NEOPLASIA : 7
TUMOR IMMUNITY

DR. FALGUNI R. SHAH,
Professor of Pathology, Smt. NHL MMC

Definition

Coordinated biologic process designed to recognize tumor cells and their products and to kill or damage them

Cancer immunoediting- effect of immune system in preventing tumor formation & select tumor cells that escape immune elimination

Host Defense Against Tumor
Tumor Immunity

- Tumor Specific Antigens (TSA)

Present only on tumor cells and not on any normal cells and can be recognized by cytotoxic T-lymphocytes.

- Tumor Associated Antigens (TAA)

Not unique to tumors and are also present on normal cells.

Tumor Antigens

- Tumor Specific Antigens (TSA)
- Cancer testis antigen
- Viral antigen
- Mucin
- Oncofetal antigens
- Antigens resulting from mutational in protein

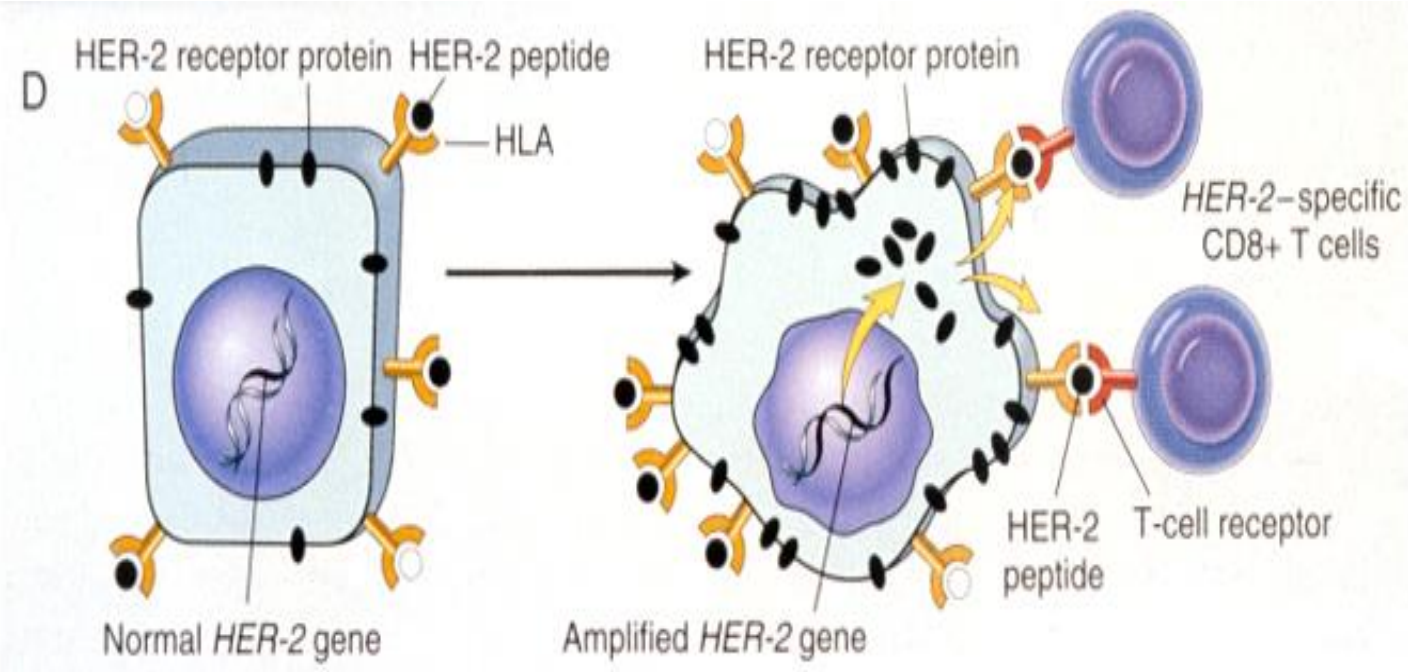
B catenin, *RAS*, *P53*,*CDK4*

Tumor Associated Antigens(TAA)

- Over expressed Antigens

e.g HER-2 (neu) in 30 % Breast cancer

(present in normal breast & ovary)


D
HER-2 receptor protein
HER-2 peptide
HLA
HER-2 receptor protein
HER-2–specific
CD8+ T cells
HER-2
peptide
T-cell receptor
Normal HER-2 gene
Amplified HER-2 gene

- Specific Antigens

e.g CD10& PSA

Expressed in normal B cells & Prostate

Used as a marker for tumors arise from these cells

Modern classification based on molecular structure and source

- Products of mutated oncogenes & tumor suppressor genes

-Synthesized in cytoplasm of tumor cells

-Recognized by CD+8 &CD4+ T cells

-p53,RAS, BCR-ABL

- Products of other mutated genes

-chemical carcinogen or radiation induced tumors

-many cellular genes mutated which products not related to transformed phenotype & have no known function

Overexpressed cellular proteins

-Melanoma –tyrosinase, enzyme involved in melanin biosynthesis produced at low levels in normal cells

Tyrosinase vaccine useful for melanoma therapy on trial

Melanoma antigen(MAGE) not expressed in normal tissue but expressed only early during development and are dysregulated due to malignant transformation

MAGE proteins also expressed in bladder, breast, skin, lung, prostate & some sarcoma

Cancer testis antigens-GAGE,BAGE & RAGE silent in normal tissue except in testis expressed in variety of malignant tumors

- Tumor antigens produced by oncogenic viruses

-produced by DNA viruses- HPV & EBV

-Immune system recognize and kill virus infected cells

- Oncofetal antigens

-expressed high levels in cancer cells & in fetus but not adult tissue

-Alpha fetoprotein(AFP) in hepatocellular carcinoma &nonseminomatous testicular tumors

-Carcinoembryonic antigen(CEA) in carcinomas of colon, pancreas, lung, stomach & heart

- Altered cell-surface Glycolipids and Glycoproteins

-Gangliosides, blood group antigens & mucins

-as diagnostic markers & targets for therapy

-Glycolipids- e.g. Gangliosides Gm2,GD2 & GD3 in melanoma

-Mucins –high mol. wt. Glycoproteins

e.g. CA-125 & CA-19 in ovarian carcinoma

MUC-1 in breast carcinoma

- Cell type-specific differentiation antigens

-normally present on cells of origin

-CD10(CALLA) & CD20- B cell derived tumors

Antitumor effector mechanism

- Cellular

Cytotoxic T lymphocytes.

Natural killer cells.

Macrophages.

- Humoral mechanisms-

complement mediated or ADCC.

Mechanisms of immunity to tumors

Cytotoxic T lymphocytes (CTL) - that are sensitized to tumor specific antigens and kill tumor cells. Play a role in virus induced malignancy

Natural Killer (NK) cells - can attack tumor cells directly without antibody coating or by Antibody Dependent Cell Cytotoxicity (ADCC) utilizing the Fc receptor on the NK cells, effective against cells with reduced MHC expression

Macrophages - activated by IFN-g elaborated by Helper T lymphocytes. Participate in ADCC and can kill tumor cells through release of TNF-a.

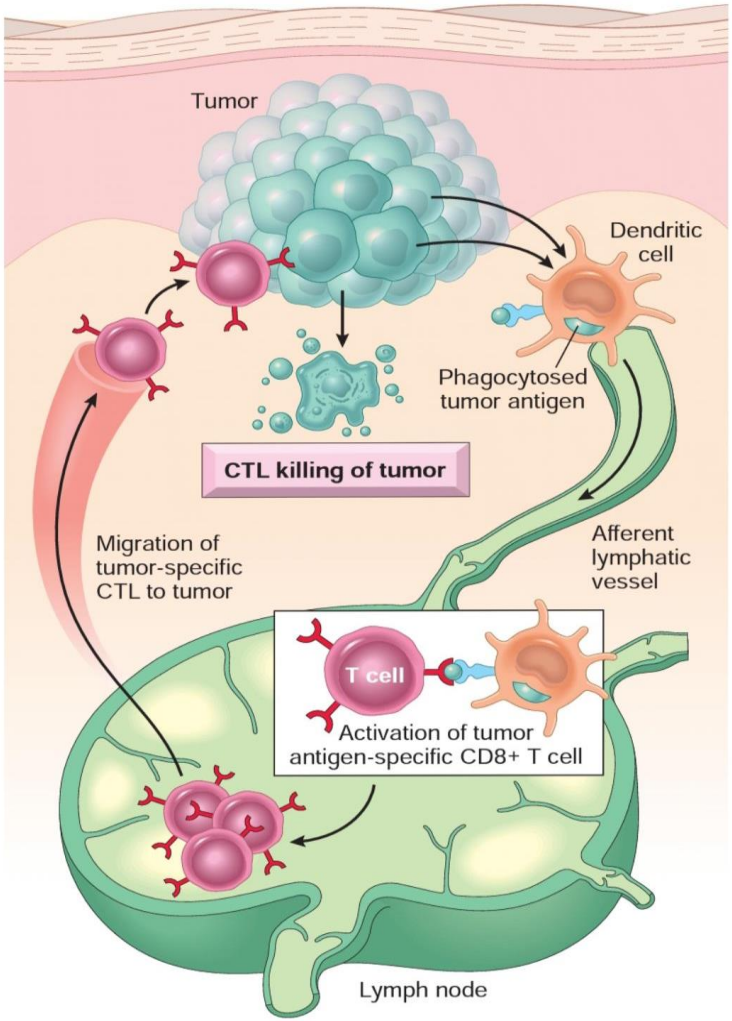


Figure 7.37 Cross-presentation of tumor antigens and induction of CD8+ cytotoxic T cell antitumor response. (Modified from Abbas AK, Lichtman AH: *Cellular and Molecular Immunology*, ed 8, Philadelphia, 2017, Elsevier.)

Figure courtesy reference : Robbins & Cotran, Pathologic Basis of Disease, Edition 10th

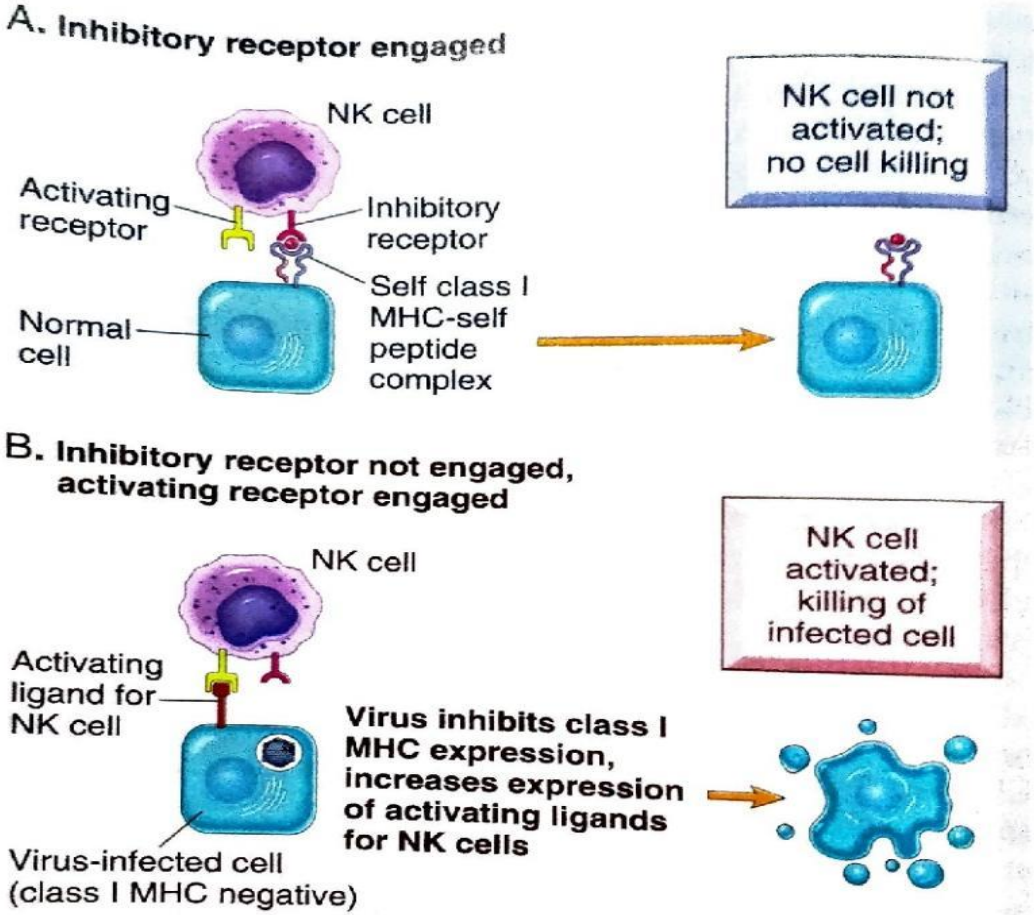
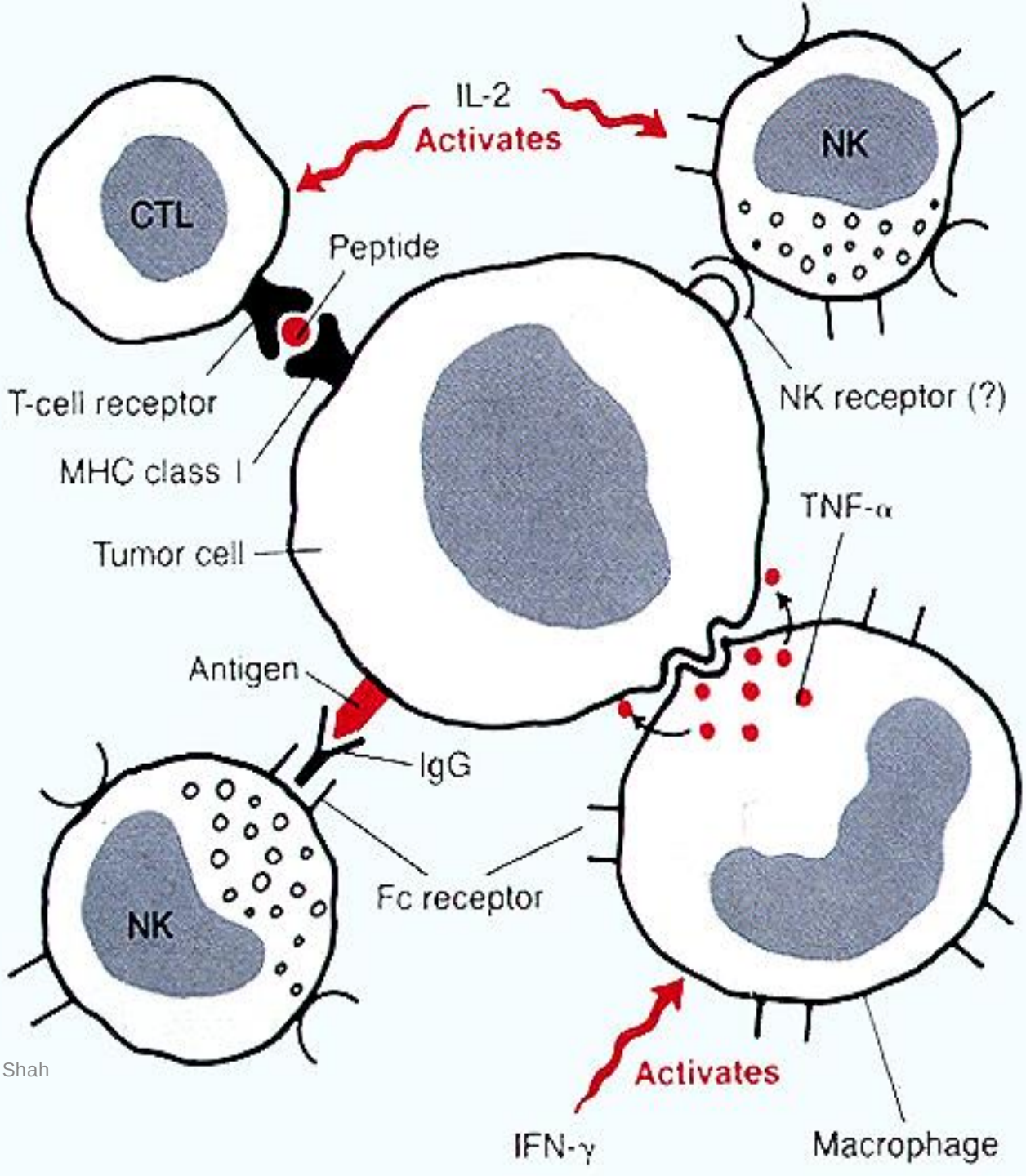


Figure 6-7 Activating and inhibitory receptors of natural killer (NK) cells. **A,** Healthy cells express self class I MHC molecules, which are recognized by inhibitory receptors, thus ensuring that NK cells do not attack normal cells. Note that healthy cells may express ligands for activating receptors (not shown) or may not express such ligands (as shown), but they do not activate NK cells because they engage the inhibitory receptors. **B,** In infected and stressed cells, class I MHC expression is reduced so that the inhibitory receptors are not engaged, and ligands for activating receptors are expressed. The result is that NK cells are activated and the infected cells are killed.

Figure courtesy reference :
Robbins & Cotran,
Pathologic Basis of Disease,
South Asia Edition, 2017



Immune surveillance:

A constant monitoring process aimed at eliminating emerging cancers

Recognition and destruction of non-self tumor cells .

Evidence for Immune Response to Tumors

1) Infiltrate of lymphocytes and macrophages associated with better prognosis in many tumors.
2) Peripheral blood NK activity correlates with survival.

3) Peripheral blood lymphocytes counts fall as cancer overwhelms host; patients develop anergy to skin tests.

4) Non-specific vaccines can stimulate macrophages and improve prognosis. IFN-g and IL-2 can stimulate NK cells and improve outcome.

5) High incidence of some tumors in immunosuppressed individuals.

6) Spontaneous regression in some tumors.

Immunosurveillance

Sporadic cancers occur in immune competent people

HOW ???

- Escape mechanisms :

Growth of antigen-negative variants.

Loss or reduced expression of HLA .

No expression of costimulatory molecule .

Immunosuppression

Antigen masking

Apoptosis of cytotoxic T cells

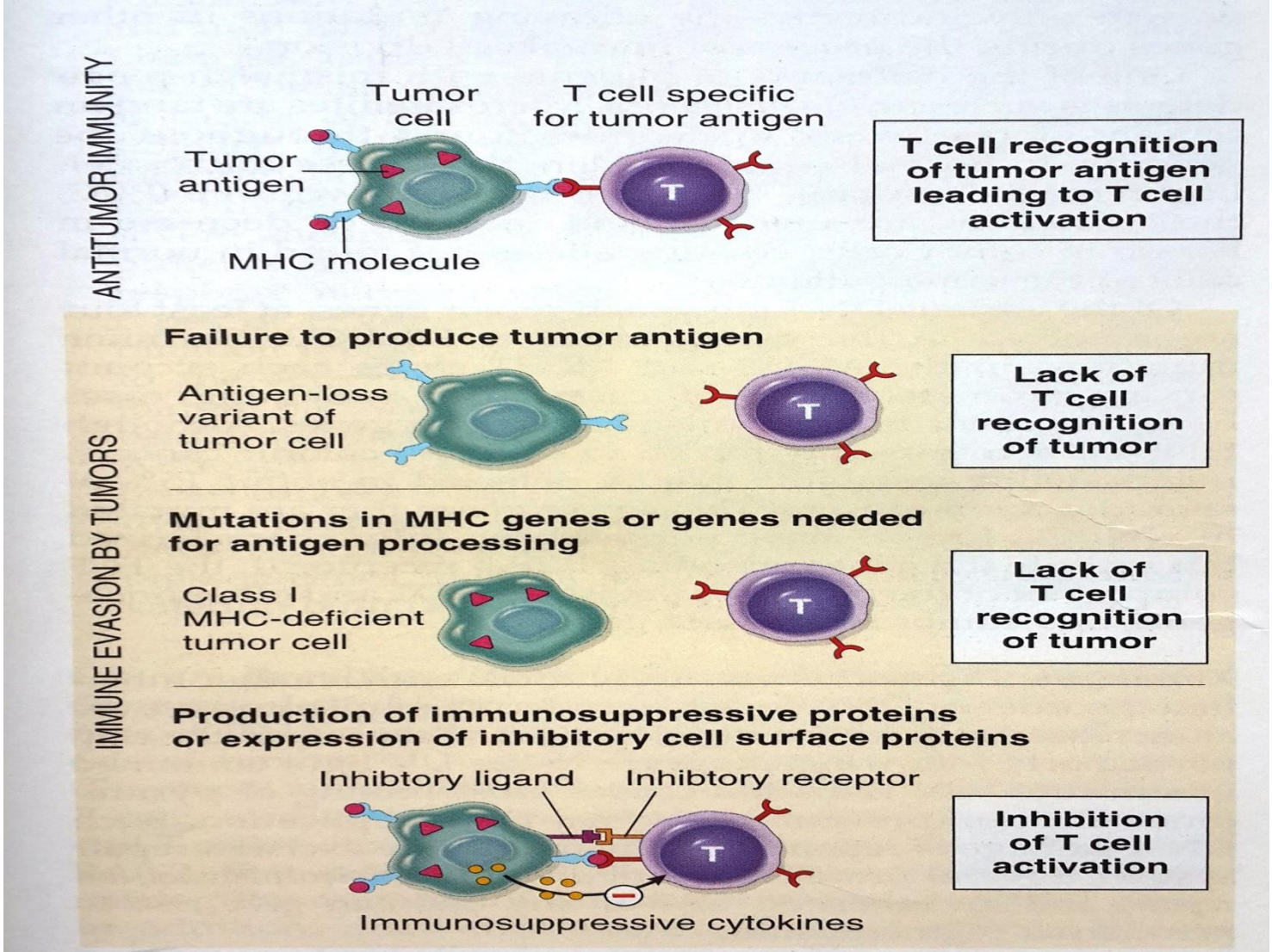


Figure 7-40 Mechanisms by which tumors evade the immune system. Tumors may evade immune responses by losing expression of antigens or major histocompatibility complex (MHC) molecules or by producing immunosuppressive cytokines or ligands such as PD-L1 for inhibitory receptors on T cells. (Reprinted from Abbas AK, Lichtman AH, Pillai S: Cellular and Molecular Immunology, 7th ed. Philadelphia, WB Saunders, 2012.)

Figure courtesy reference : Robbins & Cotran, Pathologic Basis of Disease, South Asia Edition, 2017