

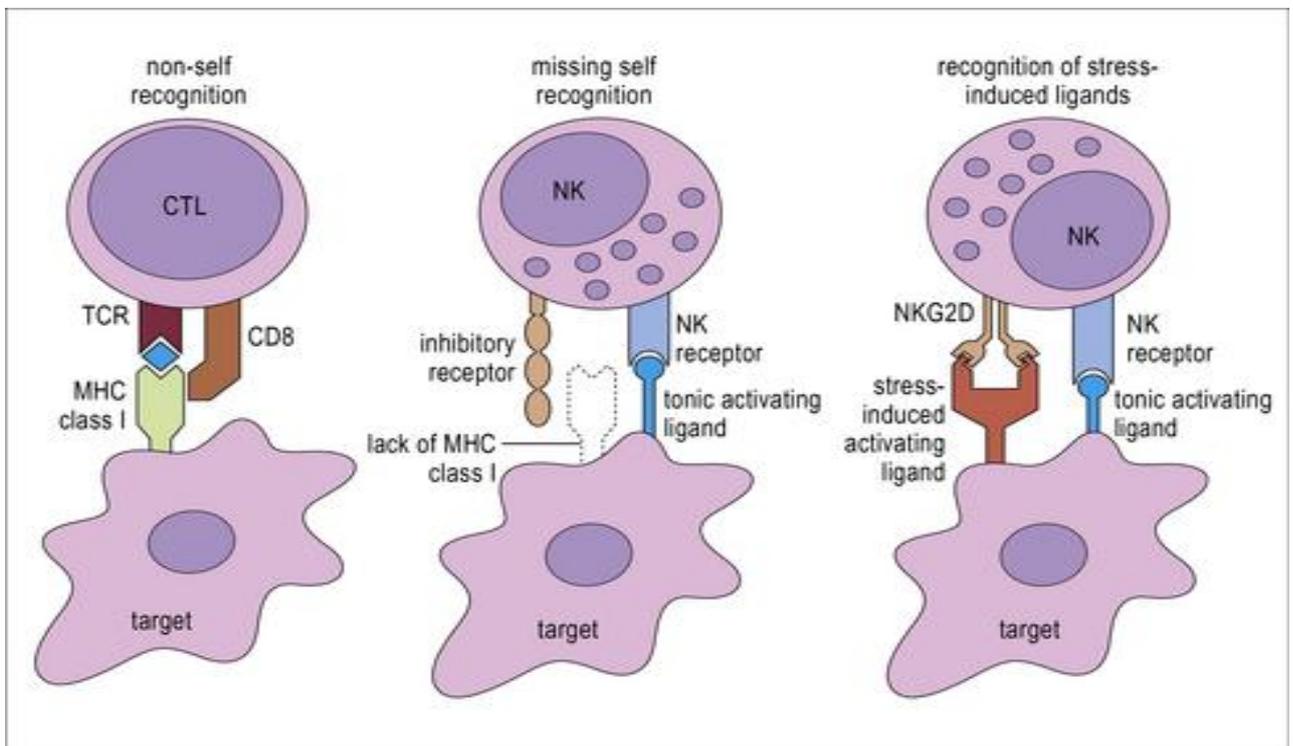
# CELL-MEDIATED CYTOTOXICITY (CMC)

## 1. Meaning

- It means **killing of abnormal body cells** (like virus-infected or cancer cells) by **immune cells**.
- It is a part of **cell-mediated immunity** (not antibody-based).
- The killing is done by **T cells, NK cells, macrophages**, etc.

## 2. Main Types of Cytotoxic Cells

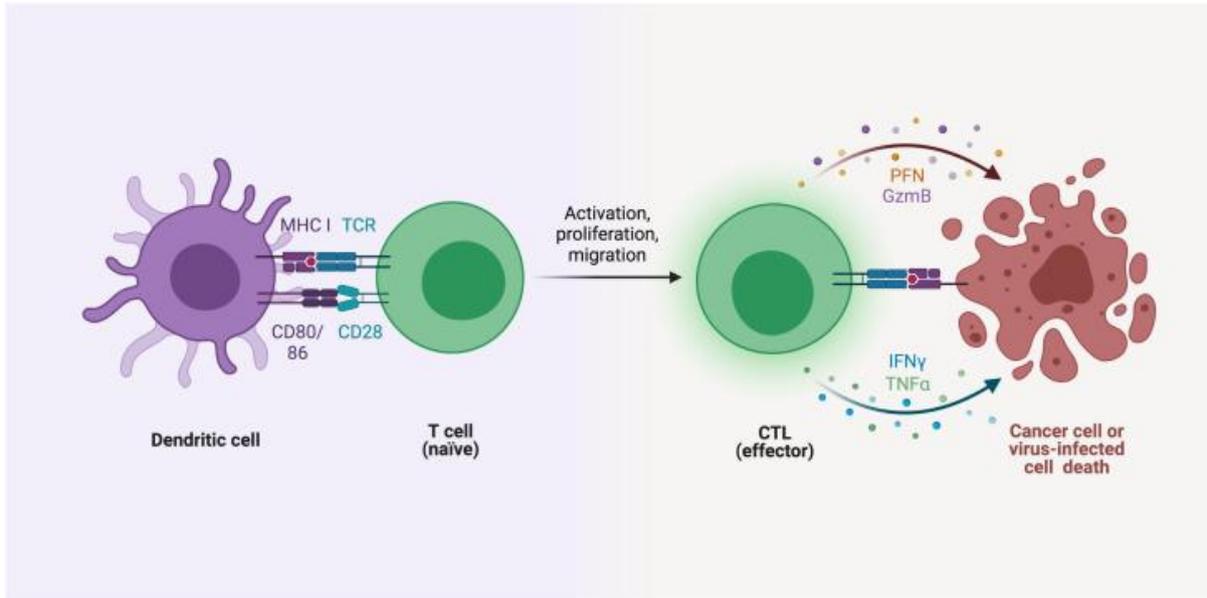
Effector Cell	Type of Immunity	Recognizes	Main Function
<b>Cytotoxic T cells (CD8<sup>+</sup>)</b>	Adaptive	Antigen with MHC I	Kill infected/tumor cells
<b>Natural Killer (NK) cells</b>	Innate	Lack of MHC I / stress ligands	Kill virus/tumor cells without prior exposure
<b>Macrophages</b>	Innate / Helper T-cell activated	Pathogen molecules / antibody-coated cells	Kill by toxic chemicals
<b>Eosinophils</b>	Innate	IgE-coated parasites	Kill parasites by toxic proteins



# A. T-Cell Mediated Cytotoxicity (Cytotoxic T Lymphocytes, CTLs)

## 1. Activation

- CD8<sup>+</sup> T cell is activated by:
  - **Antigen** presented on **MHC class I** (on infected or tumor cell).
  - **Co-stimulation** (CD28–B7 signal).
  - **IL-2** from helper T cells helps it multiply.
- After activation → becomes **Cytotoxic T Lymphocyte (CTL)**.



## 2. How CTLs Recognize Target Cells

- CTL binds to the target cell through:
  - **TCR** (recognizes antigen + MHC I)
  - **Adhesion molecules** (like LFA-1 and ICAM-1)
- Forms a tight contact area called the **immunological synapse**.

## 3. Mechanisms of Killing

### (i) Perforin–Granzyme Pathway

1. CTL releases tiny granules near the target.
2. **Perforin** makes small pores in the target cell membrane.
3. **Granzymes** (enzymes) enter through pores.
4. Granzymes activate **caspases** inside the cell → causes **apoptosis** (programmed cell death).
5. **Granulysin** also damages the target cell membrane and bacteria.

✓ **Result:** Target cell dies quietly (apoptosis), without inflammation.

### (ii) Fas–Fas Ligand Pathway

1. CTL has **Fas Ligand (FasL)** on its surface.

2. Target cell has **Fas (CD95)** receptor.
3. Binding of FasL to Fas triggers **caspase-8** → apoptosis.

✅ *Important for:* Killing self-reactive T cells and some tumor cells.

#### 4. After Killing

- CTL detaches and moves on to find another target.
- One CTL can kill **many** target cells.

## B. Natural Killer (NK) Cell Mediated Cytotoxicity

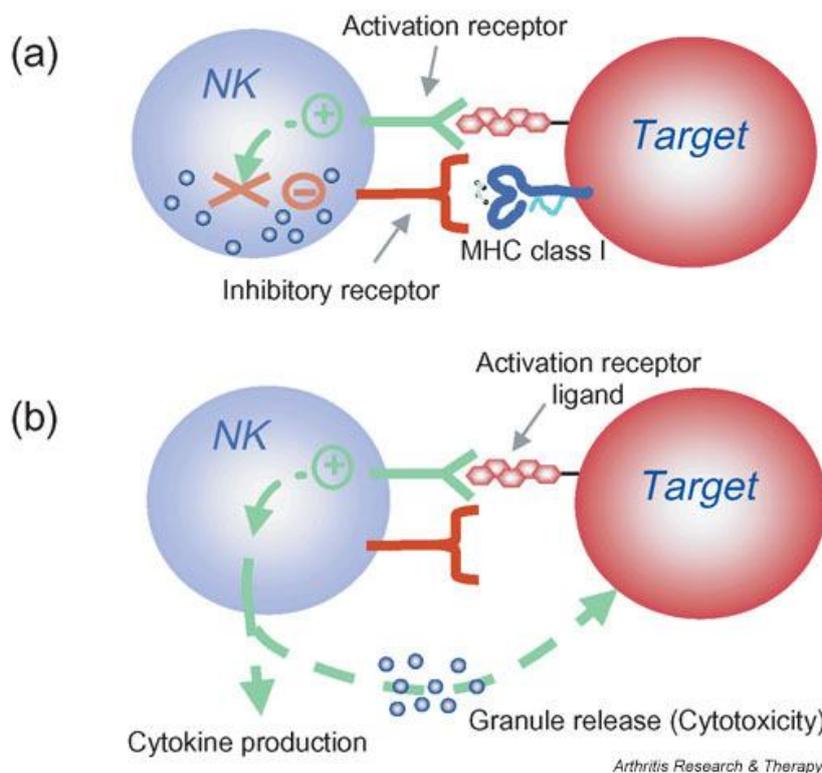
### 1. Basic Features

- NK cells are part of **innate immunity**.
- They kill **infected or tumor cells without needing prior exposure** or antigen presentation.
- Found in blood and spleen.

### 2. How NK Cells Decide to Kill

- They have two kinds of receptors:
  1. **Inhibitory receptors** – bind to **MHC class I** on normal cells → **stop killing**.
  2. **Activating receptors** – detect **stress signals or missing MHC I** → **start killing**.

✓ If MHC I is missing (as in virus/tumor cells) → NK cell attacks.



### 3. Methods of Killing

- **Perforin–Granzyme pathway** → apoptosis (same as CTLs).
- **Death receptor pathway (FasL or TRAIL)** → apoptosis.
- **Secrete cytokines (like IFN- $\gamma$ )** → activate macrophages and immune response.

### 4. Cytokines That Increase NK Cell Activity

- **IL-12, IL-15, IL-18, and Type I interferons (IFN- $\alpha$ , IFN- $\beta$ ).**

## C. Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC)

### 1. Meaning

- It is killing of a target cell that is **coated with antibodies**.
- The **effector cell** (like NK cell or macrophage) binds to the **Fc part** of the antibody and kills the target.

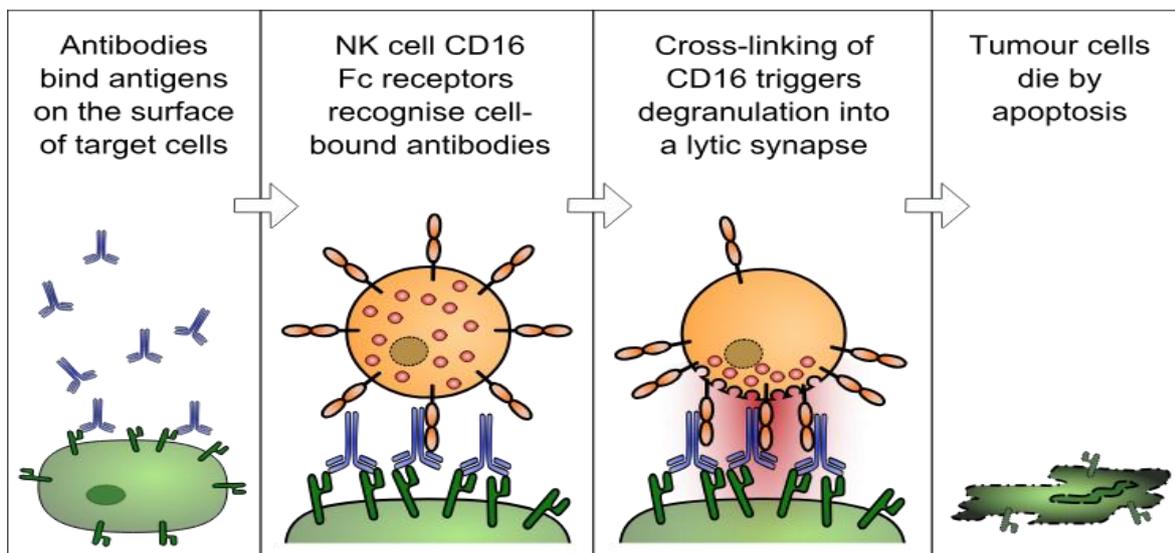
### 2. Steps in ADCC

1. **Antibody** (IgG or IgE) binds to the target cell.
2. **Effector cell** (NK, macrophage, neutrophil, or eosinophil) binds to the **Fc portion** of the antibody via its **Fc receptor**.
3. This activates the effector cell.
4. Effector cell releases **toxic molecules** → kills the target cell.

### 3. Examples of Effector Cells in ADCC

Effector Cell	Fc Receptor	Antibody Used	Function
NK cells	FcγRIII (CD16)	IgG	Perforin–granzyme killing
Macrophages	FcγRI / II	IgG	Release of ROS, NO, cytokines
Eosinophils	FcεRI	IgE	Kill parasites using major basic protein
Neutrophils	FcγRII / III	IgG	Release enzymes and ROS

✓ Used in monoclonal antibody therapies (e.g., rituximab, trastuzumab).



## D. Macrophage-Mediated Cytotoxicity

### 1. Activation of Macrophages

- Resting macrophages → weak killers.
- Become **activated** by:
  - **IFN- $\gamma$**  (from Th1 or NK cells)
  - **LPS** or bacterial products

### 2. Mechanisms of Killing

#### 1. Reactive Oxygen Species (ROS):

- Superoxide, hydrogen peroxide damage cell membranes.

#### 2. Reactive Nitrogen Intermediates (RNI):

- Nitric oxide (NO) and peroxynitrite damage DNA and proteins.

#### 3. Lysosomal Enzymes:

- Digest and degrade target cells.

#### 4. TNF- $\alpha$ secretion:

- Induces apoptosis in tumor cells.

#### 5. ADCC:

- Macrophage binds to antibody-coated cell and kills it.

### 3. Cooperation with Helper T Cells

- **Th1 cells** produce **IFN- $\gamma$** , which activates macrophages.
- Activated macrophages present antigen to Th1 cells → positive feedback loop.

