Cancer Immunology
(Study of the response of the immune system to cancer)

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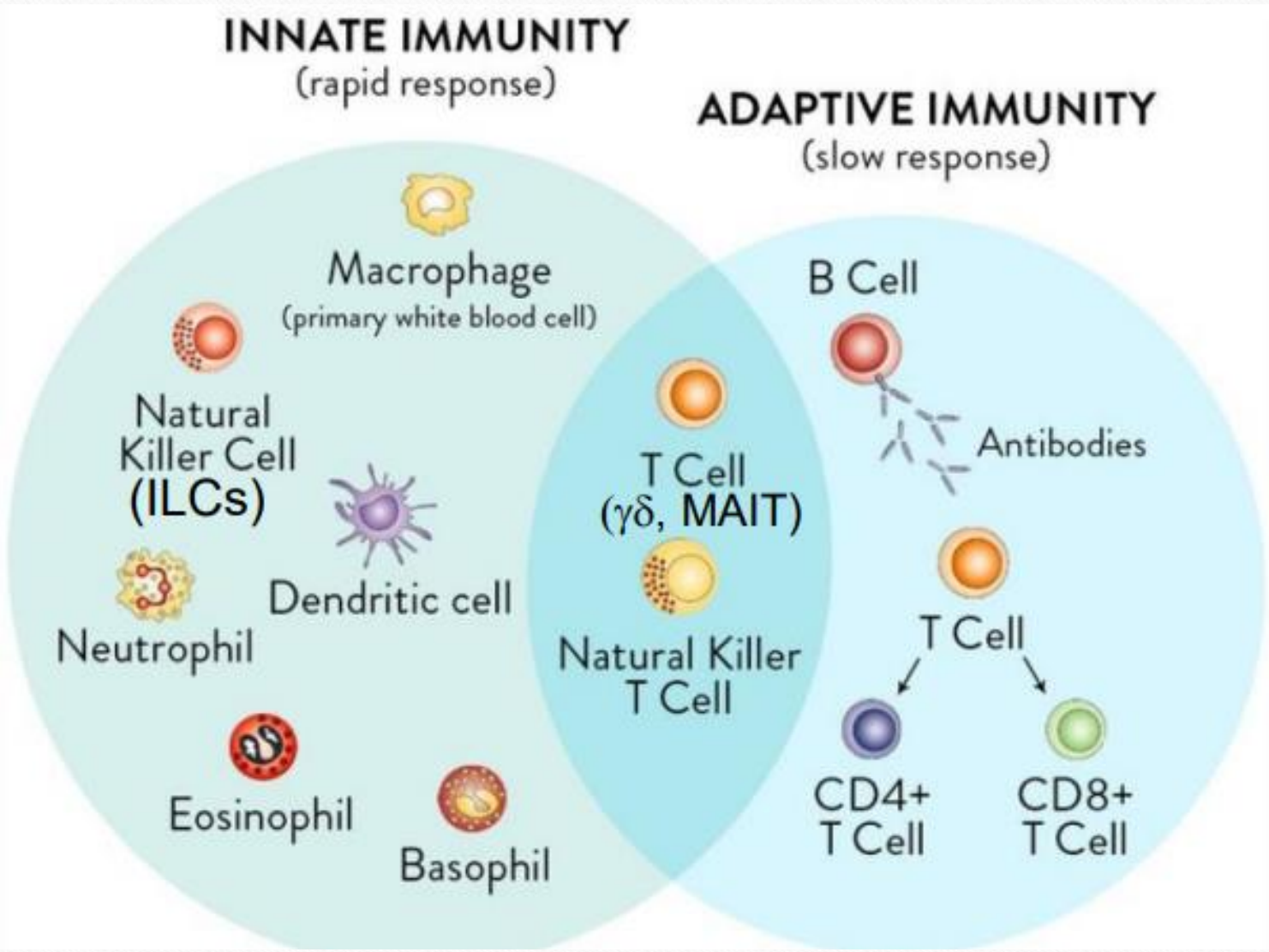
What is the source of oncogenes?

- Mutation of a normal gene = change in DNA sequence
- UV light, X-rays, natural or synthetic chemicals
- Virus (ex. HPV and cervical cancer by papilloma virus.)



ILCs –innate lymphoid cells

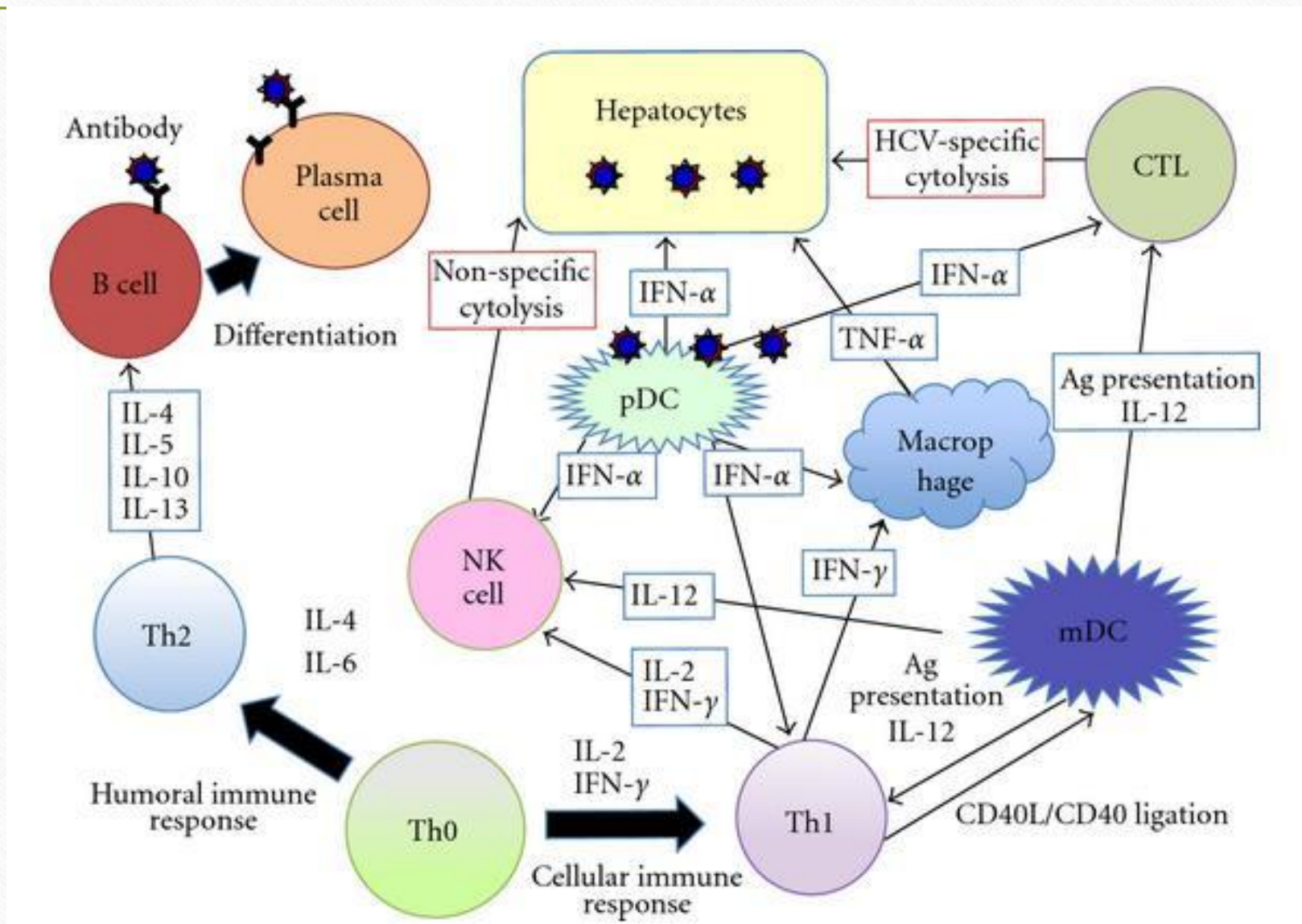
MAITs –Mucosal associated invariant T cells

γδ T cells – gamma delta T cells

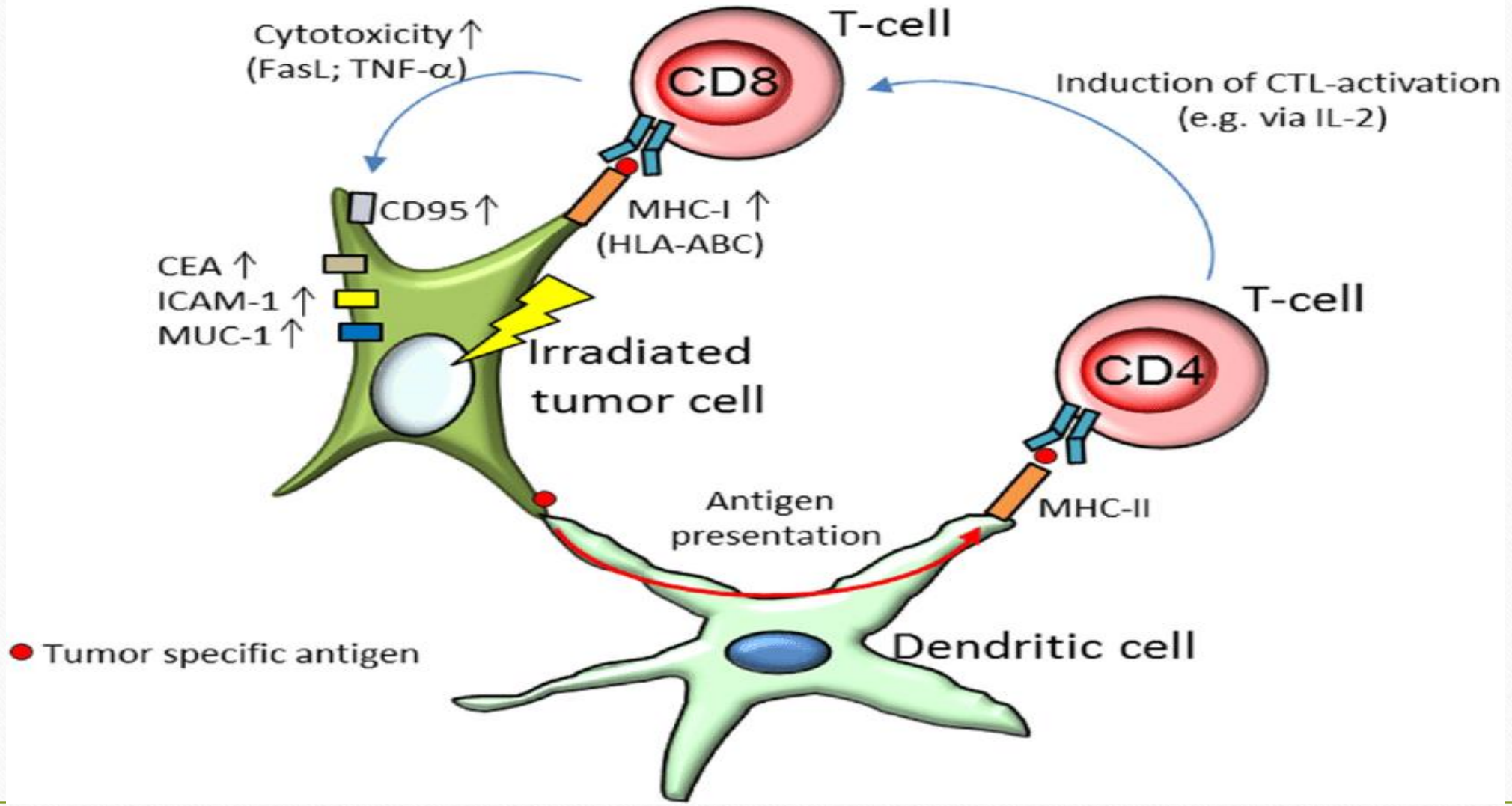
Immune response to tumor (immune surveillance)

- Cytotoxic T cells (CTL) are the **main** immune response.
  - Tumor cells ingested by APC and antigen presented by MHC1 (cross-presentation). and the stimulation of Tc by this MHC1 is (cross-priming).
  - Briefly, tumor cells infected with viral antigens present them to Tc. Activated Tc kills tumor cells and activates macrophages and other cells by IFN gamma and chemokines.
  - Th1 cell's role is in activating Tc and macrophages by secreting IFN gamma.

- Antibodies are less effective but mainly act in tumors caused by viruses that can be Killed by ADCC by NK. Or by complement activation.
- Cells that escape Tc (low MHC1) are killed by NK cells; secreting EZMs or ADCC.
- Lymphocytes in the presence of IL2(become lymphokine-activated killer cell, LAK) and have the ability to kill tumor cells escape NK cells.
- Macrophages; Stimulated by tumor-specific T cells, kill by respiratory burst metabolites or secreting TNF.


Antibody
Plasma cell
B cell
Differentiation
IL-4
IL-5
IL-10
IL-13
Th2
IL-4
IL-6
Humoral immune response
Th0
IL-2
IFN-γ
Cellular immune response
Hepatocytes
HCV-specific cytolysis
CTL
Non-specific cytolysis
IFN-α
IFN-α
TNF-α
pDC
Ag presentation
IL-12
IFN-α
IFN-α
Macrophage
NK cell
IL-12
IFN-γ
mDC
IL-2
IFN-γ
Ag presentation
IL-12
Th1
CD40L/CD40 ligation

CTL activation



Cancer- Immunity Cycle

Step 1 – Neoantigens are released by tumors and are captured by the antigen-presenting dendritic cells, which process the antigens to produce peptides that bind to (MHC).

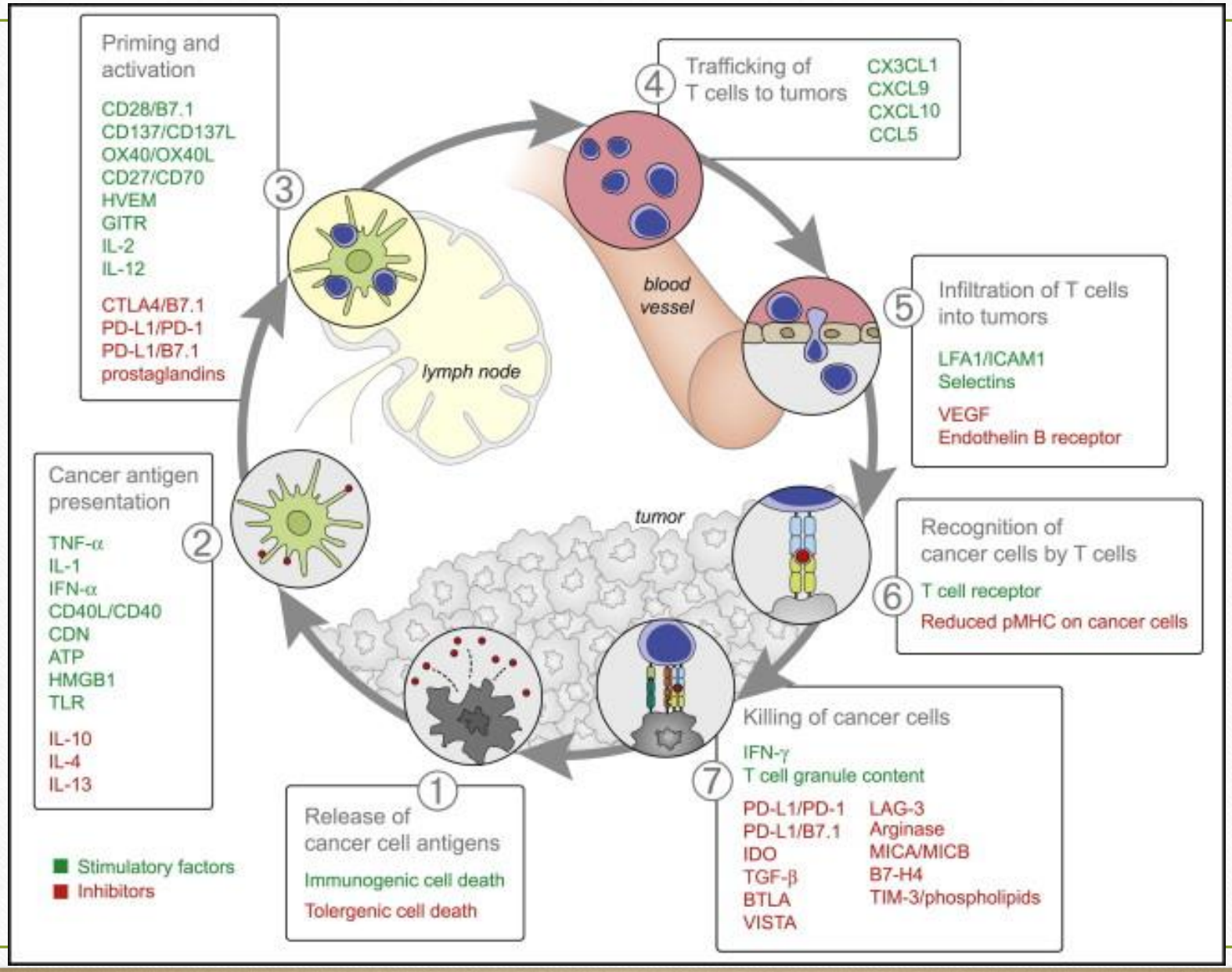
Step 2 – Peptides bound to MHC-I and MHC-II molecules are presented to T cells. $CD4^+$ T cell receptors can recognize the peptide-MHC-II molecules.

Step 3 – Effector T cells are primed and activated to respond to the tumor antigens presented. Three classes of antigens with high tumor specificity may be identified by T cells: antigens produced from mutated cells, cancer-germline genes and viral genes.

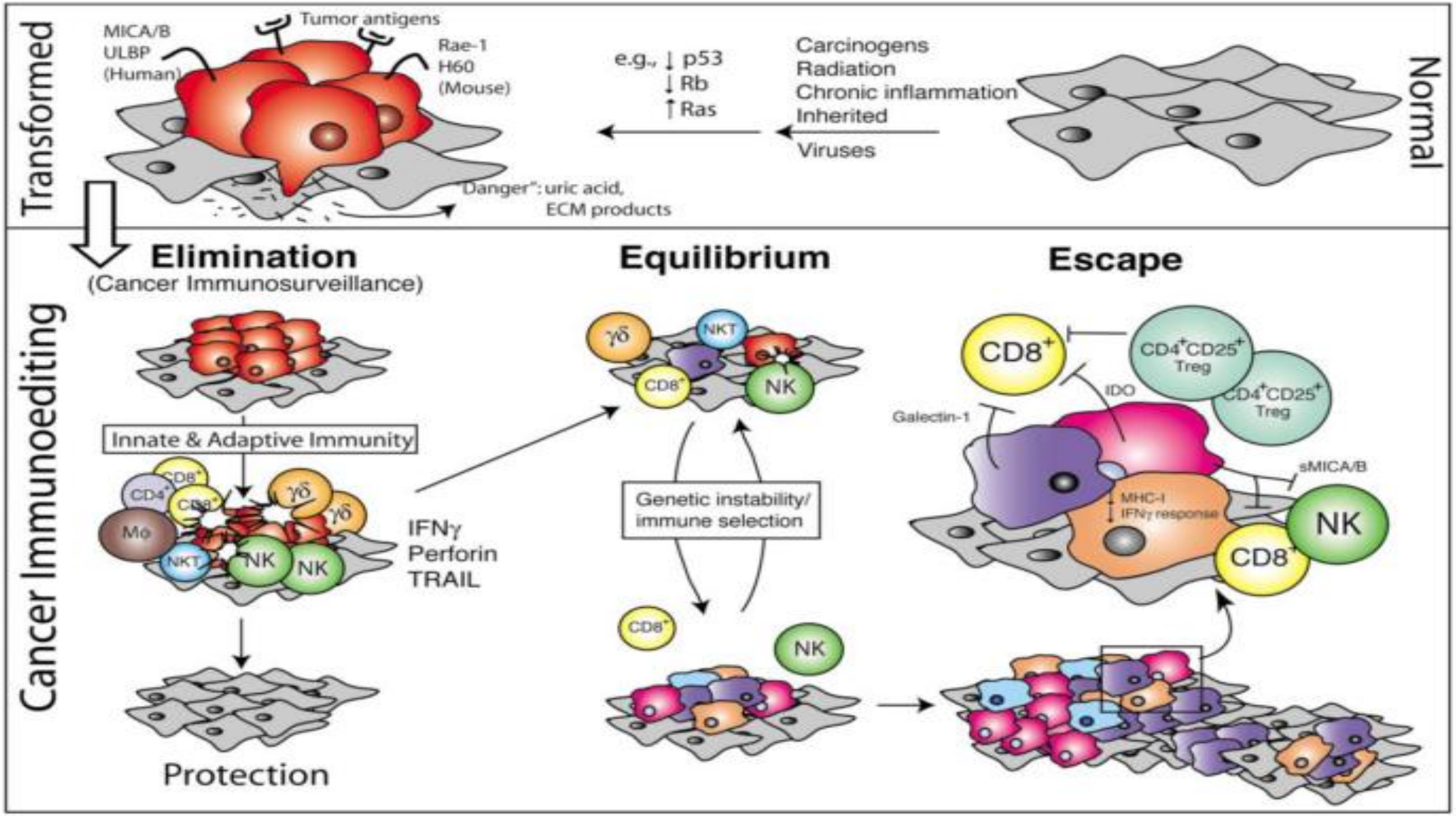
Step 4 – Activated T cells move to the tumor site and infiltrate the tumor.

Step 5 – Activated T cells bind to cancer cells. T cells are able to recognize cancer cells as foreign based on the antigens they released earlier, specifically binding to cancer cells through the interaction between the T-cell receptor and its cognate antigen bound to MHC-I on the surface of the cancer cells.

Step 6 – Activated T cells kill cancer cells. T cells eliminate cancer cells by activating a series of steps that lead to cell death. The dying cancer cell releases additional cancer-specific neoantigens (Step 1) to continue the cycle and amplify the anticancer response.


Priming and activation
CD28/B7.1
CD137/CD137L
OX40/OX40L
CD27/CD70
HVEM
GITR
IL-2
IL-12
CTLA4/B7.1
PD-L1/PD-1
PD-L1/B7.1
prostaglandins
3
4
Trafficking of T cells to tumors
CX3CL1
CXCL9
CXCL10
CCL5
blood vessel
lymph node
5
Infiltration of T cells into tumors
LFA1/ICAM1
Selectins
VEGF
Endothelin B receptor
Cancer antigen presentation
TNF-α
IL-1
IFN-α
CD40L/CD40
CDN
ATP
HMGB1
TLR
IL-10
IL-4
IL-13
2
tumor
6
Recognition of cancer cells by T cells
T cell receptor
Reduced pMHC on cancer cells
7
Killing of cancer cells
IFN-γ
T cell granule content
PD-L1/PD-1
PD-L1/B7.1
IDO
TGF-β
BTLA
VISTA
LAG-3
Arginase
MICA/MICB
B7-H4
TIM-3/phospholipids
1
Release of cancer cell antigens
Immunogenic cell death
Tolergenic cell death
Stimulatory factors
Inhibitors

Three Phases of the Cancer Immunoediting Process



Tumor-Specific Antigens	Tumor-Associated Antigens
Expressed by tumor cells	Self-antigens expressed by tumor cells
Not present in normal host cells	Present in a subset of normal host cells
Arise mostly from oncogenic driver mutations that generate novel peptide sequences (i.e. neoantigens)	Arise mostly from genetic amplification or post-translational modifications
Can also be generated by oncoviruses	Tendency for expression that is higher and preferential for tumor cells
Example: Alphafetoprotein (AFP) expression in germ cell tumors and hepatocellular carcinoma	**Example:** Melanoma-associated antigen (MAGE) expressed in the testis along with malignant melanoma

Tumor antigens

- **classification**
  - Deregulated normal antigen
  - Foreign antigens as viral origin
  - Re-expression of normal fetal antigen
  - Cell Type-Specific Differentiation Antigens

Deregulated normal antigens

1. Genetic mutation of normal cellular gene. Examples are tumor suppressor genes. The resulting protein product not found in normal cells, examples; P53, RAS proteins. expression of abnormal type as mucin (MUC-1) in breast carcinoma,
2. Abnormally located and over-expressed normal cellular proteins
   - Abnormal in site, MAGE (melanoma antigen) is normal silent antigen on testis but also in carcinoma of breast, lung and bladder
   - Tyrosinase protein normally expressed in small amount in melanocytes, over expressed in melanoma

foreign antigen

- Oncogenic viruses;
  - antigens expressed by cells infected with some DNA viruses, such as
    - human papilloma viruses (E6 and E7 proteins — a risk factor for cervical cancer
    - KSHV (***Kaposi's*** sarcoma-associated herpesvirus ***)*** , the virus that can cause Kaposi's sarcoma
    - Epstein-Barr virus (EBV) — EBNA-1 protein. predisposes to Burkitt's lymphoma
    - hepatitis B — predisposes to liver cancer
  - RNA viruses, retrovirus (HTLV-1) in T cell leukemia.

Oncofetal antigens

- Oncofetal antigens, present during fetal development but lost during adult life. Reappear with cancer
  - Alpha feto proteins in hepatic carcinoma
  - Carcino-embryonic antigen (CEA)in cancer of intestine (colon, pancreas and stomach).
- Cell type specific differentiation antigens, present in different tumors derived from the same cell origin, CD10 and CD20 in B cell derived tumors.

Evasion of immune system

1. Tumor cells express little antigens cause little immune response, while those caused by virus oncogene cause more effective immune response.

2. Very rapid tumor spread.

3. MHC 1 down regulation that can not be recognized by CTL

- The products of tumor cells suppress the anti-tumor immune response as TGF beta, fasL and the involvement of CTLA-4 or PD-1, T reg.

4. Hidden tumor surface antigens under cover.

5. Myeloid-derived suppressor cells (MDSCs) are a heterogeneous collection of cell types, including precursors of dendritic cells, monocytes, and neutrophils.

- Recruited to tumors and suppress anti-tumor innate and T cell responses.

6. M2 cells are macrophage confined to tumors and promote tumor angiogenesis which favors tumor growth.

Immunotherapy

- Or biologic therapy

1. Augment the host immune response against tumor (active therapy)
2. transfer tumor-specific antibodies or T cells (passive therapy)
3. Treatment with cytokines.

Active therapy, vaccination

- Vaccination with killed tumor cells or tumor antigens with adjuvants.
- Most of them are therapeutic except viral vaccine in tumor caused by virus; it is preventive as HPV in cervical carcinoma

1-DNA vaccine contains Tumor gene.

2-Vaccination with killed tumor cells in to host DC (*in vitro*) then inject these cells back to the host. Adjuvant cytokines are used.

3- Tumor antigens vaccine with adjuvants as cytokine (IFN gamma, IL-12, IL-2) or accessory molecule as B7.

4- Injection of polyclonal lymphocytes activator at site of tumor growth as BCG vaccine or anti-CD3 antibody.

5- anti-idiotype antibodies

Mouse immunized with antigen, select the antibody produced, re-inject the antibody in other mouse to form anti-idiotype for that antibody; the anti-idiotype resembles antigen in shape. Then use this anti-idiotype as vaccine (it resemble antigen).

Passive immunotherapy

-Transfer of immune-effective T cells or antibodies.
Adoptive cell transfer.
-Tumor-infiltrating lymphocytes (TIL) from similar patients, or lymphokine-activated killer(LAK) (T cells culture with IL-2 and tumor antigen), is re-transferred to the patient. As in prostate cancer Inject T cells carry receptors specific for cancer antigens called chimeric antigen receptor.

Cytokine treatment

- Interleukin-2 and interferon-α are examples of cytokines, proteins that regulate and coordinate the behavior of the immune system against the tumor.
  - Interferon-α is used in the treatment of hairy-cell leukemia, AIDS-related Kaposi's sarcoma,
  - Interleukin-2 is used in the treatment of malignant melanoma and renal cell carcinoma.

Block inhibitory pathways

- Block CTLA-4 in melanoma
- Block PD1 in advanced cancers
- Complications; autoimmunity and inflammation
- Using BCG at site of cancer activate T cells against tumor as in bladder cancer

Therapies that Might Affect the Cancer-Immunity Cycle