

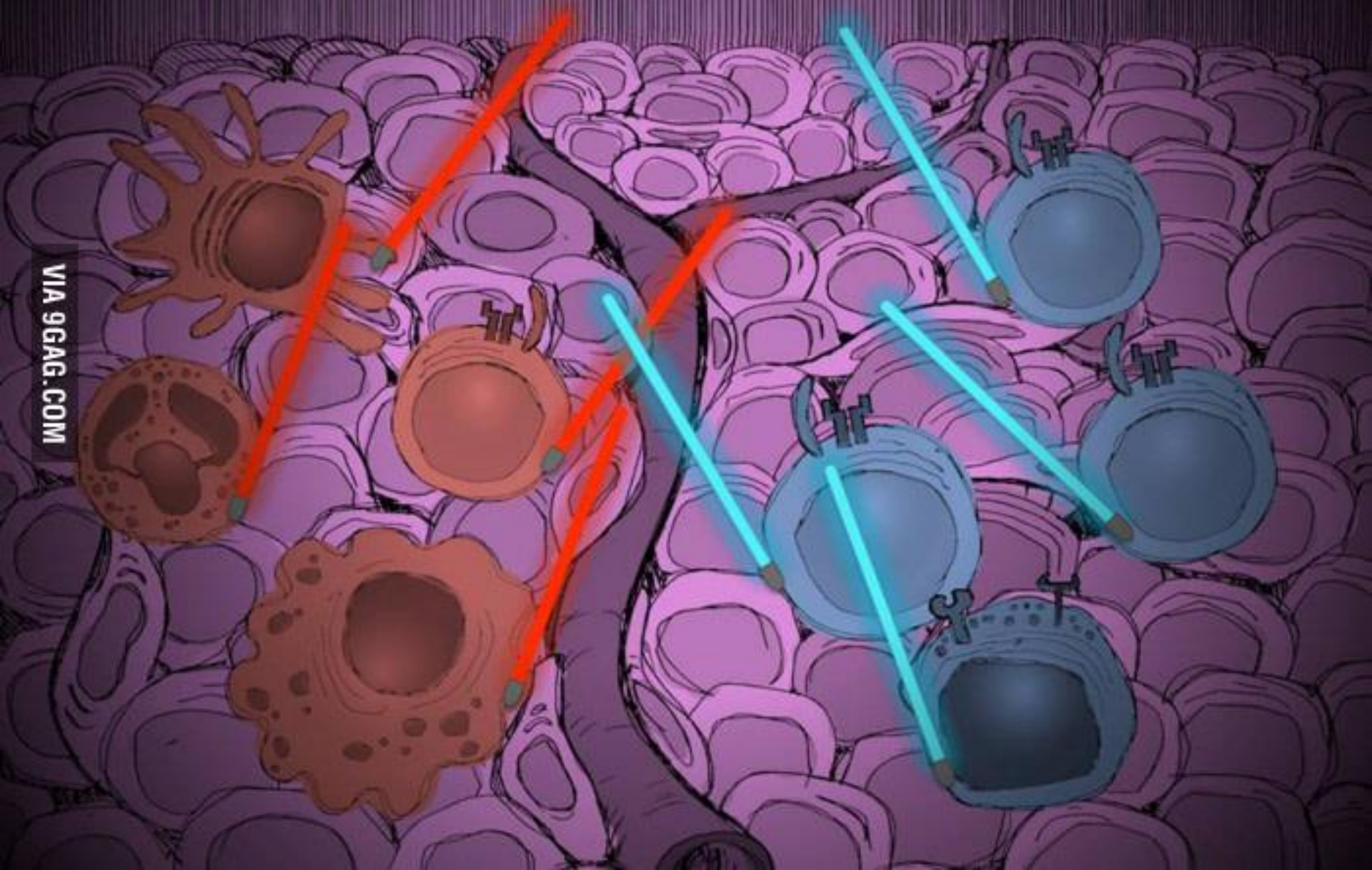
Teaching unit13

Immune response to tumors

TUMOR WARS

THE LYMPHOCYTE AWAKENS

VIA 9GAG.COM



Immune response to tumors

- Tumor antigens
- Antitumor immunity
- The role of immune cells against tumors
- How tumor avoids immune response
- Immunotherapy of tumors

Immune response to tumors

"The idea that a small group of tumor cells arises and expresses a new antigenic potential on membranes, induces an effective immune response followed by tumor regression without any visible clinical hint of its existence is unacceptable."

Macfarlane Burnet, immunologist 1957.

Immune response to tumors

- Both in response to transplants and in response to tumors, the immune system responds, not to microorganisms, but to non-infectious cells that it recognizes as foreign.
- These antigens can be expressed on any type of cell that is malignant, so it is obvious that there must be special mechanisms for inducing an immune response against different cell types.
- The main mechanism by which malignant cells are eliminated involves CTL.

Immune response to tumors

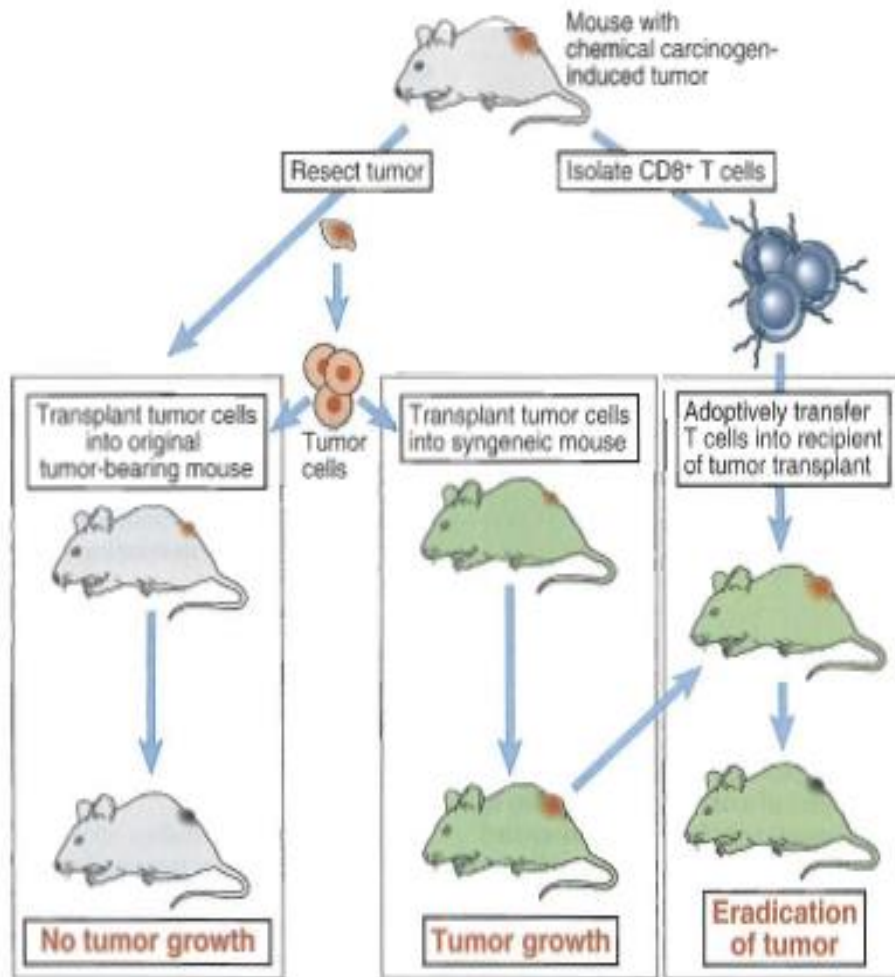
- tissue organization-anoikis
- immune system-immune surveillance

One of the physiological roles of the immune system is to destroy or prevent tumor cells from multiplying

-THEORY OF IMMUNE SURVEILLANCE

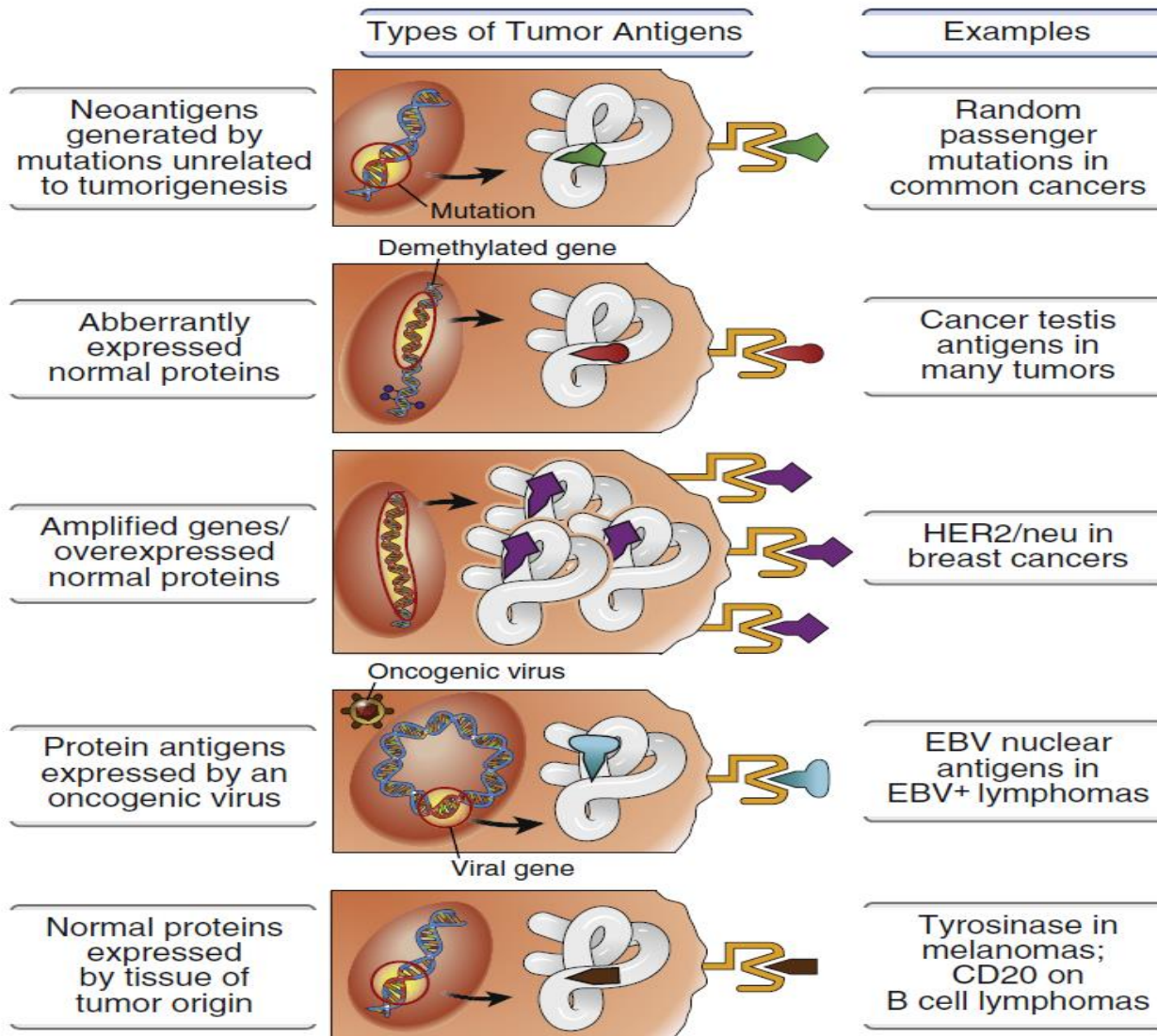
Evidence	Conclusion
Lymphocytic infiltrates around some tumors and enlargement of draining lymph nodes correlate with better prognosis	Immune responses against tumors inhibit tumor growth
Transplants of tumors between syngeneic animals are rejected, and more rapidly if the animals have been previously exposed to the tumors; immunity to tumor transplants can be transferred by lymphocytes from a tumor bearing animal	Tumor rejection shows features of adaptive immunity (specificity, memory) and is mediated by lymphocytes
Immunodeficient individuals have an increased incidence of some types of tumors	The immune system protects against the growth of tumors
Therapeutic blockade of T cell inhibitory receptors such as PD-1 and CTLA-4 leads to tumor remission	Tumors evade immune surveillance in part by engaging inhibitory receptors on T cells

Immune response to tumors



- methyl-cholanthrene MSA
- specificity
- memory

Malignant tumors express different types of molecules that immune system can recognize as –**tumor antigens**

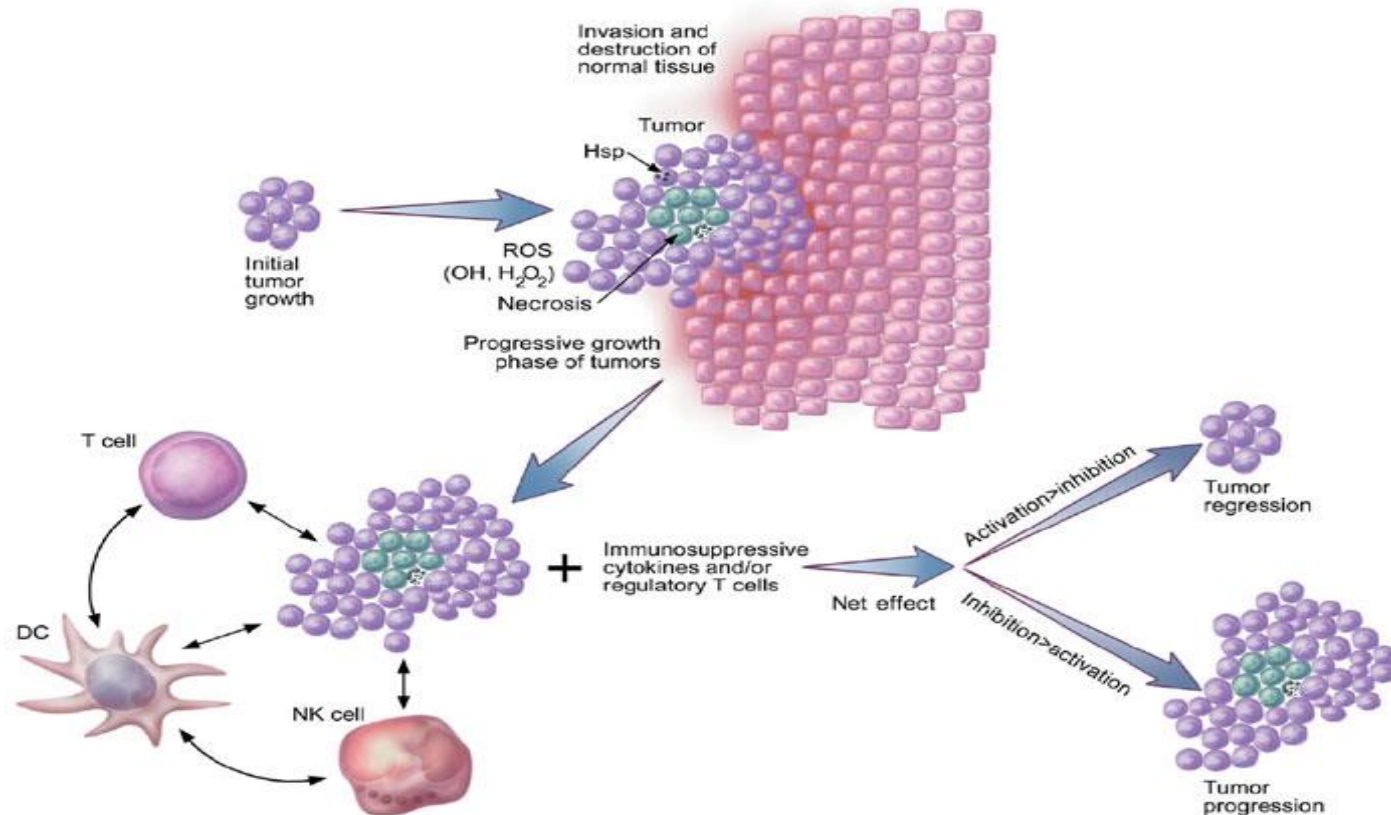


- Oncofetal antigens – AFP,CEA
- Altered glycolipids and glycoproteins- CA-125

Tumor antigens

- mutated host cell proteins
- normal cellular proteins that are overexpressed (tyrosinase)
- expression of normal genes at the wrong time and in the wrong tissue
- products of oncogenic viruses
- oncofetal antigens

Immune response to tumors



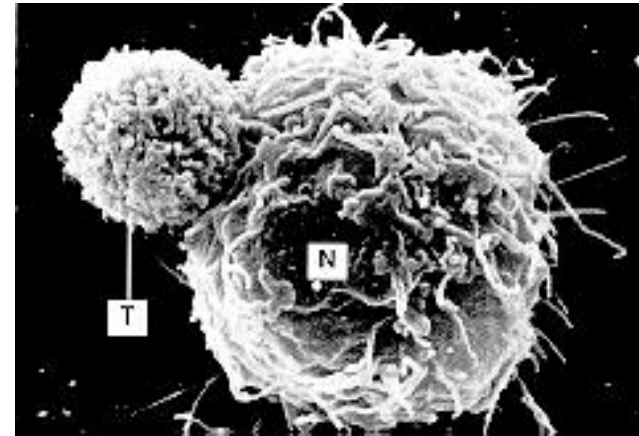
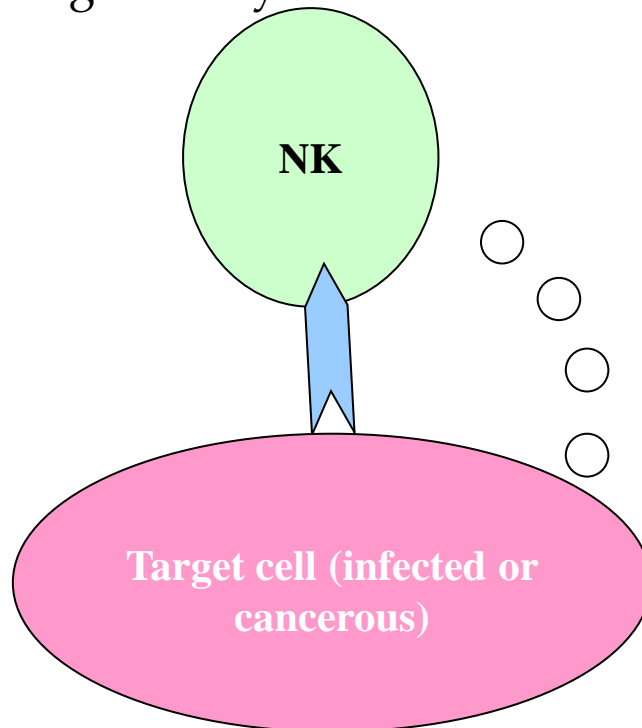
Tumors can trigger an immune response (expression of tumor antigens in MHC I) but also to suppress the same (activation of T regs which secrete IL-10 and TGF β).

Non-specific immune response to tumors

NK cells

Tumor cells produce oxygen radicals and "stress ligands"

Those molecules are recognized by NK cells



Tumor-associated macrophages- TAMs

- Virchow, 1863. leukocytes in and at the border of the tumor tissues.
- TAMs make the greater part of the leukocyte infiltrate around many tumors.
- Infiltration of mononuclear cell in tumor tissue.
- Mantovani- the first to examine tumor chemoattractants for monocytes.
- CCL2, CSF, VEGF-chemoattractants for monocytes, released by tumors cells.
- TAMs affect tumor growth in two ways: progressive and regressive.

Tumor-associated macrophages- TAMs

- Ability of TAMs to express different functional programs, either cytotoxic and anti-tumor or pro-tumor and pro-angiogenic, reflects the plasticity of macrophages in response to various factors in the inflammatory environment.
- This is often simplified to a dichotomy between
 - classically activated M1 macrophages
 - alternatively activated M2 macrophages

TAMs and tumor progression

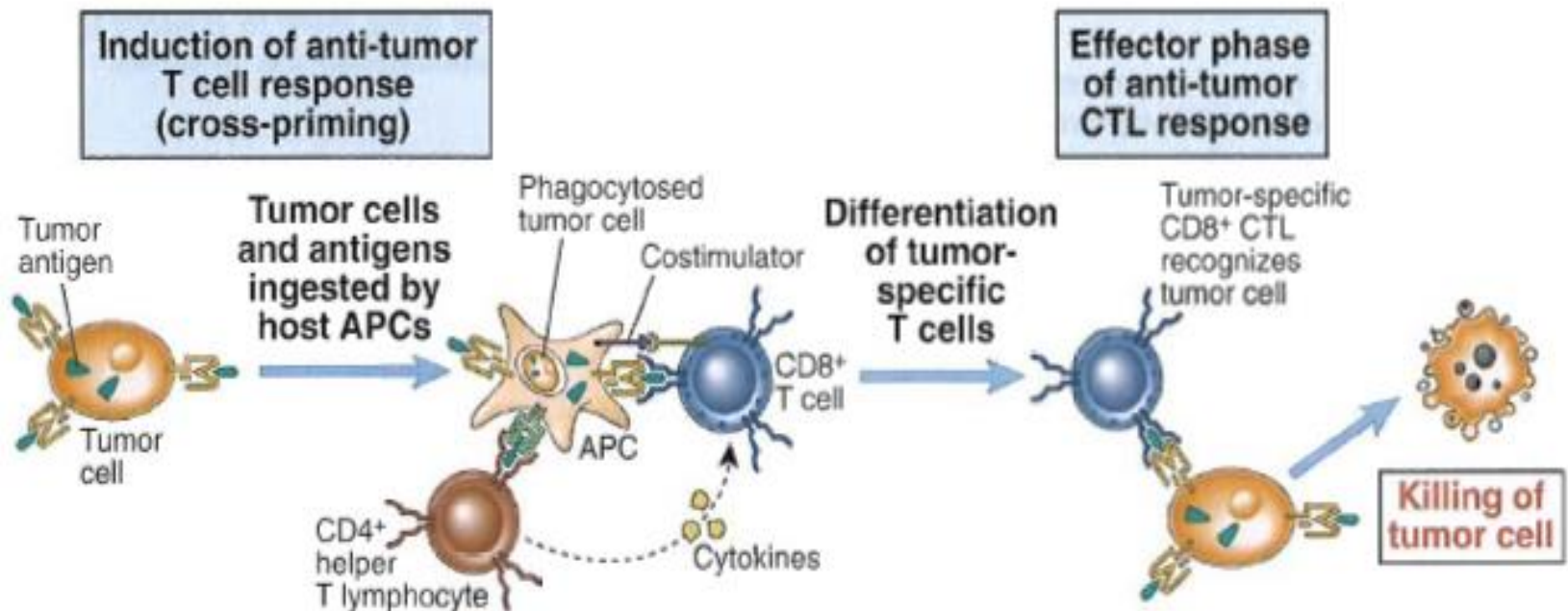
- Macrophages play an important role in tumor angiogenesis. They can induce the growth and development of blood vessels in several ways.
- Macrophages directly secrete pro-angiogenic factors. Today, more than 20 molecules are known that are secreted by macrophages and affect the proliferation, migration and differentiation of endothelial cells: Transforming growth factor- α and - β , insulin-like growth factor-1, PDGF and VEGF.
- Macrophages also modify the ECM. The composition of the ECM influences the growth of new blood vessels. Macrophages remodel the ECM by producing some of its components or by secreting proteases. They actively synthesize metalloproteinases MMP-2 and MMP-9, which are very active in the neovascularization of many tumors.

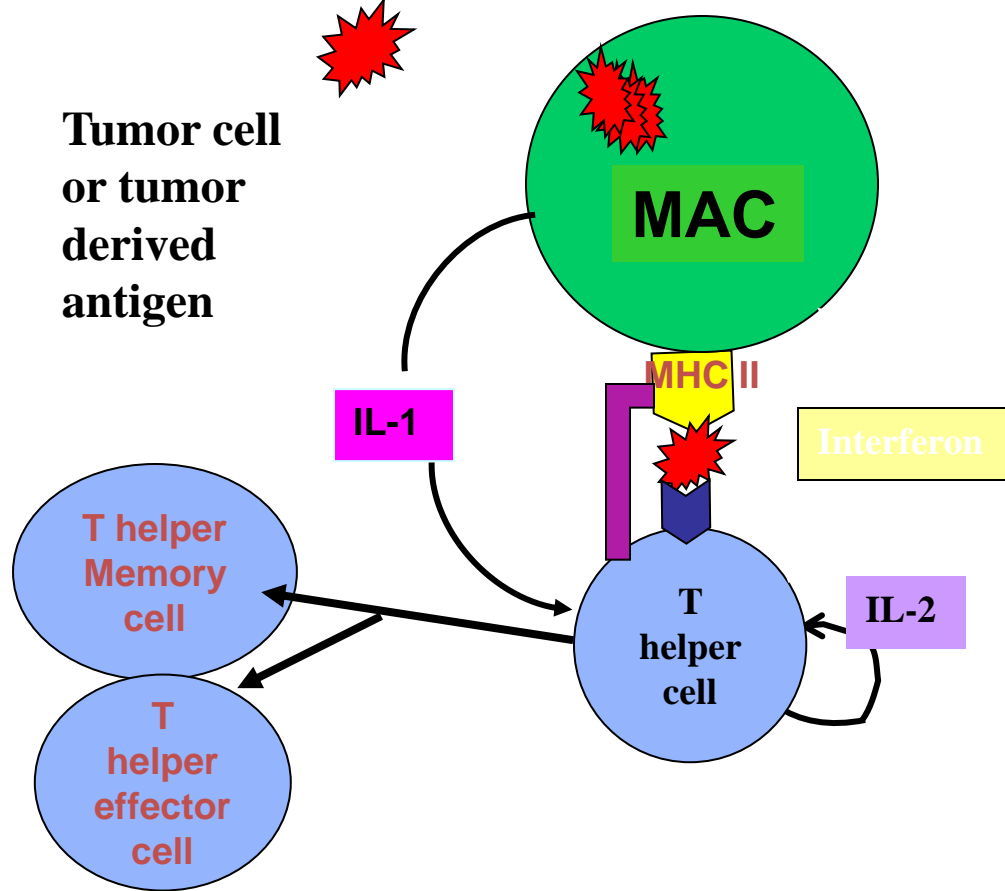
TAMs and tumor regression:

Mechanism	Mediator(s)
Direct cellular cytotoxicity	Cell to cell contact
Antibody-dependent cellular cytotoxicity	Fc receptor (CD16)
Secreted products (cytotoxic/cytostatic)	Eicosanoids(PGs, LTs)
	Cytokines (IL-1, TNF- α)
	Free radicals (RIO, NO)
Macrophage-induced apoptosis	TNF- α , IL-1 β , RIO, NO

Specific immune response to tumors

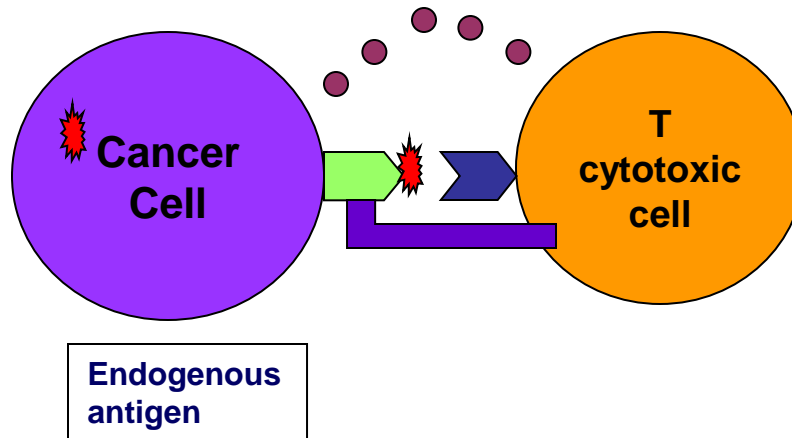
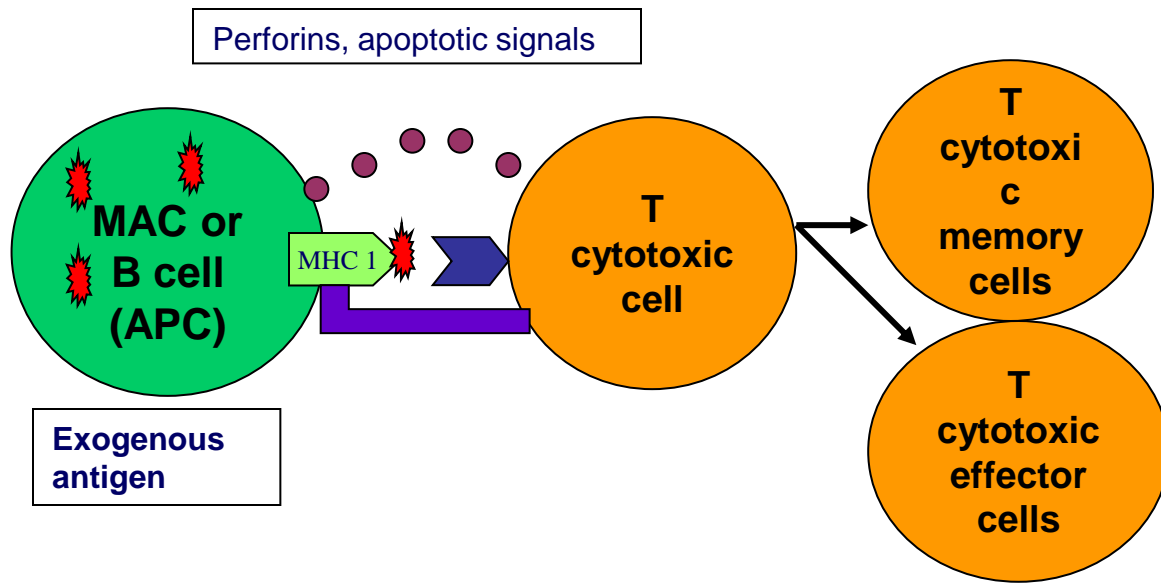
- CD4+ T lymphocytes
- CTLs
- cross presentation

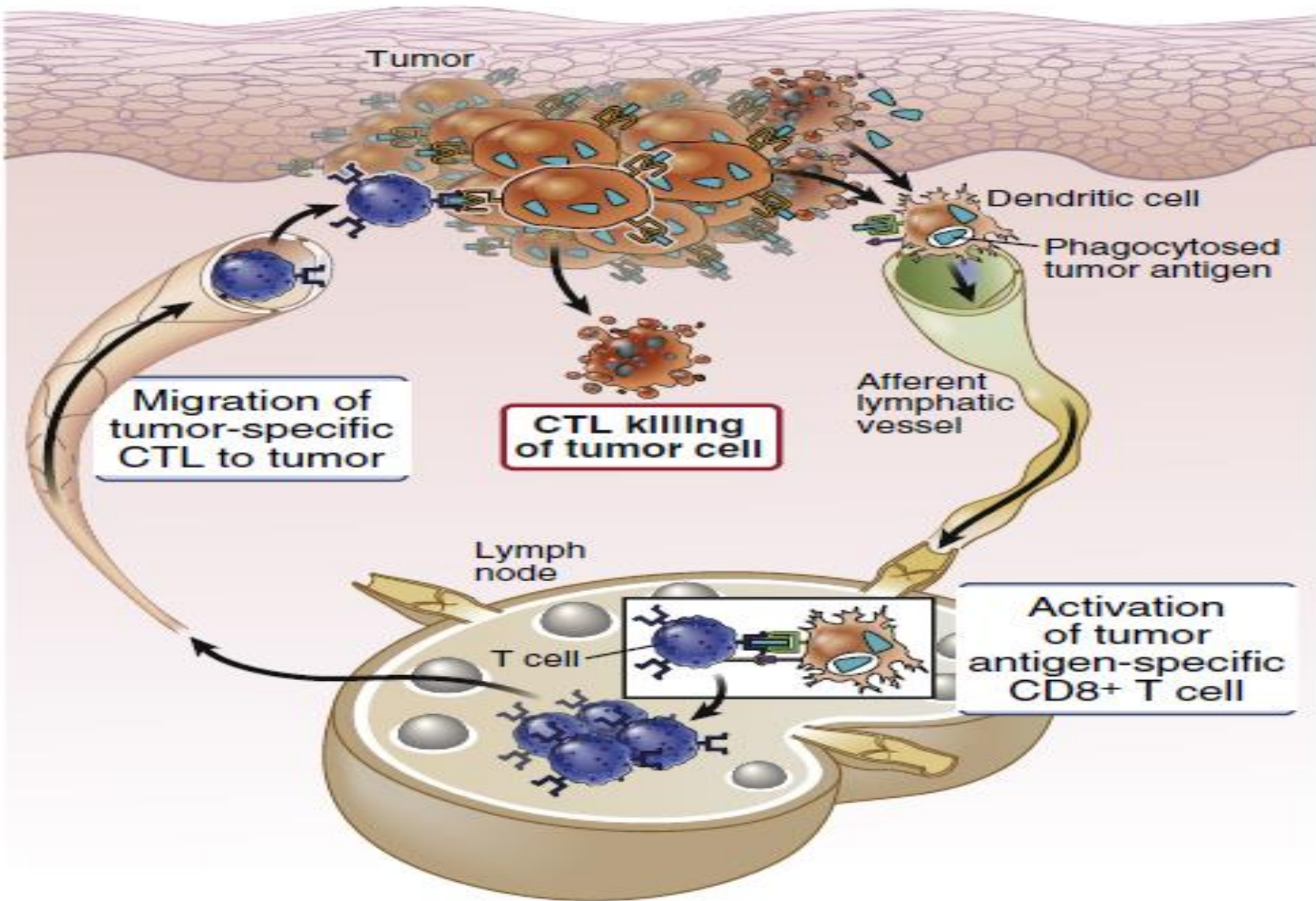


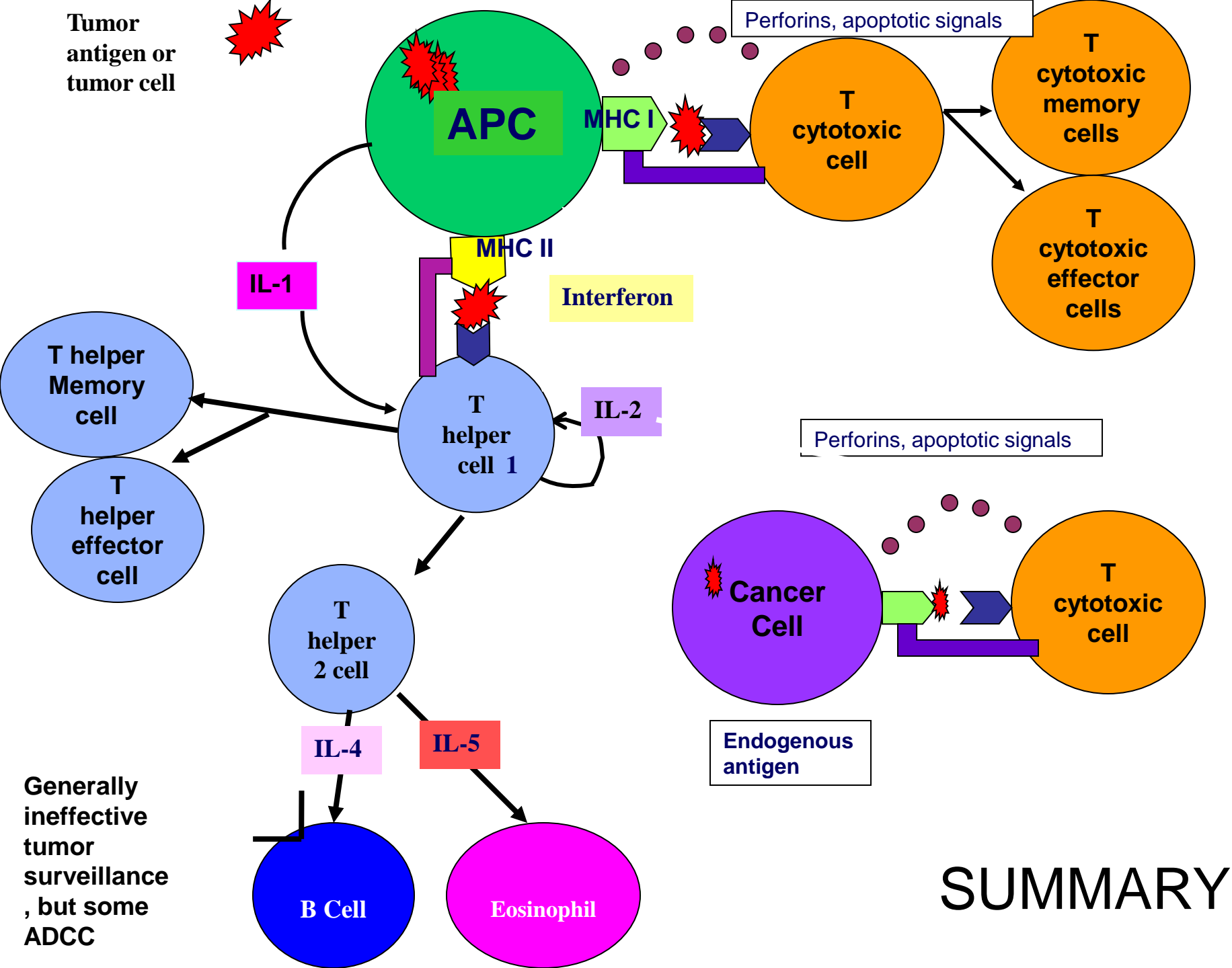


Macrophages and dendritic cells can directly "attack" tumor cells and present tumor antigens to CD4 lymphocytes

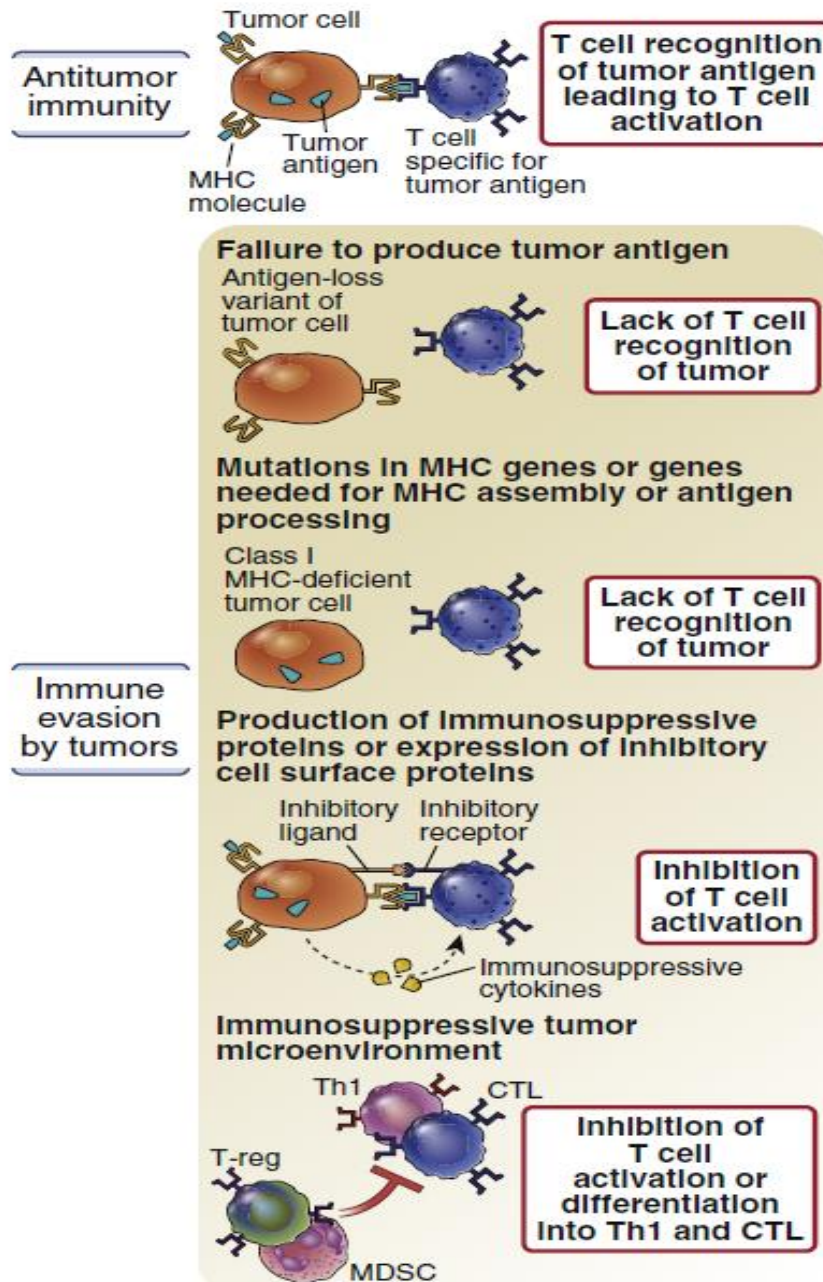
CTLs in immune surveillance







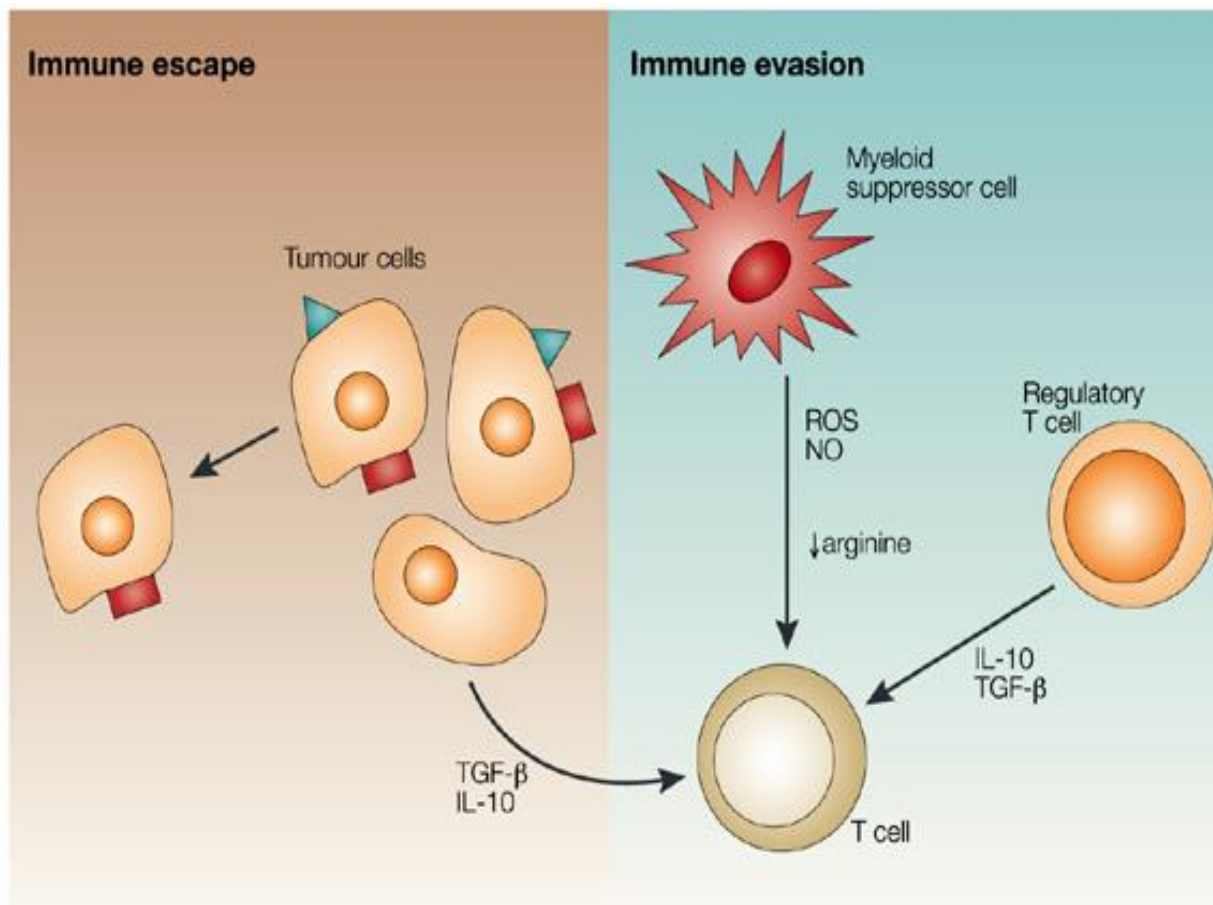
How do tumors evade the immune response?



- Tumor antigens induce immune tolerance
- Regulatory T lymphocytes
- The tumor does not express antigens
- Decreased expression of costimulators and MHC molecules I and II classes
- Antigen masking
- Secretion of cytokines that inhibit the immune response

How do tumors evade the immune response?

Immunosuppressive products TGF- β



How do tumors evade the immune response?

Fas ligand-Fas receptor

