κ B in tumor cells and thus promotes their survival and proliferation. It induces the synthesis of MMP-9 and chemokine MCP-1, which regulates monocyte infiltration into tumor tissue. It promotes angiogenesis and induces DNA damage, inhibits DNA repair and functions as growth factor for tumor cells



Clear proof of the existence of a link between chronic inflammation and tumors is the finding that **the use of non-steroidal anti-inflammatory drugs reduces the incidence of cancer.**

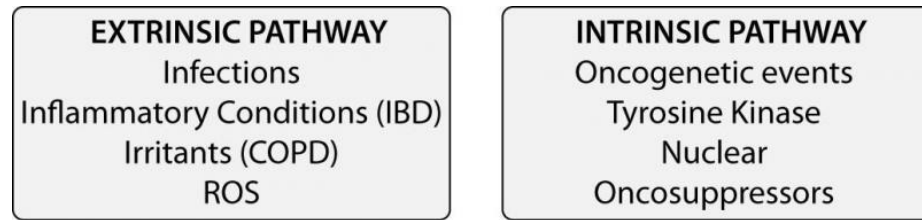
Cyclooxygenase-2 (COX-2) is overexpressed in intestinal epithelial cells and in colorectal cancer. By increasing the synthesis of prostaglandins, this enzyme controls inflammation (acts as a vasodilator) and angiogenesis, increases hematopoietic cell homing into the tumor tissue. It also affects the adhesion and apoptosis of epithelial cells and regulates the functions of the immune system.

- ✓ Long-term treatment with non-specific cyclooxygenase inhibitors (aspirin) reduces the risk of colon cancer by about 50%.
- ✓ A specific inhibitor COX-2 does not prevent cancer but increases survival after surgical resection in those patients diagnosed with colon cancer with increased expression COX-2 or with mutated forms of the gene.

Mechanisms of malignant cell transformation and tumor development in the inflammatory microenvironment

Carcinoma can be induced at the site of chronic inflammation.

An inflammatory microenvironment can create conditions characterized by genetic instability that favors the accumulation of genetic mutations.

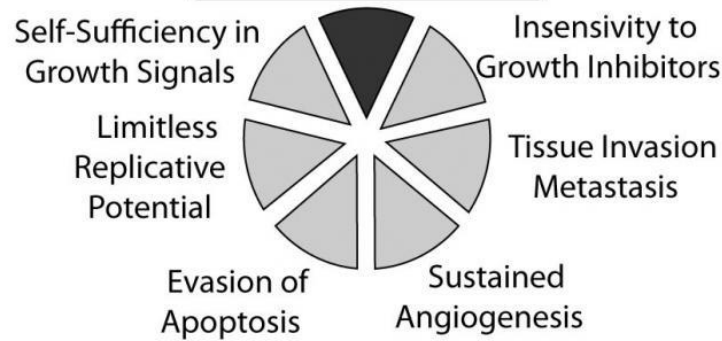


TRANSCRIPTION FACTORS
NFkB, STAT3, HIF

INFLAMMATORY CELLS
TAM, MDSC, Mast Cells,
PMN, Eosinophils

SOLUBLE MEDIATORS
Cytokines (TNF, IL-1, IL-6)
Chemokines (CCL2, CXCL8)
COX2, VEGF

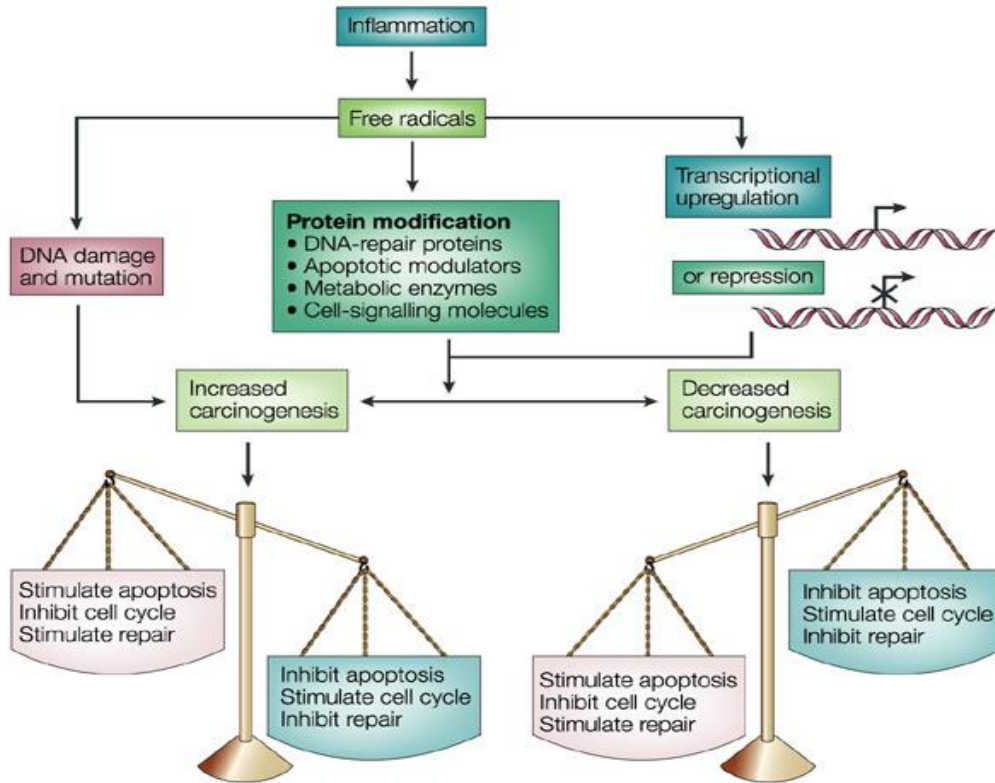
**CANCER-RELATED
INFLAMMATION**



Chronic inflammation can contribute to increased frequency of DNA mutations or genetic instability in several ways...

- ...Tissue damage and repair increase the degree of proliferation in the affected tissue, which consequently increases the possibility of mutations or chromosomal translocations during mitosis.
- ... During inflammation, free oxygen and nitrogen radicals can reduce DNA repair gene expression and enzyme activity of MLH-1, MSH-2, and MSH-6, which results in increased genetic instability and an increased rate of replication errors.

Reactive oxygen and nitrogen radicals produced by inflammatory cells **induce a series of cellular damages:**



...breaks or mutations of a single DNA base.

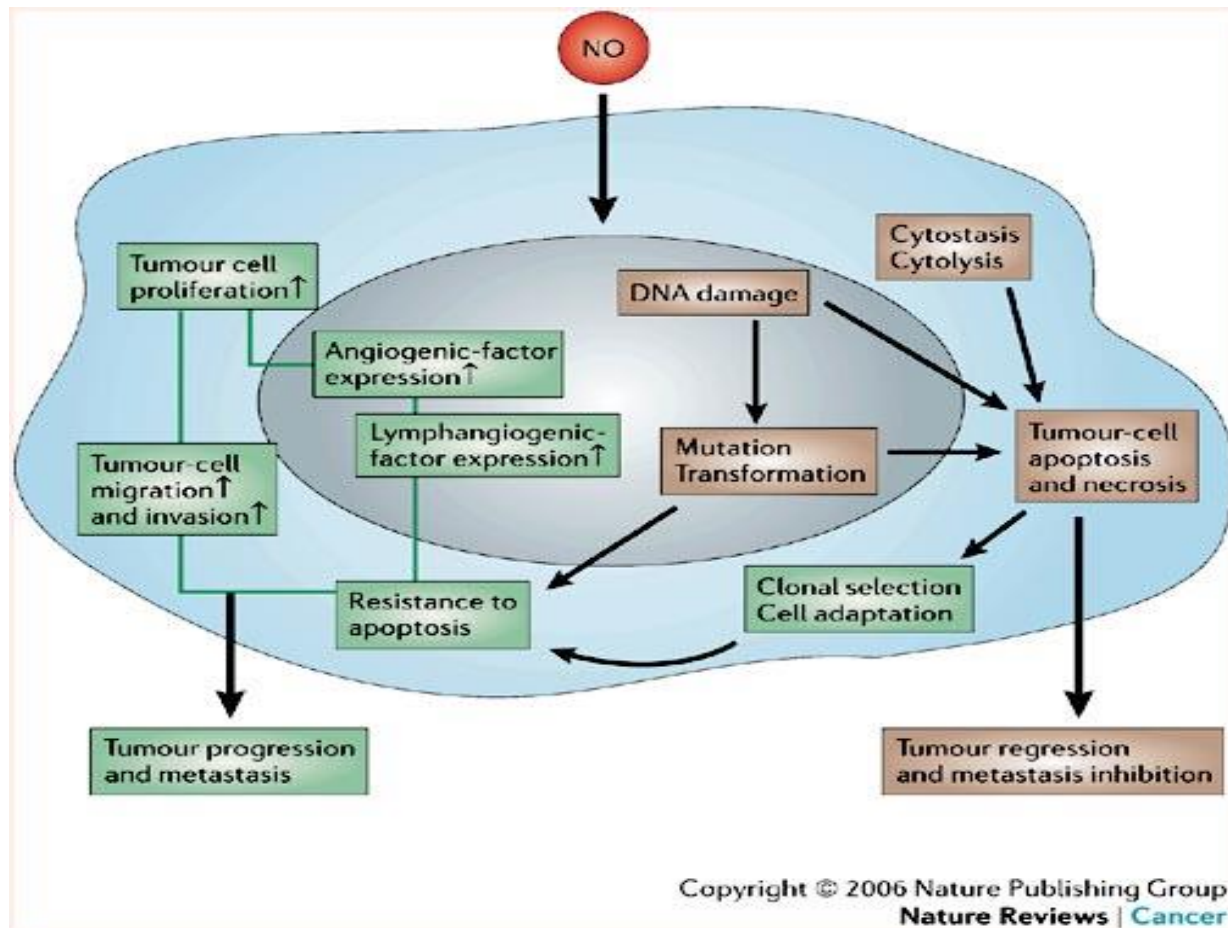
... mutations of anti-oncogenes

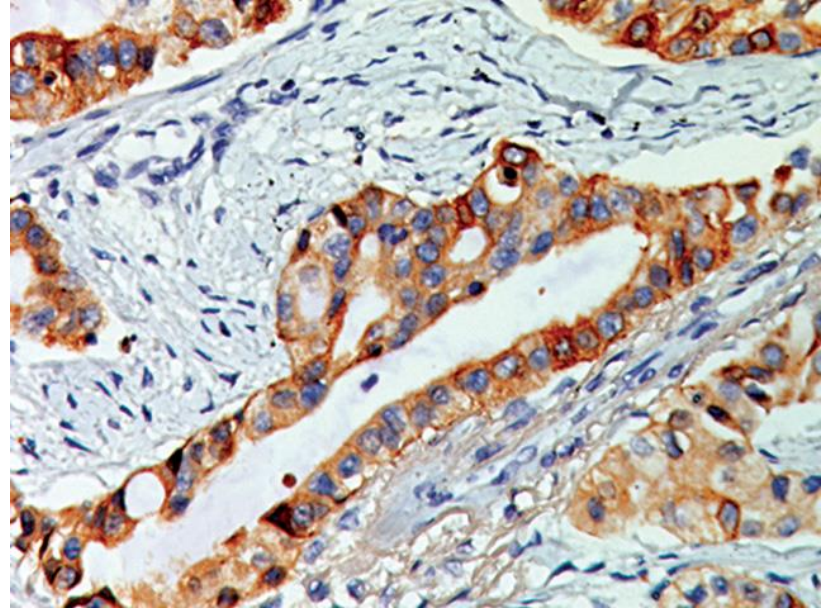
...epigenetic modifications

...post-translational modification proteins that control apoptosis, survival, DNA repair and cell cycle.

The antitumor role of NO is reflected in the fact that it can induce DNA damage, increase angiogenesis, and stimulate the proliferation and invasion of malignant cells.

NO, in high concentration, has **antitumor effect** by inhibiting proliferation and inducing apoptosis in tumor cells.





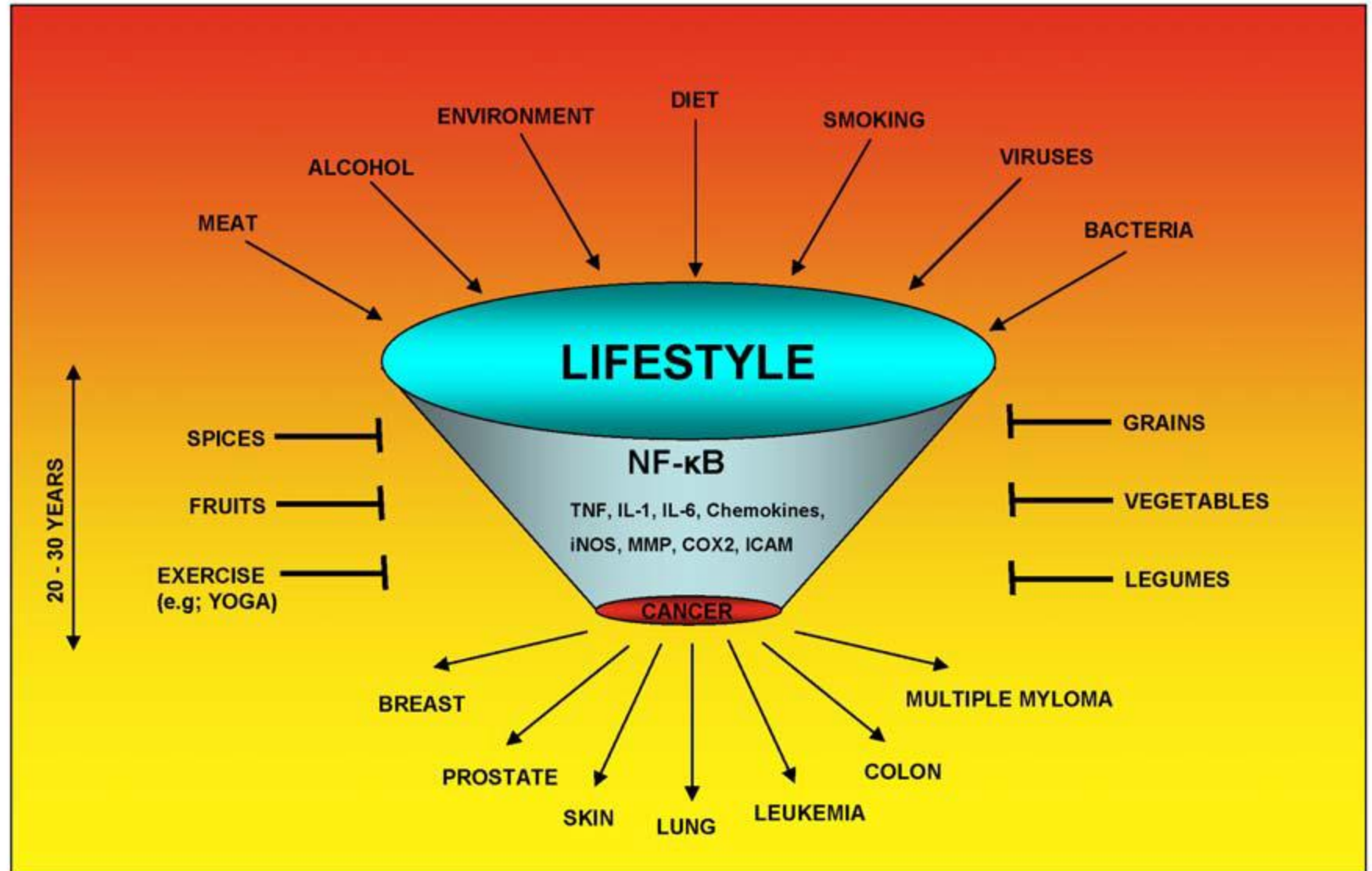
Expression COX-2 in colon cancer

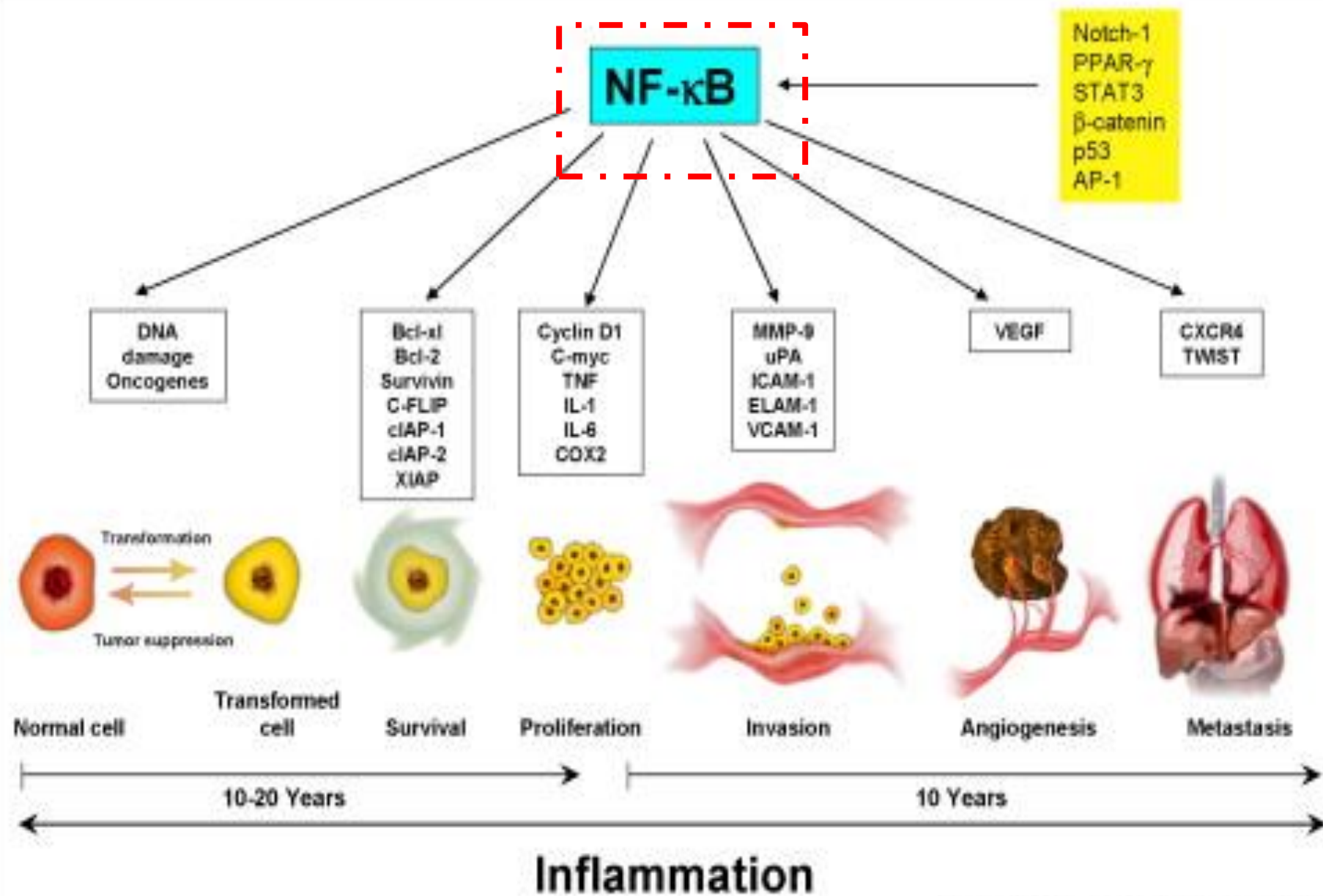
COXs are enzymes responsible for the synthesis of prostaglandins (PGE₂). It is overexpressed in almost all tumors, even at a very early stage of tumor development.

PGE₂ affects the degree of DNA mutations and promotes tumor progression by modulating angiogenesis, apoptosis and metastasis formation.

Several transcription factors activated in inflammatory microenvironment significantly influence the initiation and progression of tumors, of which **NF- κ B** and **STAT3** are the most important

NF- κ B

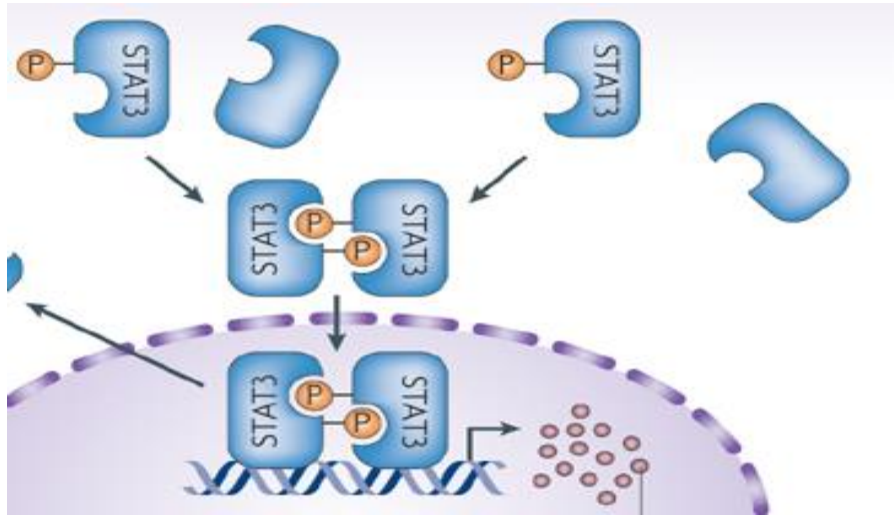




Transcription factor **STAT3** contributes to...

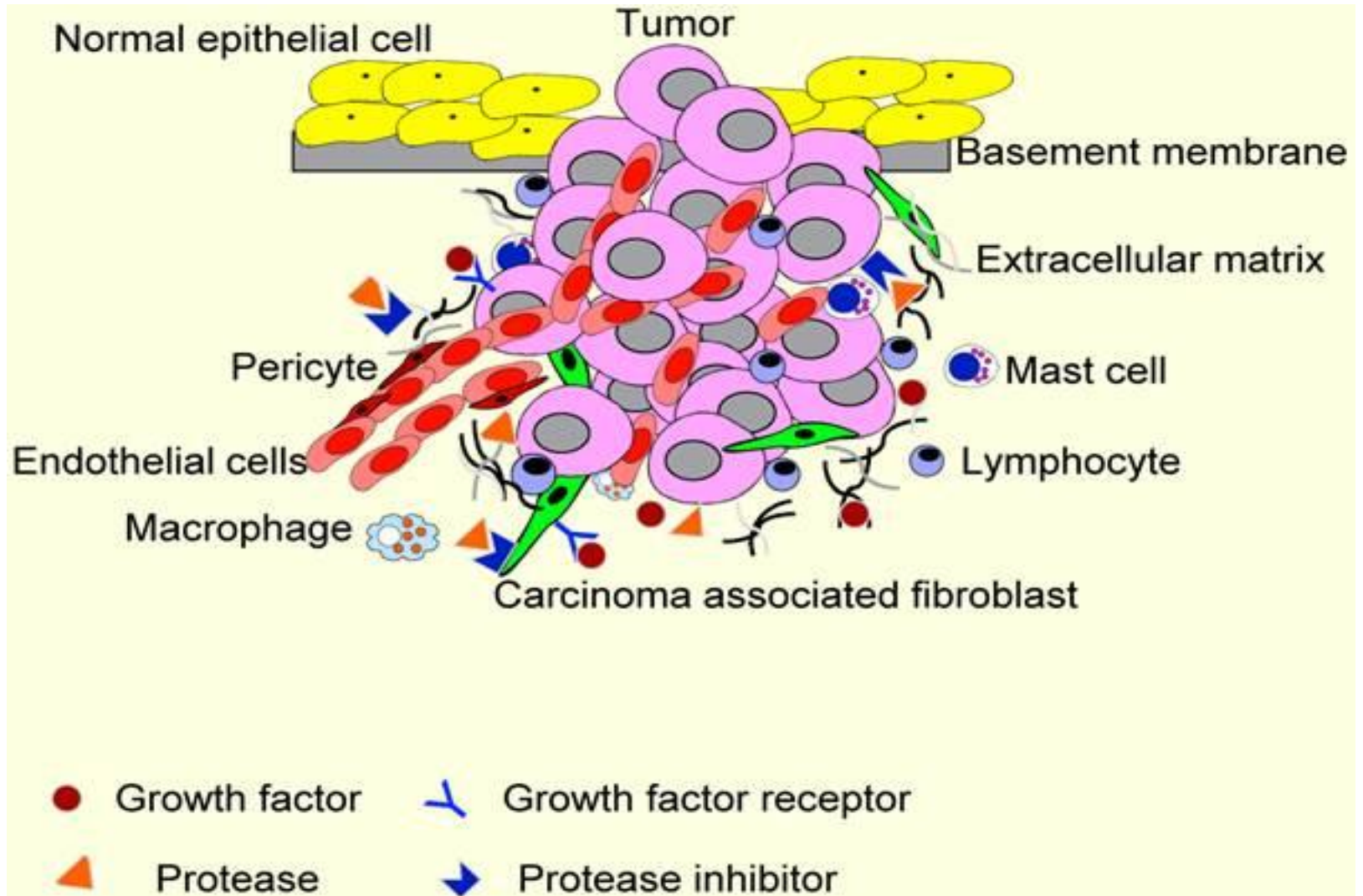
... the survival, proliferation and dissemination of tumor cells by controlling the expression of several genes involved in the cell cycle, as well as the c-Myc oncogene.

... recruiting hematopoietic cells into the tumor tissue by controlling the production of chemotactic factors, as well as their receptors in the infiltrating cells



Activation of STAT3 in tumor-associated macrophages has an anti-inflammatory effect, and in dendritic cells it prevents their complete maturation. It inhibits the synthesis of pro-inflammatory cytokines (eg IL-12) and at the same time promotes the alternative activation of macrophages.

Tumor microenvironment



Cancer-associated fibroblasts (CAFs)...



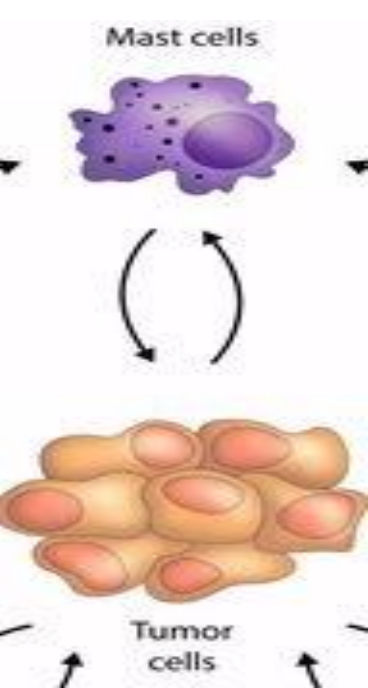
Cancer-associated
fibroblasts

They express **alpha-smooth muscle actin** and acquire the characteristics of myofibroblasts.

They can differentiate already existing normal fibroblasts from stem cells present in the tissue.

The protumor effect of CAFs is manifested by the secretion of soluble factors that induce angiogenesis, attract inflammatory cells and directly support the growth and dissemination of malignant cells.

They secrete SDF-1/CXCL12 chemokines, TGF- β and matrix metalloproteinases.



Mast cells...

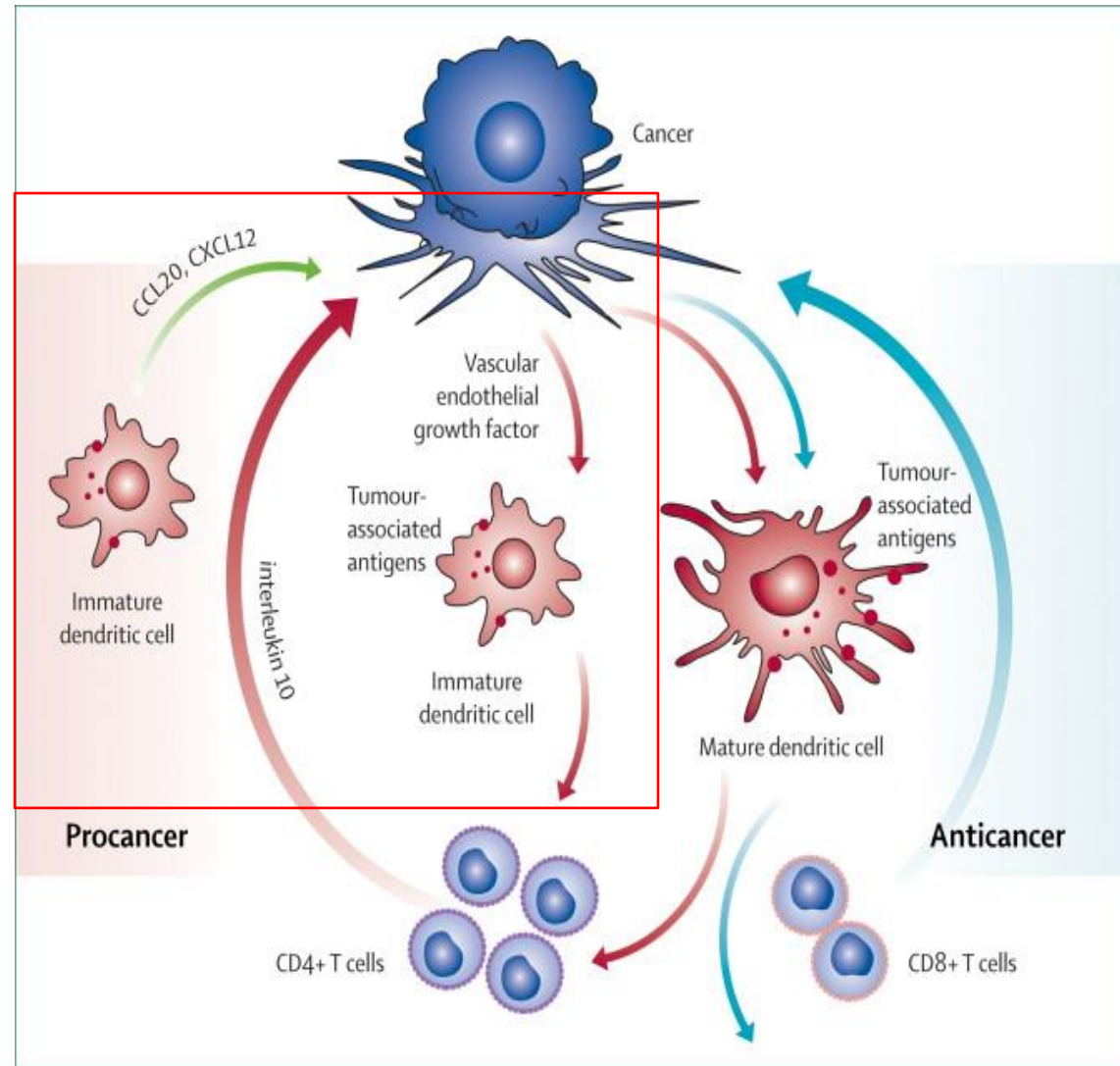
... release **heparin** and **histamine** which affect angiogenesis, but **MMP-2** and **MMP-9**, as well as serine proteases, have a particularly important proangiogenic effect....

...they also secrete **several growth factors** (FGF-2, VEGF, TGF- β , TNF and IL-8) that not only affect angiogenesis but also recruit and activate bone marrow-derived cells into the tumor tissue.

Conventional dendritic cells (DCs)

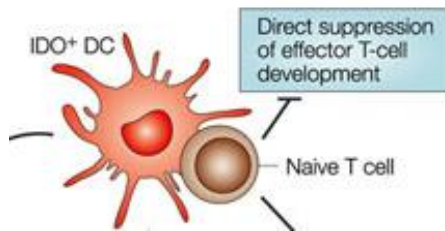
DCs are present in chronically infected tissue or in a tumor, but **phenotype** of these cells is altered

Tumor cells or stromal cells produce anti-inflammatory molecules (**IL-10, TGF- β , IL-6, VEGF and prostaglandins**) that contribute to the state of reactivity DCs in the tumor microenvironment



Plasmacytoid dendritic cells

Plasmacytoid DCs isolated from human tumors have immunosuppressive properties.



They induce immune tolerance *in vivo* and *in vitro* by expressing an immunosuppressive enzyme **IDO** (*Indolamine 2,3-DiOxygenase*), and by using inducible costimulatory ligands (**ICOS-L**, English *Inducible COStimulator Ligand*) activate T lymphocytes that produce IL-10.

Granulocytes

Neutrophils are the first cells to infiltrate the site of infection or tissue damage.

These cells generate a strong angiogenic effect by releasing MMP-9 as well as various cytokines.

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.

Tumor-associated eosinophils can have **cytotoxic effect** on tumor cells, and can 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.

Tumor-associated macrophages (TAMs)

One of the main cellular components in the tumor tissue.

MCP-1 is the main chemokine responsible for TAM recruitments.

TAMs affect tumor growth in two ways:
regressive and **progressive**.

TAMs and theirs"polarization"

