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.)

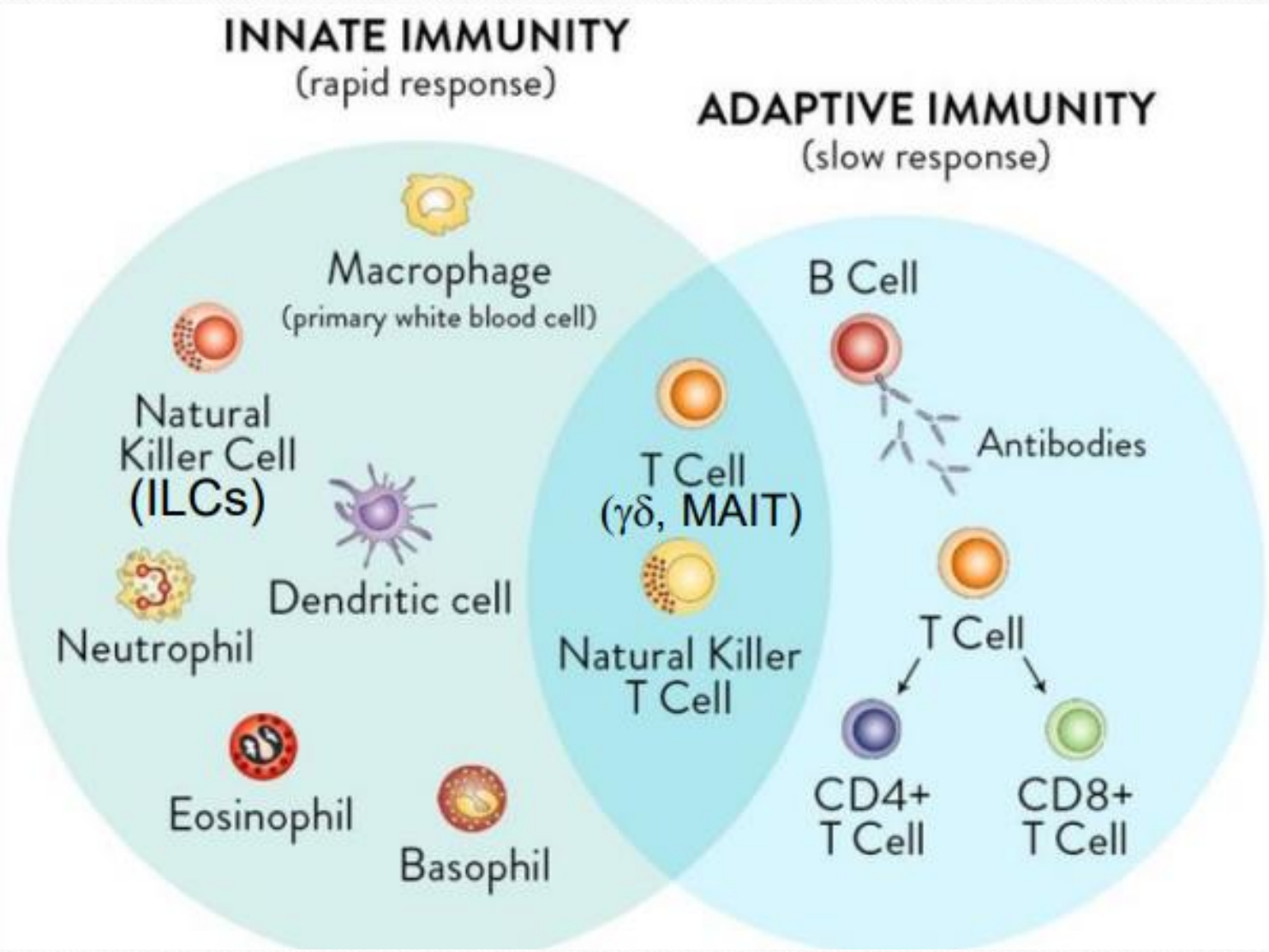
Immune response to tumor (immune surveillance)

- Is daily continuous screening of all body cells by immune system to recognize and destroy tumor cells.
- The main cells involved in immune surveillance are:

1. Macrophage
2. NK cells
3. Cytotoxic T- cells
   - Tumor cells presented Ags by MCH I and thus will be recognized by immune surveillance cells.

What are the evidences on the immune system role against tumor cells?

1. Immunosuppressed patients (ADIS), depression in T-Helper cells. E.g: Kaposi sarcoma by weak virus A.
2. Age people (young, old).
3. Abs and T- lymphocytes cells detected in tumors.
4. Immunization against some tumor. E.g: vaccine against HBV reduce Hepatocellular carcinoma.



ILCs –innate lymphoid cells

MAITs –Mucosal associated invariant T cells

γδ T cells – gamma delta T cells

Tumor antigens

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

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 trace amount of normal cells
Arise mostly from oncogenic driver mutations (e.g: P53)that generate novel peptide sequences (i.e. neoantigens)	Arise mostly from genetic amplification or post-translational modifications
Can also be generated by oncoviruses (HBV and HPV)	Tendency for expression that is higher and preferential for tumor cells
	Example: -Oncofetal Ags (AFP, CEA) - HER2 in normal cells and overexpression on breast cancer.

Cancer- Immunity Cycle

Step 1 FIRST SIGNAL – 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 1).

Step 2 – Peptides bound to MHC-I and MHC-II molecules (APC) 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 by second signal.

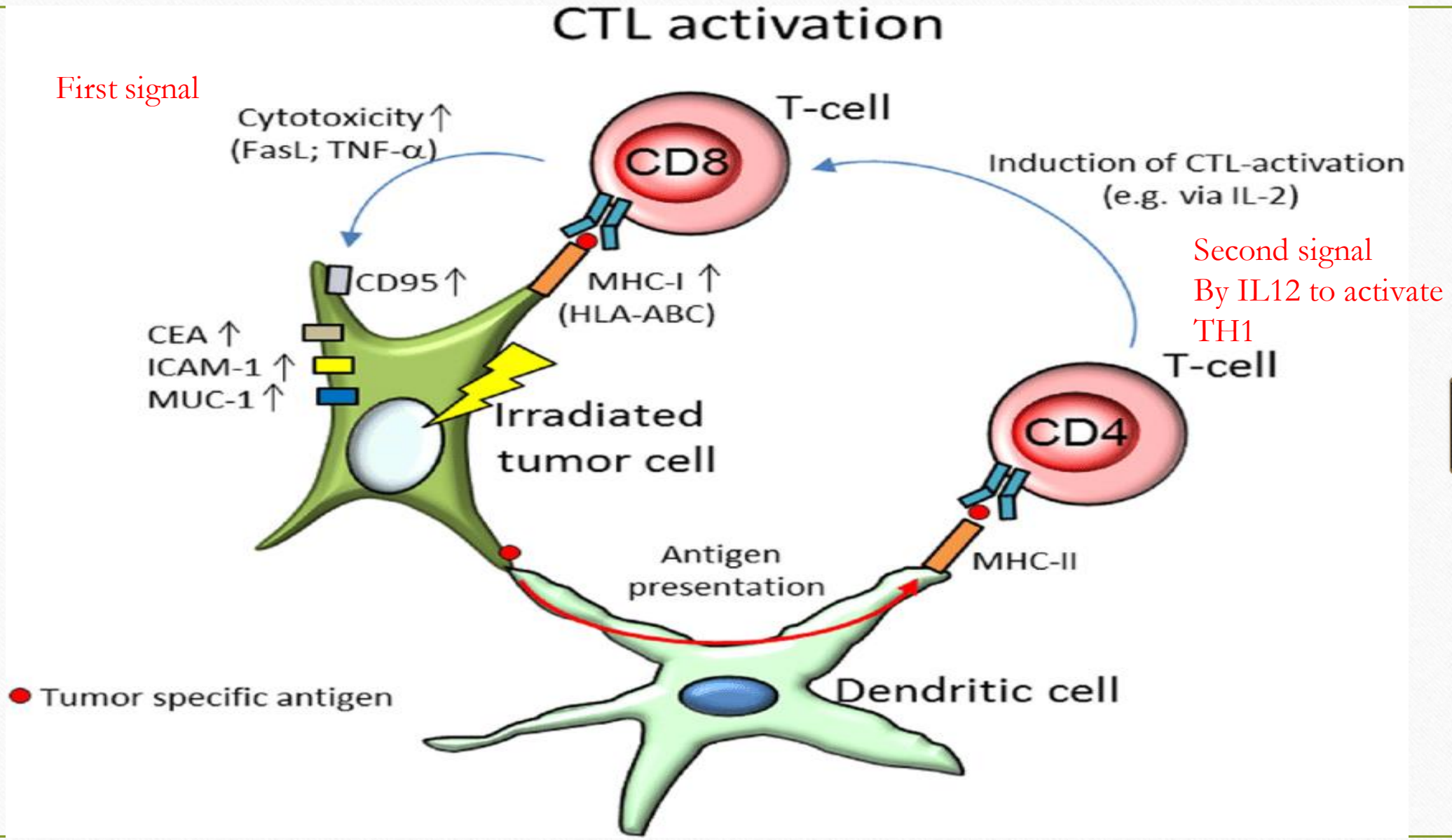
TH1 release cytokines: by IL 12

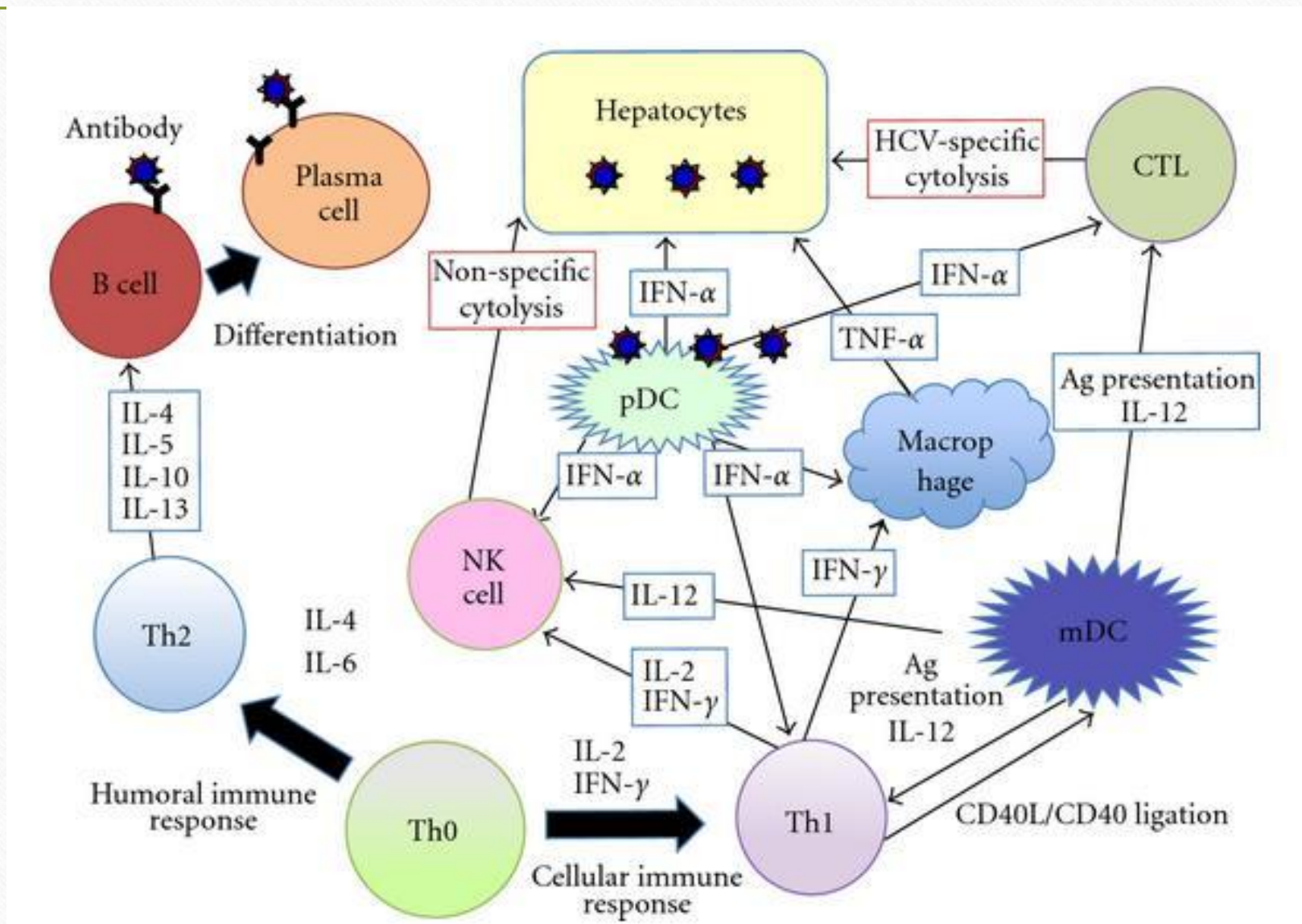
- IL2 activation Cytotoxic T- cells and direct attack tumor cells
- IFN gamma activation macrophages (which increase presenting Ags and have a role direct cytotoxic against target cells and release TNF) and activation NK cells.
- TNF direct attack tumor cells.

Lymphocytes in the presence of IL2(become lymphokine-activated killer cell, LAK) and have the ability to kill tumor cells escape NK cells.

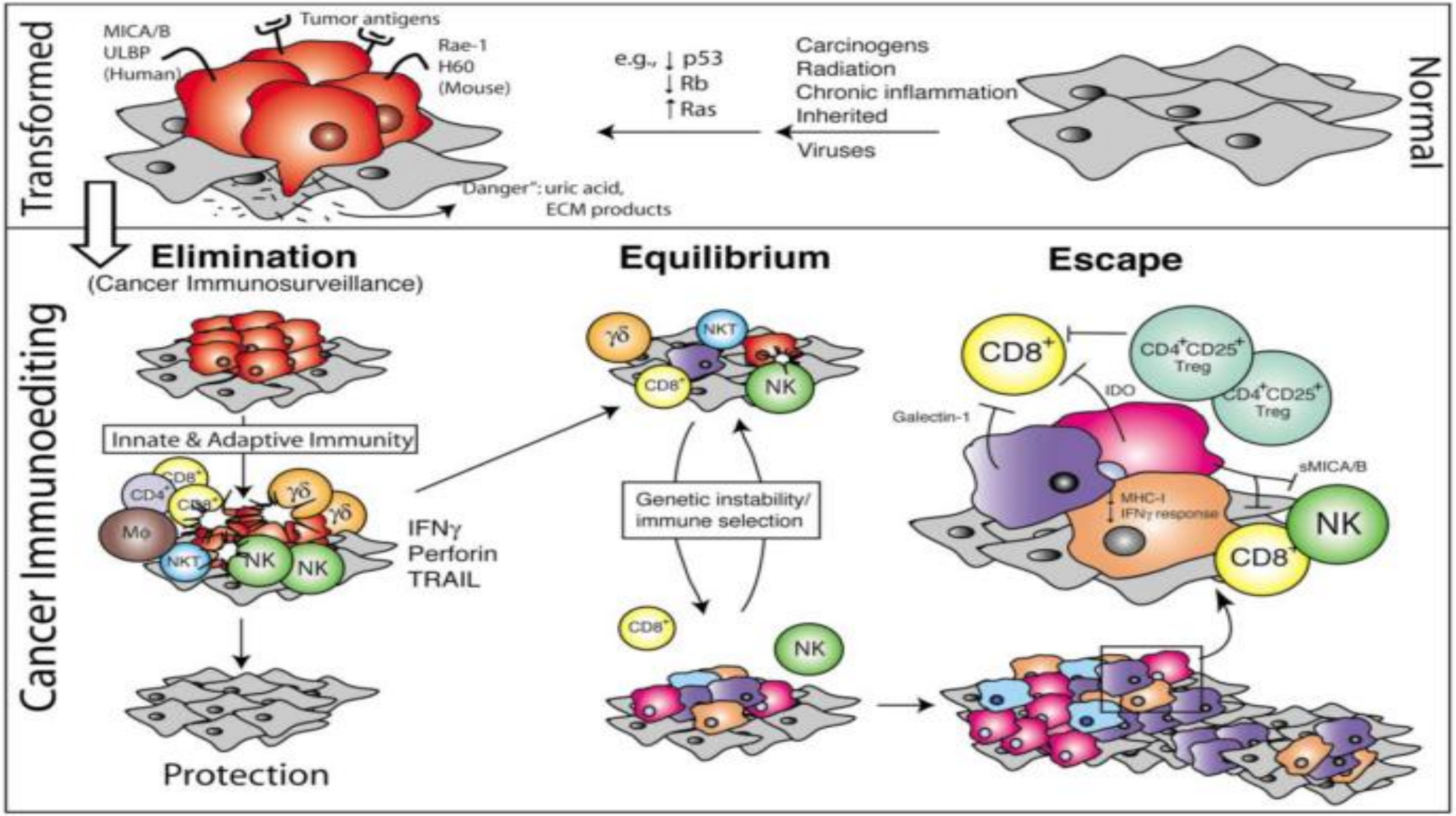
TH2 mediated by MHCII: release cytokines BCGF, BCDF

- Proliferation B- cells and differentiation plasma cells to produce Abs to make opsonization, ADCC, and complement activation.


CTL activation
First signal
Cytotoxicity ↑
(FasL; TNF-α)
T-cell
CD8
Induction of CTL-activation
(e.g. via IL-2)
Second signal
By IL12 to activate
TH1
CD95 ↑
MHC-I ↑
(HLA-ABC)
CEA ↑
ICAM-1 ↑
MUC-1 ↑
Irradiated
tumor cell
T-cell
CD4
Antigen
presentation
MHC-II
Tumor specific antigen
Dendritic cell


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

Three Phases of the Cancer Immunoediting Process



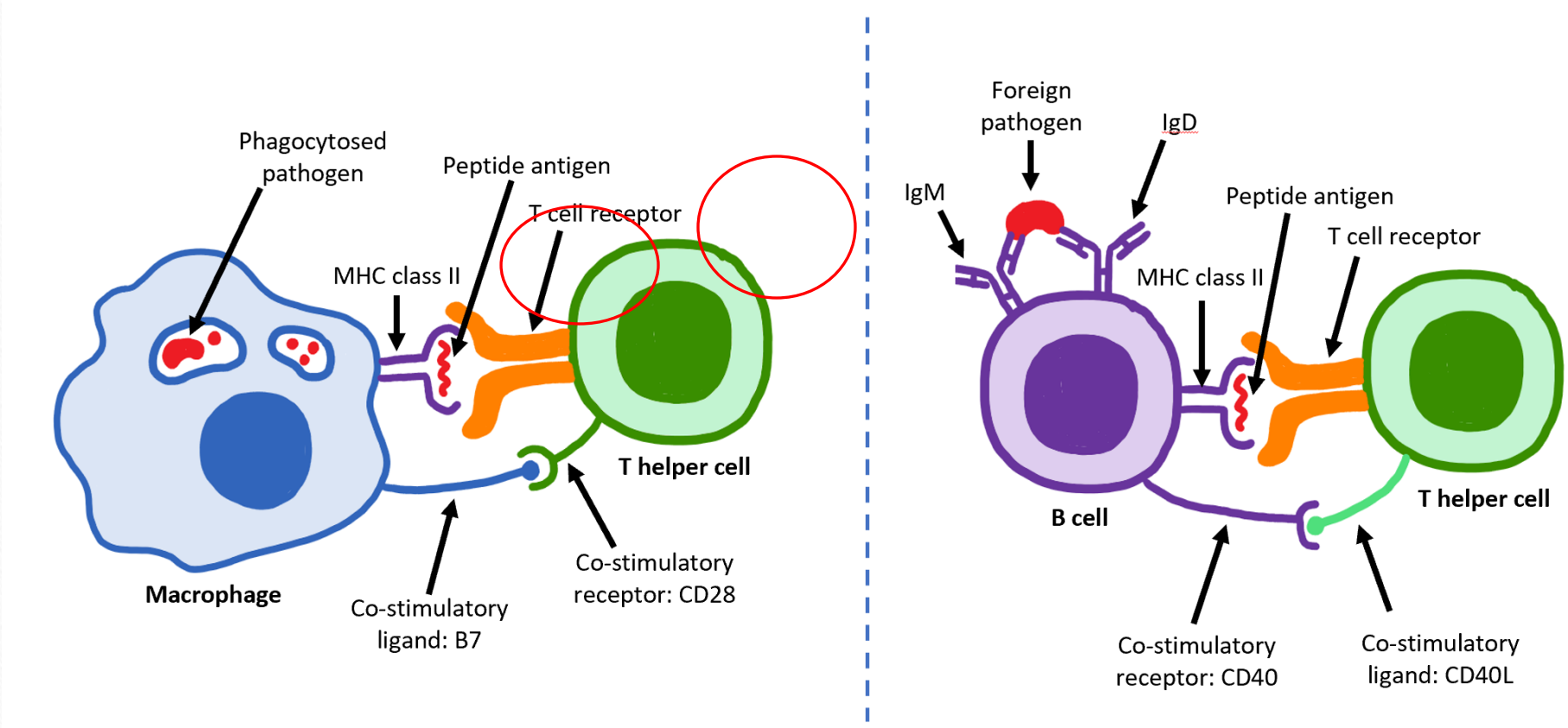
Evasion of immune system

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
4. The products of tumor cells suppress the anti-tumor immune response as Transforming growth factor (TGF beta) which inhibition proliferation of lymphocytes and macrophage.

5. Increase T reg of immune system, which mean suppression of immune system by inhibit T cell response.
6. Tumor cells express Fas Ligand that bind to Fas receptor on Tc and destroyed it.
7. Tumor cells express too small Ags called (sneaking through) or lack Ags.
8. Hidden tumor surface antigens under cover by immune system that make fibrin to avoid the spread of tumor.
9. Antigenic shedding by tumor cells.
10. Antibodies Blocking through Fc regions and become nonfunctional.

11. Lack of co-stimulation

That is precursor to initiate signal 1 and 2. Tumor cells block the gene of B7 expression



12. 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.

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

Immunotherapy

- Specific include (

A. Passive (Humoral, Cellular, and Combined)

B. Active (Tumor vaccine).

- Non specific like vaccine BCG on the tumor site led to increase cell mediate immunity.

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 or (*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.
Or called Adoptive cell transfer.
-Tumor-infiltrating lymphocytes (TIL) from patient to activate Tc,
-Or (NK cells culture with IL-2 for 3 days), lymphokine-activated killer cells (LAK)is re-transferred to the patient. As in prostate cancer Inject T cells carry receptors specific for cancer antigens called chimeric antigen receptor.
Note: the role of IL2 activation NK cells and Tc

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.
- Using BCG at site of cancer activate T cells against tumor as in bladder cancer.