T-cell mediated immune response

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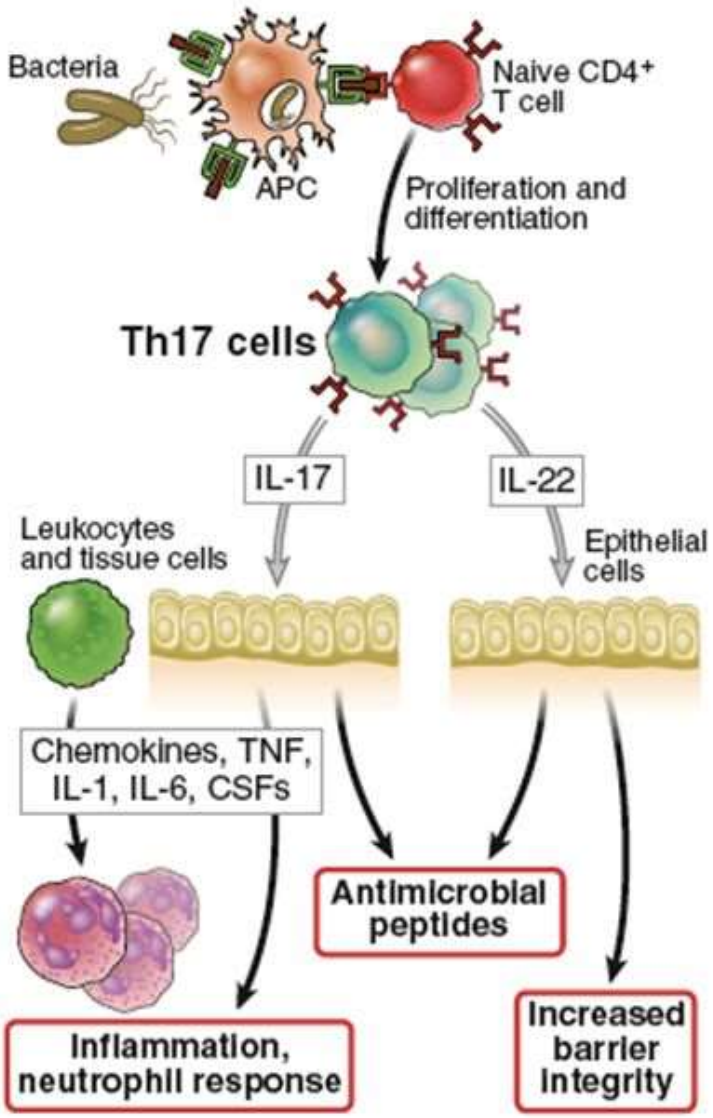
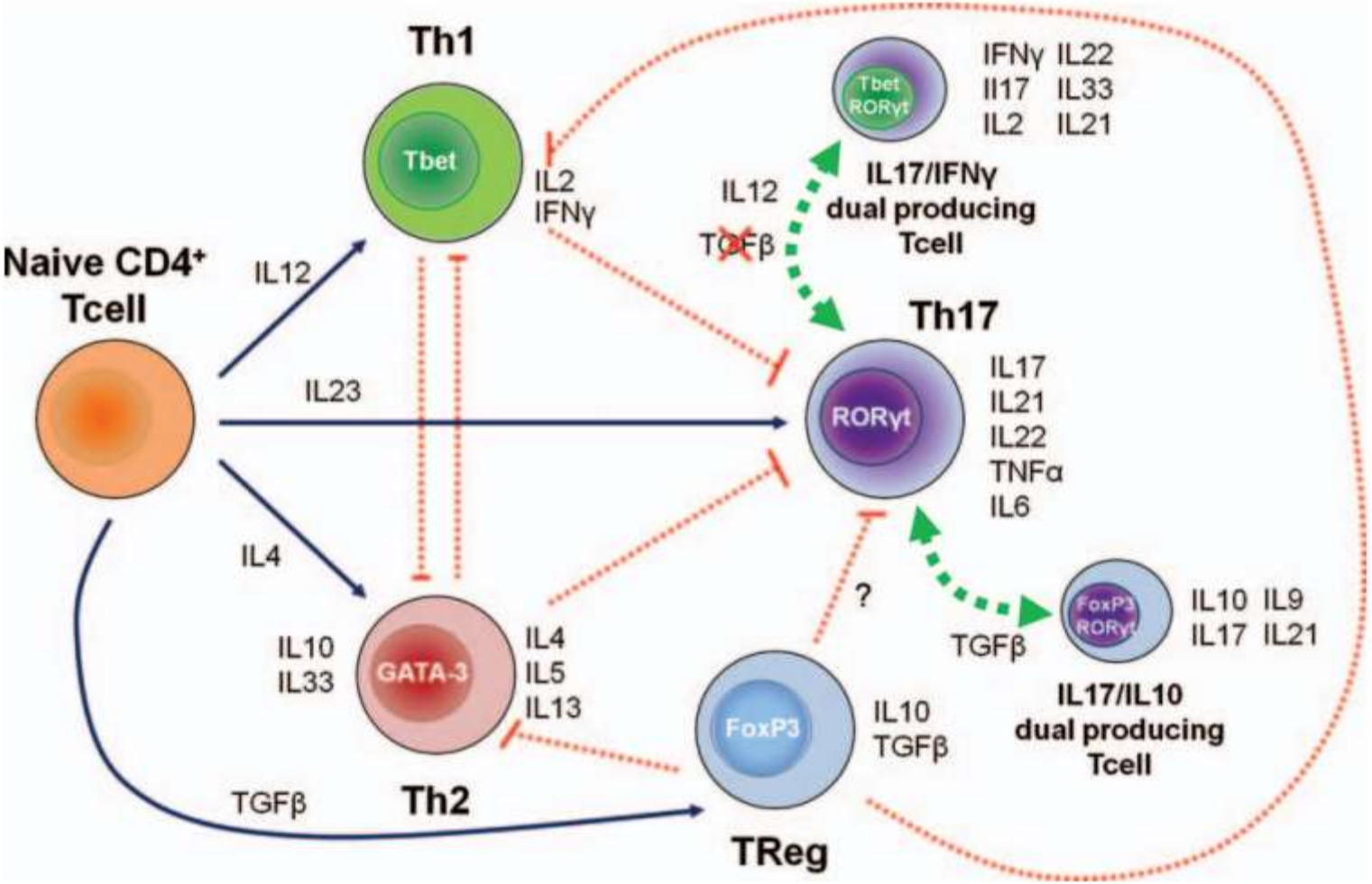
Effector function of Th17

- 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
  - cause some autoimmune diseases.

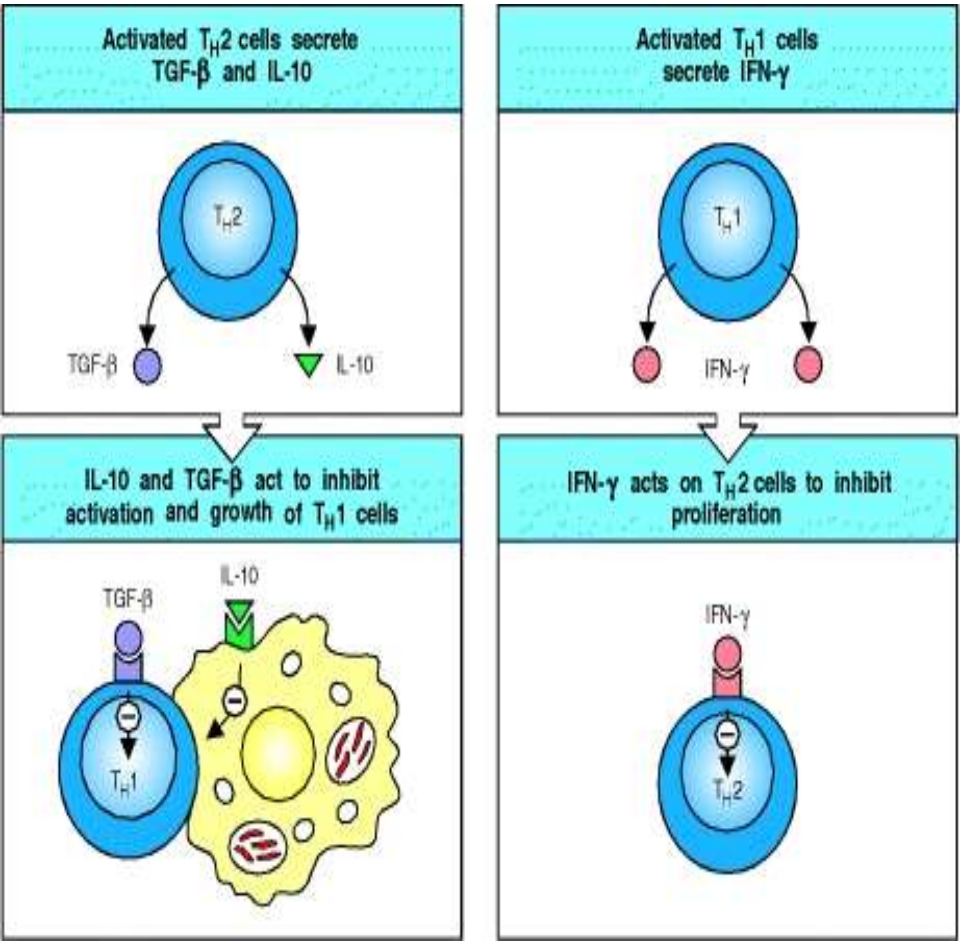
Effector functions of T_H17 Cells



Each subset inhibit other



Two subsets regulate each other



- TH2 cells make **IL10** ,
- and IL-4 which acts on macrophages to inhibit TH1 activation, perhaps by blocking macrophage IL-12 synthesis. TGF-β ,which needed for TH1 cells (left panels). Decrease auto-immunity
- TH1 cells make IFN-γ, which inhibit IL-4 and blocks the growth of TH2 cells (right panels). Decrease allergy

- These effects allow either subset to dominate a response by suppressing outgrowth of cells of the other subset. This help in using cytokines as therapy??.

CYTOKINES & DISEASE

Event	Development of tuberculoid leprosy	Development of lepromatous leprosy
T_H activation: cytokine production	Activation of T_H1: production of IFN-γ	Activation of T_H2: production of IL-4
Effector cell stimulation: effects on mycobacteria	Activation of macrophages: intracellular digestion of mycobacteria in cytoplasmic vesicles	Activation of B cells: antibodies have no access to intracellular mycobacteria
Resulting pathology	Some inflammatory tissue damage, but destruction of mycobacteria	Growth of mycobacteria and severe tissue damage

Table 3.3 The influence of cytokine production on disease pathogenesis following infection of macrophages by *Mycobacterium leprae*.

Cytotoxic T cells

- T cells that express CD8 molecule on their surface and they represent 30% of T cells in the periphery
- killing tumur 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
- TC 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 CD8 T 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. endogenous Ag processing in side any infected cell in the presence of MHC 1 plus expression of co-stimulatory molecules (high amount) ,

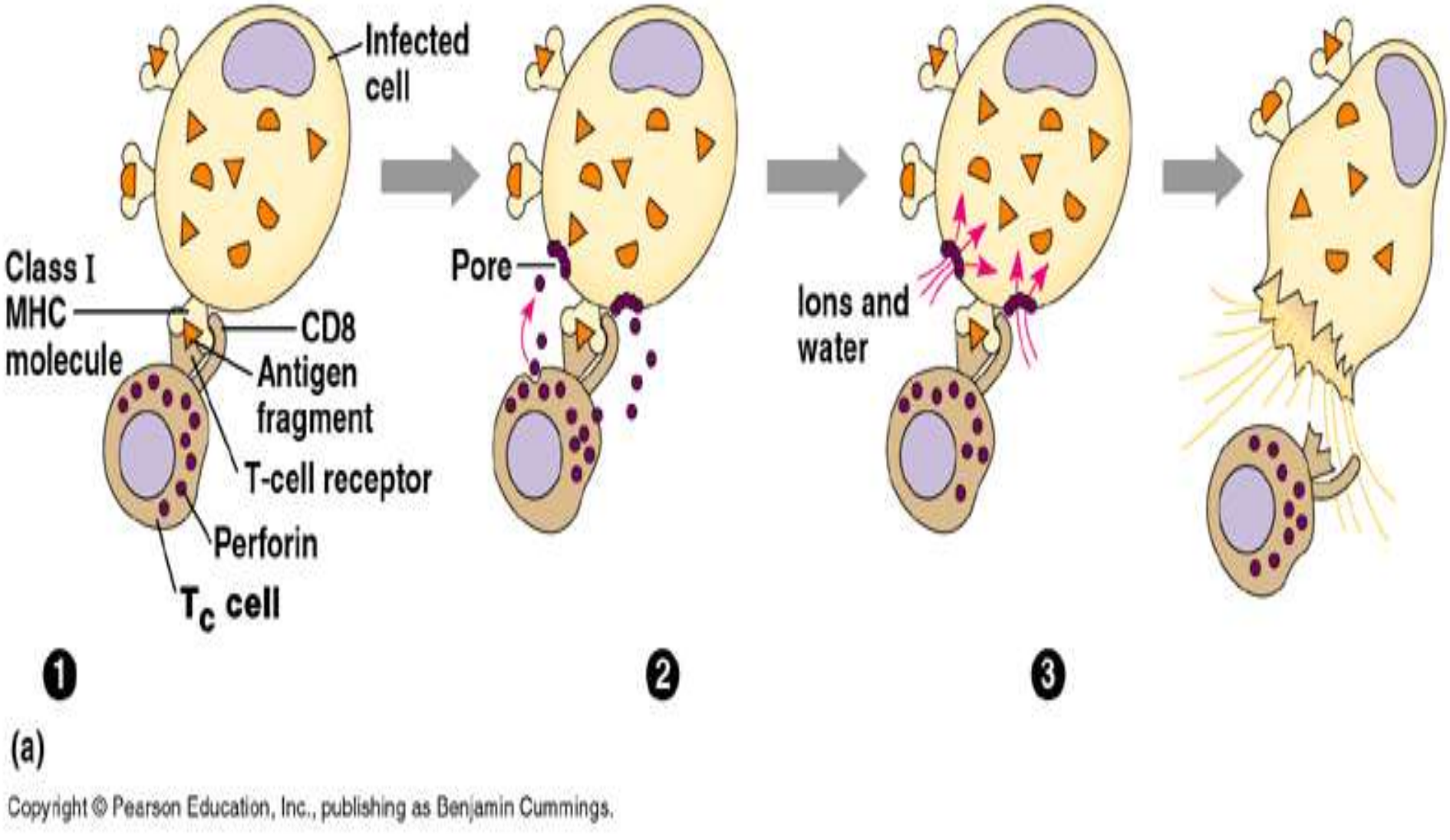
2-indirectly by TH1 cells that secret IFN gamma to stimulate CD8

Killing by CD8 cells

1- production of perforins

2-secretion of granzymes

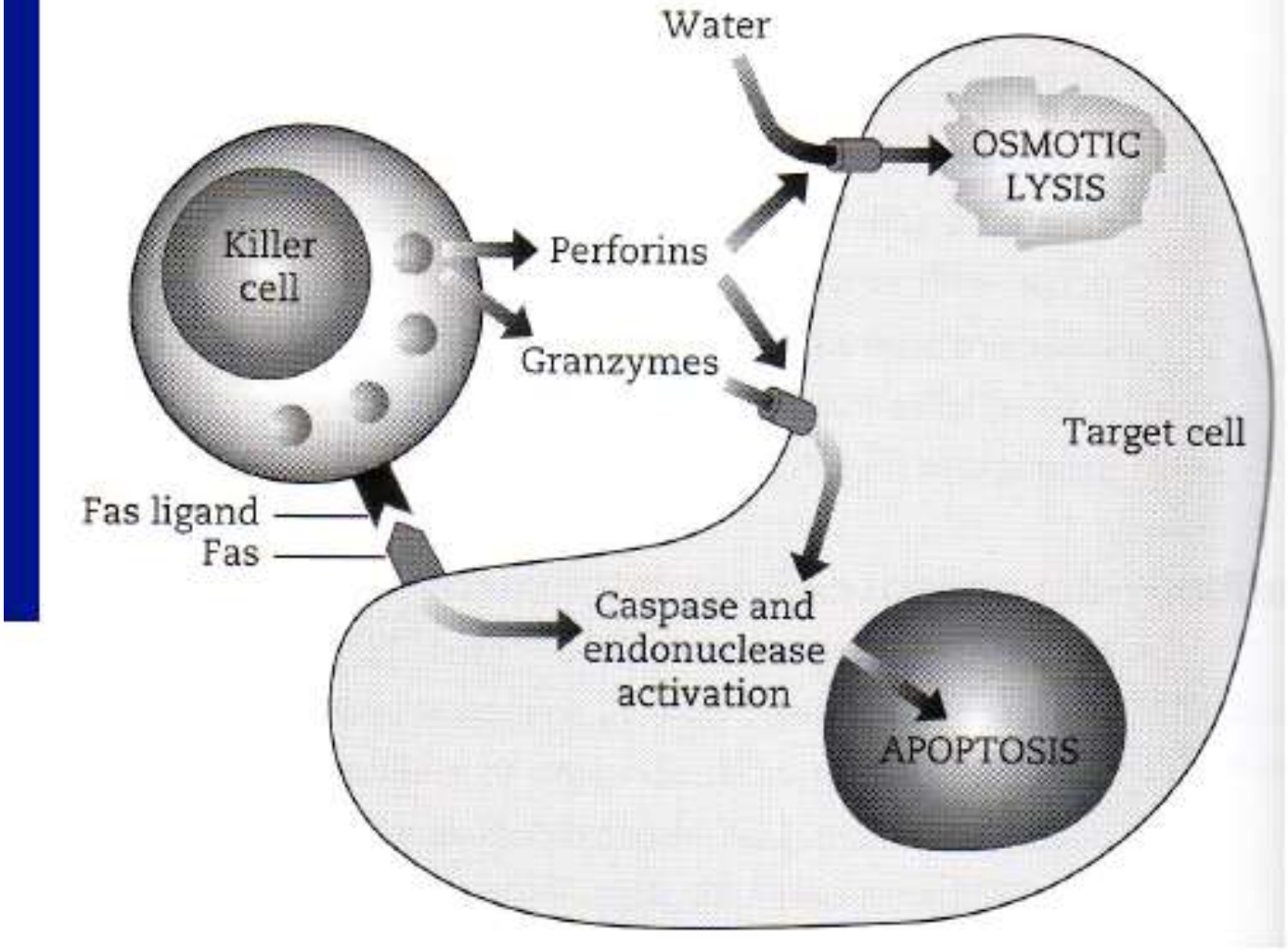
3-induction of apoptosis by activation fasL-fas pathway



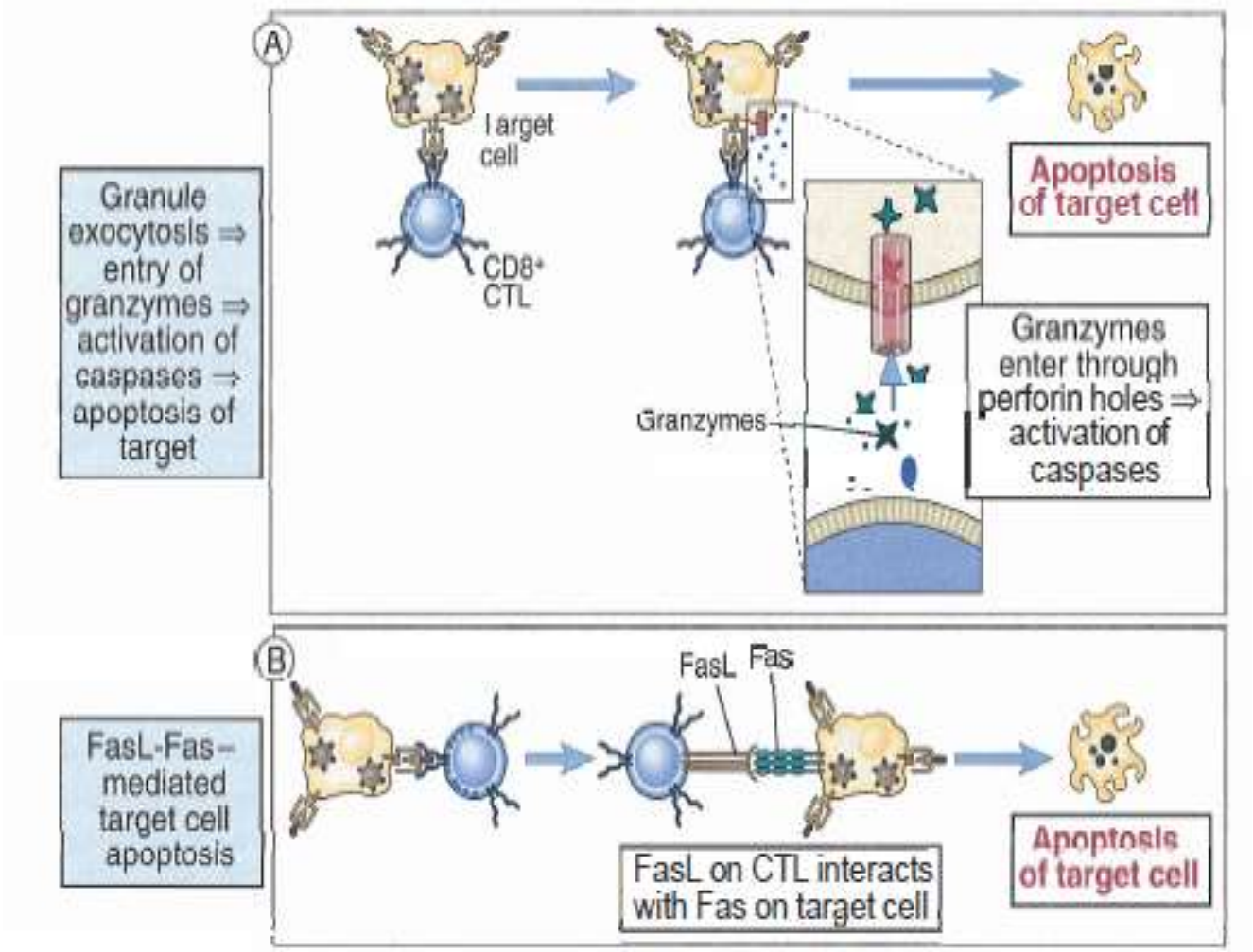
Fas-FasL

- Most important death receptor when bound the caspases activated in target cell and 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

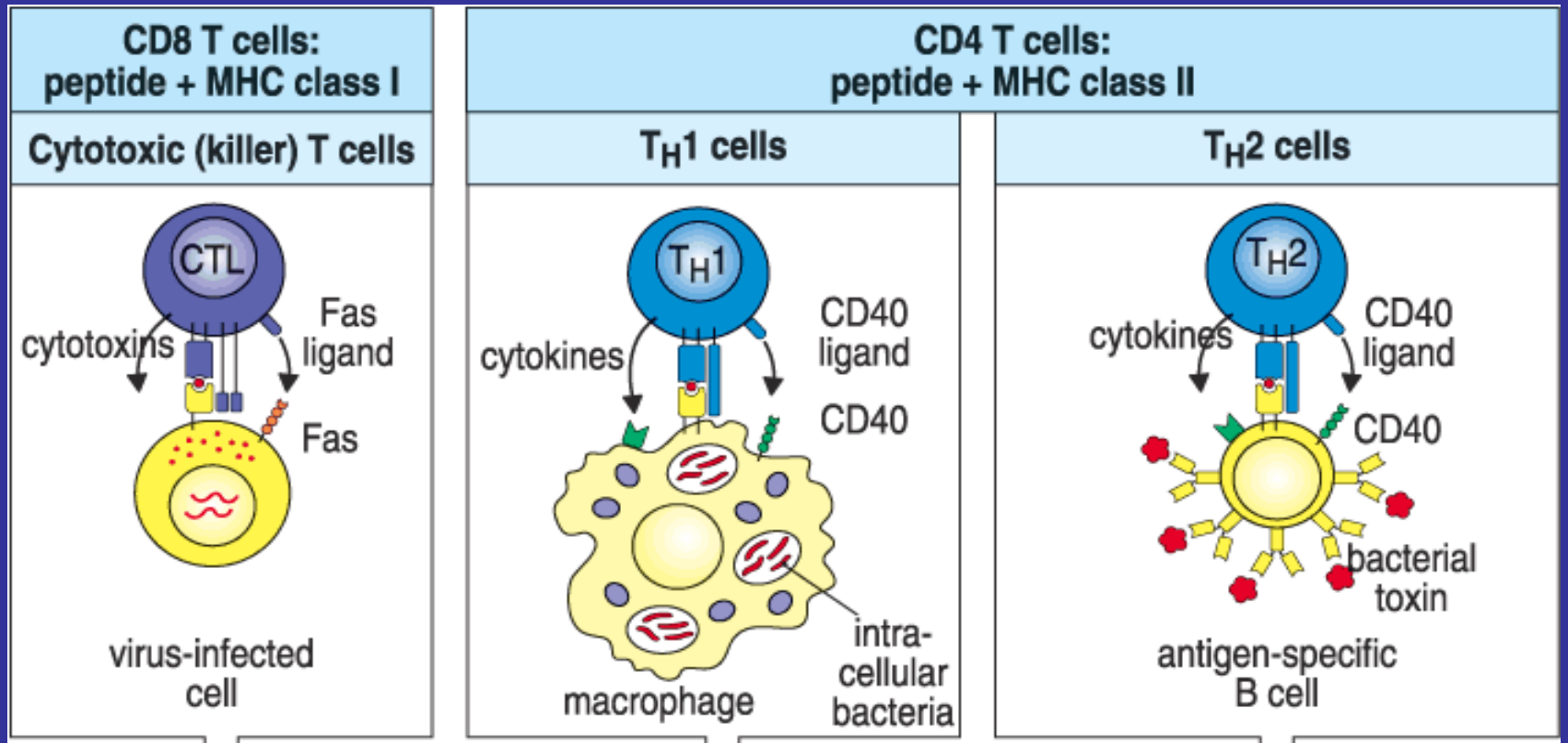
MECHANISMS OF TARGET CELL KILLING



CTL function



Effector molecules of T cell subsets



Cytotoxic effector molecules	Others
Perforin Granzymes Fas ligand	IFN-γ TNF-β TNF-α

Macrophage-activating effector molecules	Others
IFN-γ GM-CSF TNF-α CD40 ligand Fas ligand	IL-3 TNF-β (IL-2)

B-cell-activating effector molecules	Others
IL-4 IL-5 CD40 ligand	IL-3 GM-CSF IL-10 TGF-β Eotaxin

Fig 8.31 © 2001 Garland Science

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). Proteins from a virus that infects a specific cell type cells taken into APC 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, 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

Memory T cells

- Both CD4+ and CD8+ memory T cells can be subdivided into 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 tissu

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.

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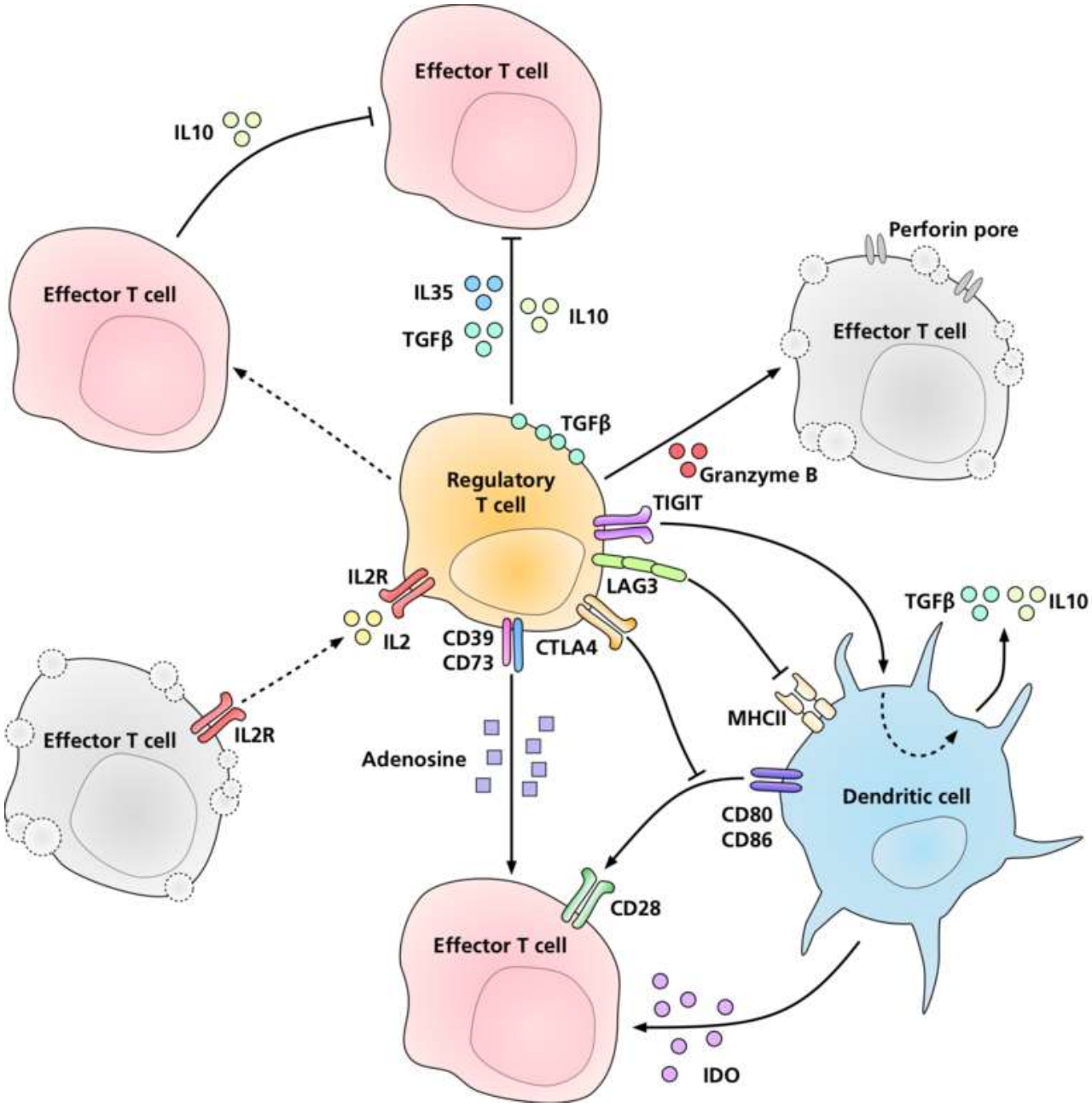
New T cell phenotypes

- Regulatory T cells
  - Naturally occurring (CD25 and CD4 positive)
  - Induced (IL-10 and TGF-β)

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-β. And IL-2***
- ***Functions***
- Production of the immunosuppressive cytokines IL-10 and TGF-β.
- 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


Effector T cell
IL10
Effector T cell
IL35
TGFβ
IL10
Perforin pore
Effector T cell
TGFβ
Granzyme B
Regulatory
T cell
TIGIT
LAG3
IL2R
IL2
CD39
CD73
CTLA4
TGFβ
IL10
Effector T cell
IL2R
Adenosine
MHCII
Dendritic cell
CD80
CD86
CD28
Effector T cell
IDO

T reg cytokines

- TGF-β 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; staphylococcal enterotoxins and streptococcal M protein, Others include EBV and HIV.

- Pathology; Bind in-appropriately to the outer part of Vß 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 Vß domain is higher than to have both Ag specific Vα and Vß 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 shock.

MECHANISM OF ACTION

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