

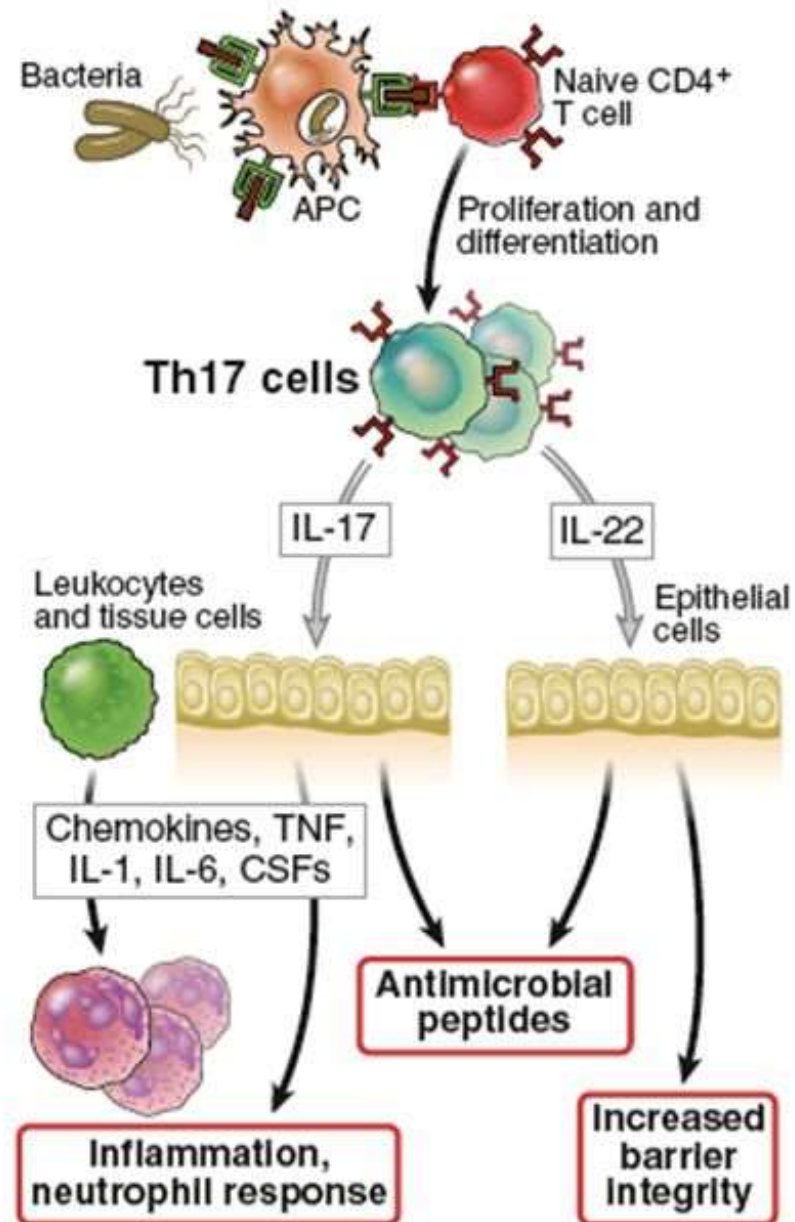
# T-cell mediated immune response

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# Effector function of Th17

- The TH17 subset is primarily produce IL-17 that involved in
  - Secret IL-17 that recruit neutrophils and macrophages to site of infection,
  - inducing inflammation
  - may cause some autoimmune diseases.

# Effector functions of $T_H17$ Cells



# Cytotoxic T cells

- T cells that express CD8 molecule on their surface and they represent 30% of T cells in the periphery
- killing tumor cells and virally infected cells (tissue and APC)
- CD8 activation need cytokines as IL-2 from CD8, type 1 IFN (interferon) from infected cells, IL-12 and IFN gamma from TH1 and infected DC
- Class I MHC molecules (infected nucleated body cells) expose foreign proteins
- CTL cell releases perforin and granzymes, proteins that form pores in the target cell membrane; causing cell lysis and/or apoptosis
- A membrane-bound effector molecule expressed on CTL cells is Fas ligand. When this binds to Fas on a target cell it activates apoptosis in the Fas-bearing cell.

# Naïve CD8 activation

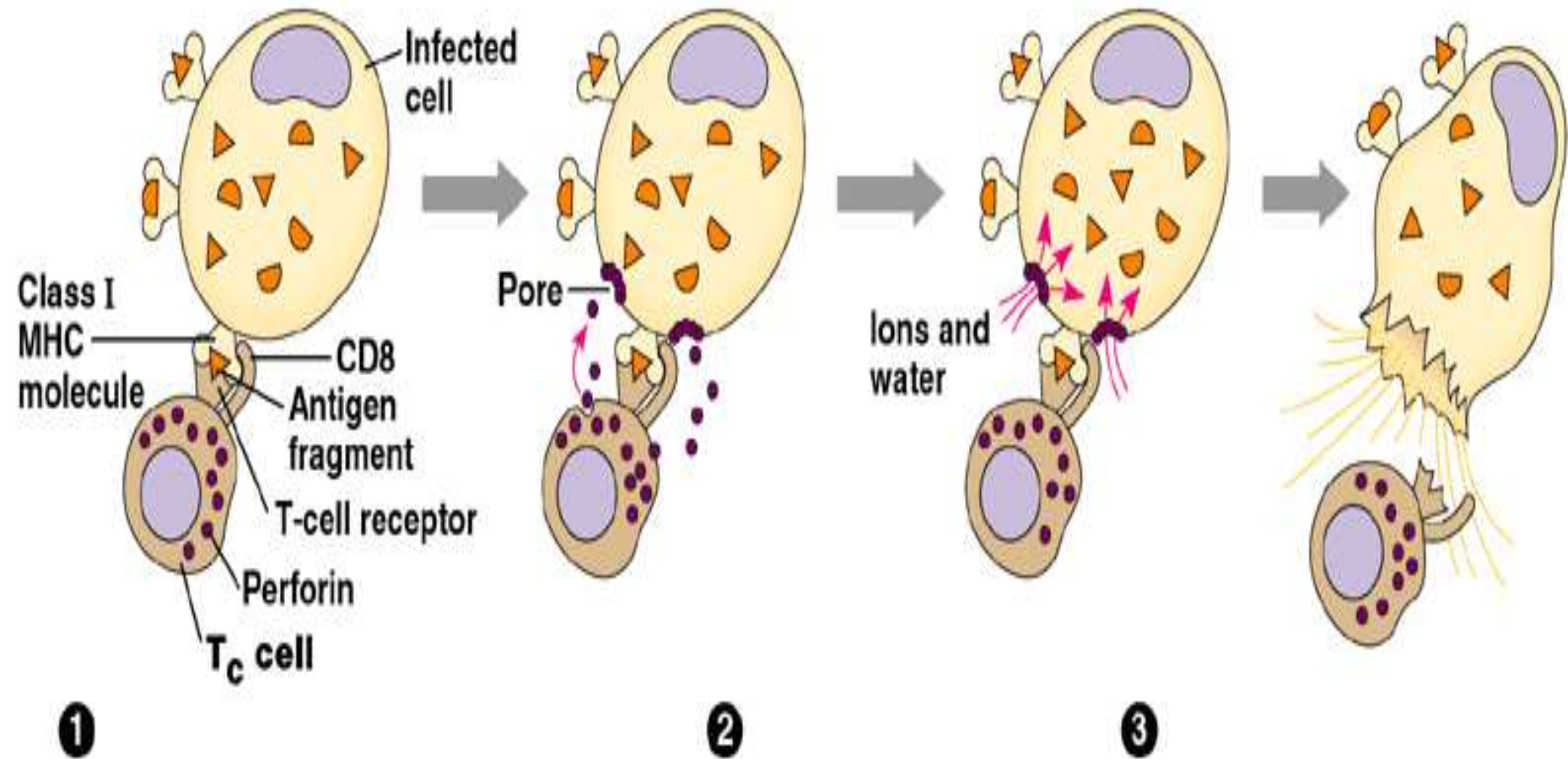
- 2 ways for activation

1-Directly.

2-indirectly by TH1 cells that secrete IFN gamma to stimulate CD8

# Direct Killing by CD8 cells

- 1- production of perforins and secretion of granzymes
- 2-induction of apoptosis by activation fasL-fas pathway



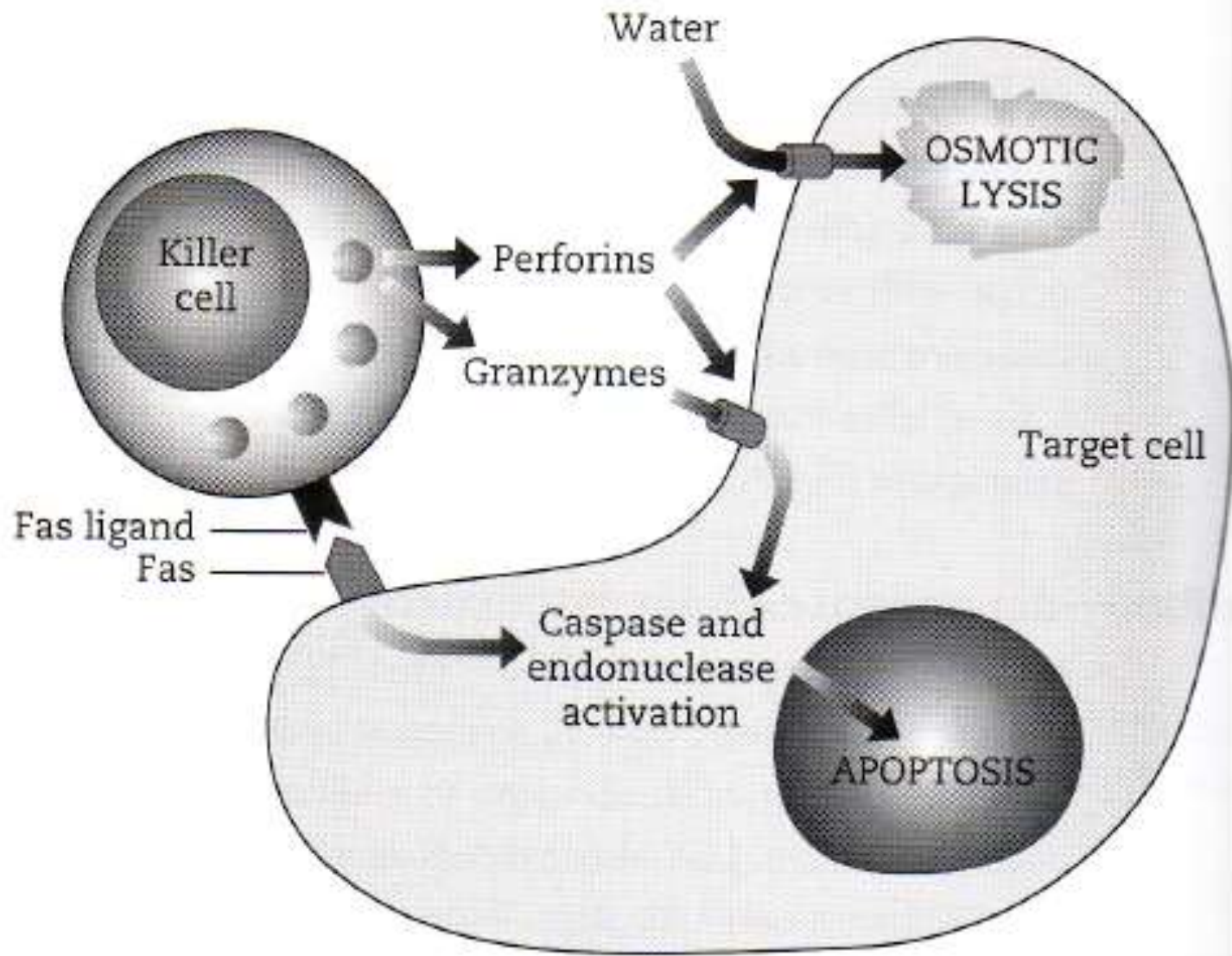
(a)

# Fas-FasL

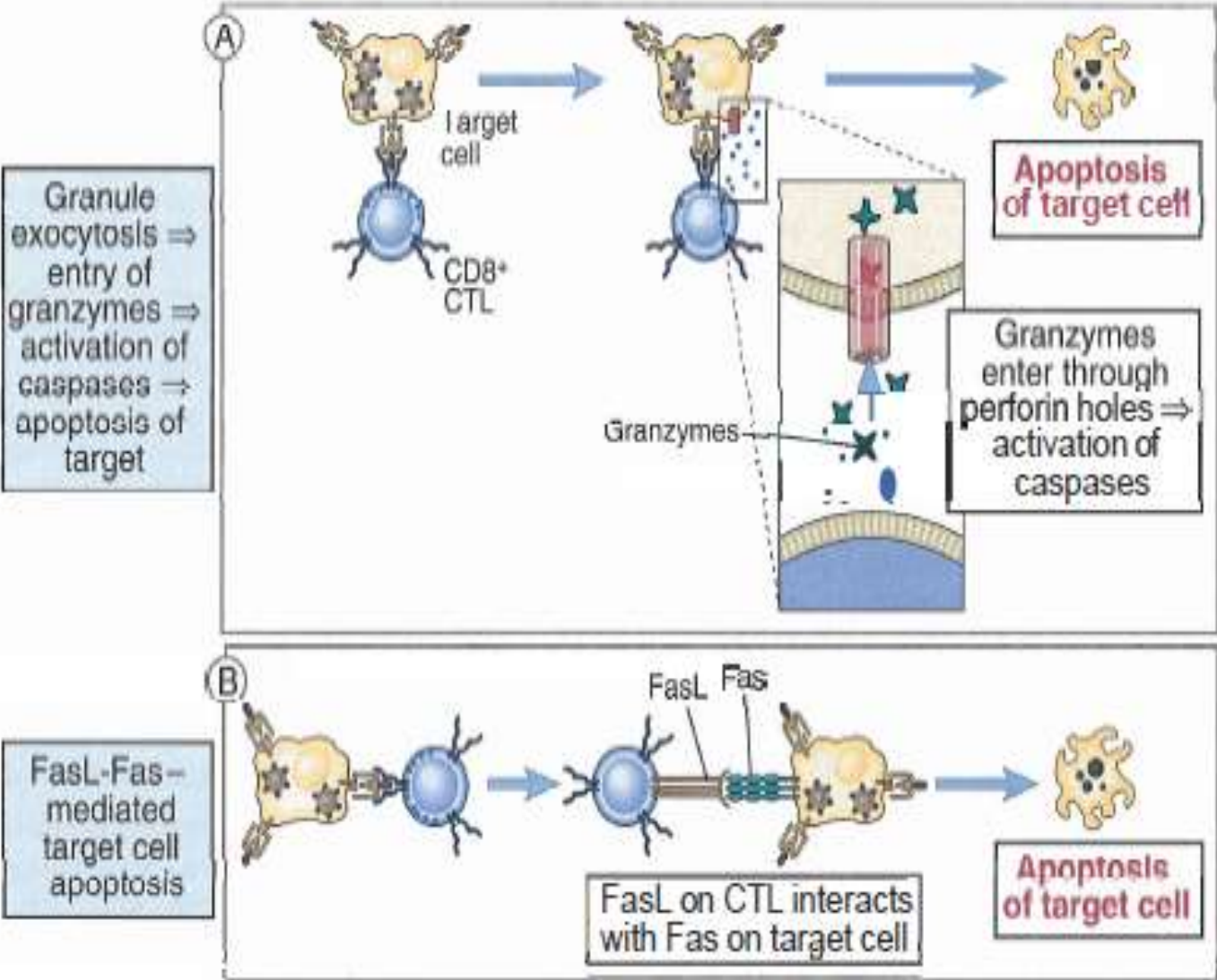
- Most important death receptor, when they bound the caspases will be activated in target cell and then apoptosis
- Help in NK and CD8 killing of target cell
- Help in T cell regulation
  - Killing of T cell by NK after activation (activation induced cell death (AICD))
  - Mutation in FAS or fas L gene lead to AUTOIMMUNE LYMPHOPROLIFERATIVE SYN (alps): lymphocyte accumulation, defective apoptosis and humeral autoimmunity



# MECHANISMS OF TARGET CELL KILLING



# CTL function



Pathogen group	adaptive response		
	Ab (B cell)	TC cells (CTLs)	TH cells
extracellular bacteria	bound Ab initiates total immune response*	not effective	B cell expansion
intracellular vesicular bacteria	internal pathogen renders Ab useless	cytosolic replication of bacteria can cause T C response	hyperactivation of macrophages by TH1 caused by vesicular replication
viruses	free viruses are bound & neutralized	TC cells kill virally infected cells	activate B cell
helminths	antibody-mediated cell-dependent cytotoxicity (ADCC)	not effective	B cell expansion

# Cross presentation

- The class I MHC pathway of antigen presentation to CD8+ T cells requires that protein antigens be present in the cytosol of infected presenting cells so that these proteins can be degraded in proteasomes and can then enter the endoplasmic reticulum via the TAP transporter (protein transporter).
- Virus that infects a specific cell type taken into APC by phagocytosis but these APCs are not infected by the virus and do not endogenously synthesize viral antigen. the immune system deals with this problem by the process of cross presentation.
- In this process; dendritic cells ingest infected cells, tumor cells, or proteins expressed by these cells, express them on MHC2 **and besides that they transfer the protein antigens into the cytosol, and process the antigens to enter the class I MHC antigen presentation pathway for recognition by CD8+ T cells besides Th1**

# Memory T cells

- Both CD4+ and CD8+ memory T cells (CD45RO+) can be subdivided into 2 subsets based on their homing properties and functions.
- Central memory T cells express the chemokine receptor CCR7 and L-selectin and home mainly to lymph nodes.
- Effector memory T cells, on the other hand, do not express CCR7 or L-selectin and home to peripheral sites, especially mucosal tissues.
- During a secondary infection, memory T cells in peripheral tissues can be directly activated by pro-inflammatory cytokines to induce effector functions and can interact with antigen-bearing dendritic cells to generate a localized secondary effector T-cell response outside of the draining lymphoid tissue

# Regulation of T lymphocyte responses

- To prevent tissue damage as a result of over stimulation
- To prevent auto-immunity
- Methods
  - After clearing the Ag CTLA-4 expressed instead of CD28 on T cells which bind B7 on APC and inhibit T cell activity
  - persistent activation of T cells lead to activation induced cell death (AICD) by surface interactions of fas-fasL on Tc cells and natural killer cells with the target T cell
  - elimination of Ag result in passive cell death
  - CD4 reg in the presence of IL-10 and TGF beta
  - PD-1 on T cells; programmed cell death 1, PD-1 recognizes two ligands, called PD-L1 and PD-L2; PD-L1 is expressed on APCs and many other tissue cells, and PD-L2 is expressed mainly on APCs. Engagement of PD-1 by either ligand leads to inactivation of the T cells or rarely conversion to T reg.

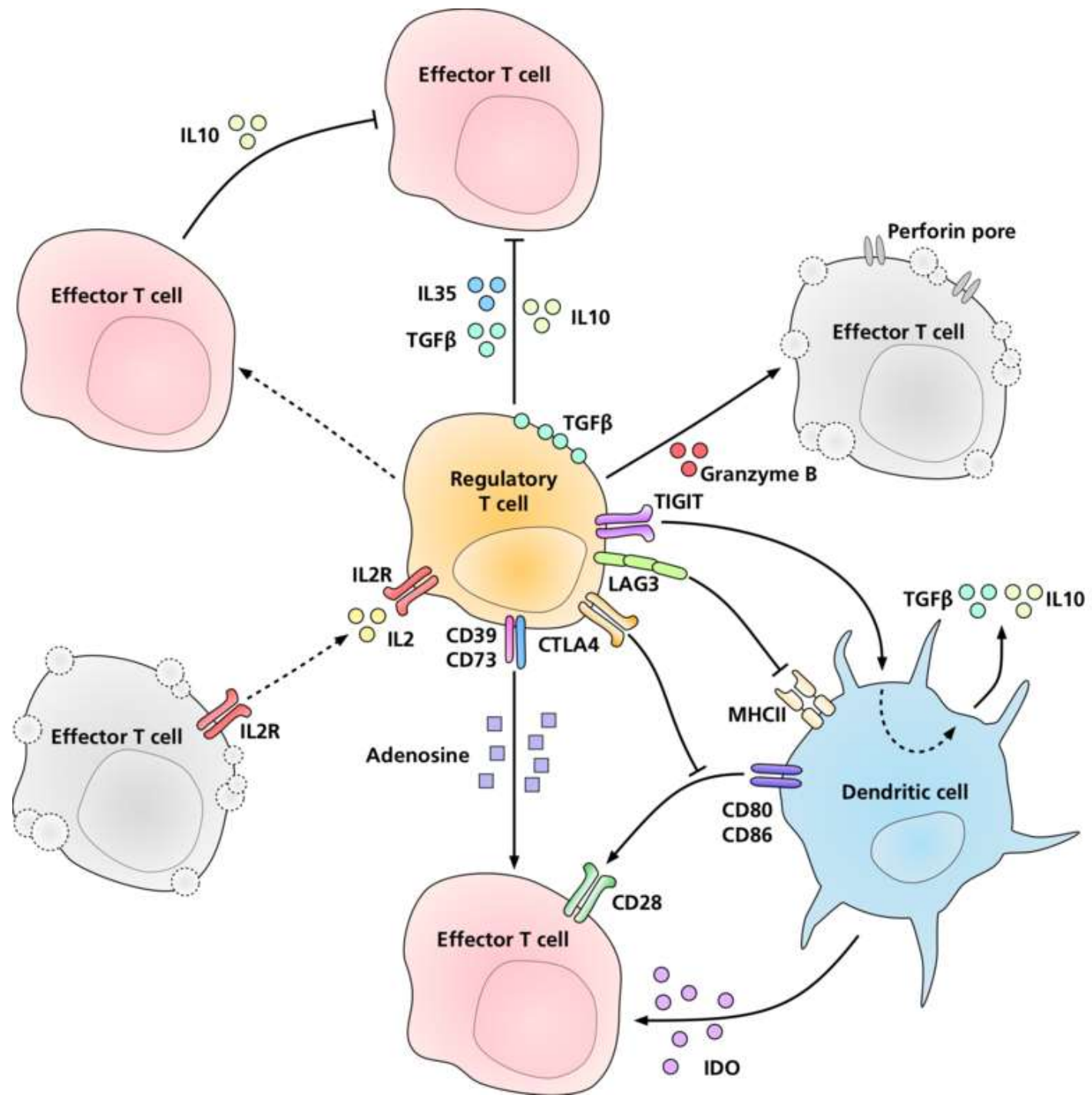
# New T cell phenotypes

- Regulatory T cells
  - Subset of CD4 T cells
  - Naturally occurring (FoxP3, CD25 and CD4 positive)
  - Induced (IL-10 and TGF- $\beta$ )

# T reg

- ***Regulatory T cells are generated mainly by self antigen recognition in the thymus (central) and by recognition of self and foreign antigens in peripheral lymphoid organs (peripheral)***
- ***Differentiated from CD4***
- ***The generation of some regulatory T cells requires the cytokine TGF- $\beta$ . And IL-2***
- ***Functions***
- Production of the immunosuppressive cytokines IL-10 and TGF- $\beta$ .
- Consumption of IL-2. Because of the high level of expression of the IL-2 receptor, these cells may absorb IL-2 and deprive other cell populations of this growth factor, resulting in reduced proliferation and differentiation of other IL-2–dependent cells.
- Reduced ability of APCs to stimulate T cells. One proposed mechanism of this action is dependent on binding of CTLA-4 on regulatory cells to B7 molecules on APCs,
- Secret granzyme B act on activated T cells





# T reg cytokines

- TGF- $\beta$  inhibits T cells and macrophages
- Interleukin-10.
  - IL-10 is an inhibitor of a activated macrophages and dendritic cells and TH1 and CD8 cells
  - By inhibition the production of IL-12 by activated dendritic cells and macrophages (inhibit TH1 and CD8)
  - IL-10 inhibits the expression of costimulators and class II MHC

# Privileged sites

- Immune response do not normally occur in these sites
- Anterior chamber of eye and testes
- Because high inhibitory proteins
  - IL-10 TGF beta
  - Migration inhibition factor
  - Expression of Fas L on their cells

# In appropriate T cell activation; T cell stimulation by Super antigens

- **Super antigens;** are a class of antigens which cause non-specific activation of T-cells resulting in and massive cytokine release from macrophages
- **Causes;** exoproteins, which include toxic shock syndrome toxin-1 (TSST-1), the staphylococcal enterotoxins, the exfoliative toxins (ETA and ETB), and leukocidin. and exotoxins A from streptococcal *Streptococcus pyogenes* leading to toxic shock-like syndrome, Others include EBV and HIV.
- **Pathology;** Bind in-appropriately to the outer part of V $\beta$  domain of the TCR and to outer part of MHC 2 and cause activation of massive no. of T cells and huge amount of produced cytokines, as the frequency of T cells that have Ag specific V $\beta$  domain is higher than to have both Ag specific V $\alpha$  and V $\beta$  TCR (10% : 0.01%)
- **Immunological effects;** increase in IL1, TNF alpha and IL2 as a result of increased macrophage activation by T cells....fever, massive vascular leakage and toxic shock syndrome (TSS).

# MECHANISM OF ACTION

- Binding to MHC class II
- Binding to T cell receptor
- T cell signalling

