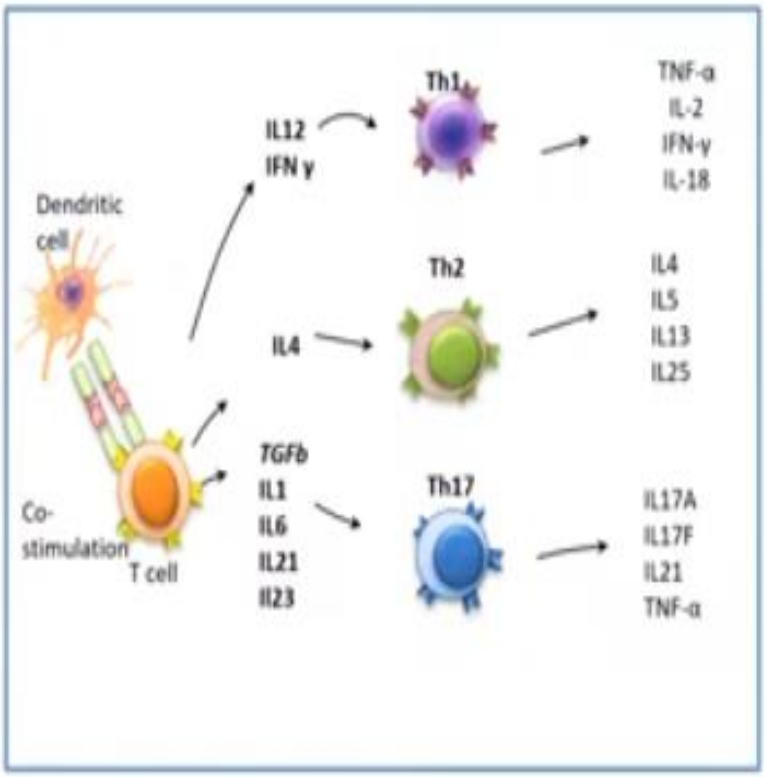
T-cell mediated immune response

Dr.Eman Albataineh,
Prof. Immunology
College of Medicine, Mutah university



Macrophages

Eosinophils

Neutrophils

Th1:
Intracellular pathogens:
Bacteria, Virus, mycobacteria
Tissue Repair,
Foreign bodies

Th2:
Parasites, Allergens
Drug as Antigens

Th17:
Extracellular pathogens:
Candida, Fungi, Bacteria

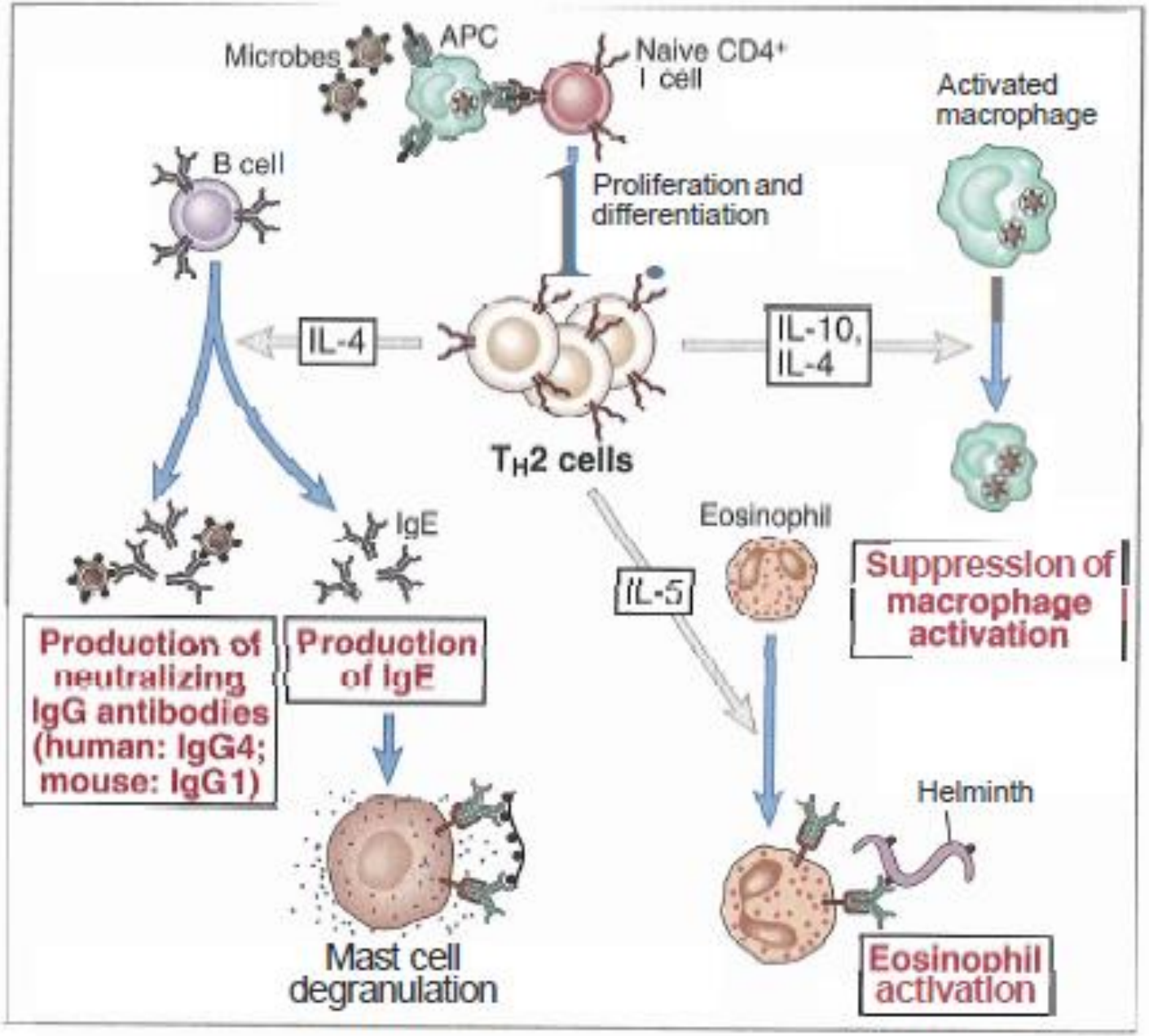
Th1:
Phagocytosis
Killing
Granuloma Formation
Hypersensitivity Type IV

Th2:
Atopic: IgE
Antibody-Mediated: IgG or IgI
Mast-cell Degranulation
Hypersensitivity Type I-III

Th17:
Anti-microbial Peptides
Inflammation
Barrier Integrity
Hypersensitivity Type IV

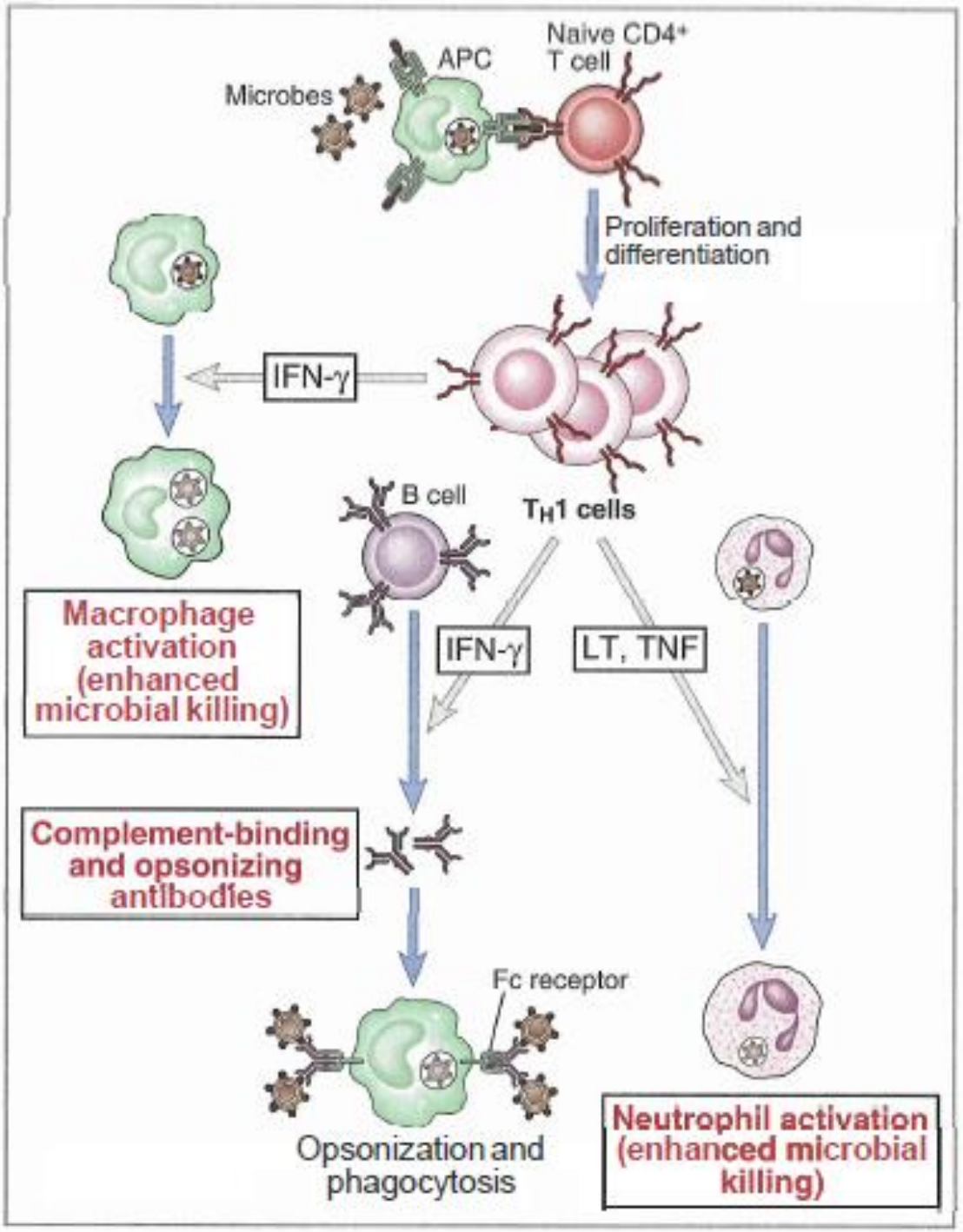
Th2

– TH2 functions
  - Bind B cell and secret IL-4 that lead to B cell activation and antibody secretion as IGE and IGG and suppress Th1 and mcrophages
  - Secret IL-5 to Activate eosinophils to react against worms
  - Secret IL-10 that suppress macrophages and suppress Th1 and macrophages
  - IL-13: Shares many functions with IL-4, including promoting B cell activation


Microbes
APC
Naive CD4+
T cell
Activated
macrophage
B cell
Proliferation and
differentiation
IL-4
IL-10,
IL-4
TH2 cells
IgE
Eosinophil
IL-5
Suppression of
macrophage
activation
Production of
neutralizing
IgG antibodies
(human: IgG4;
mouse: IgG1)
Production
of IgE
Helminth
Mast cell
degranulation
Eosinophil
activation

Th1

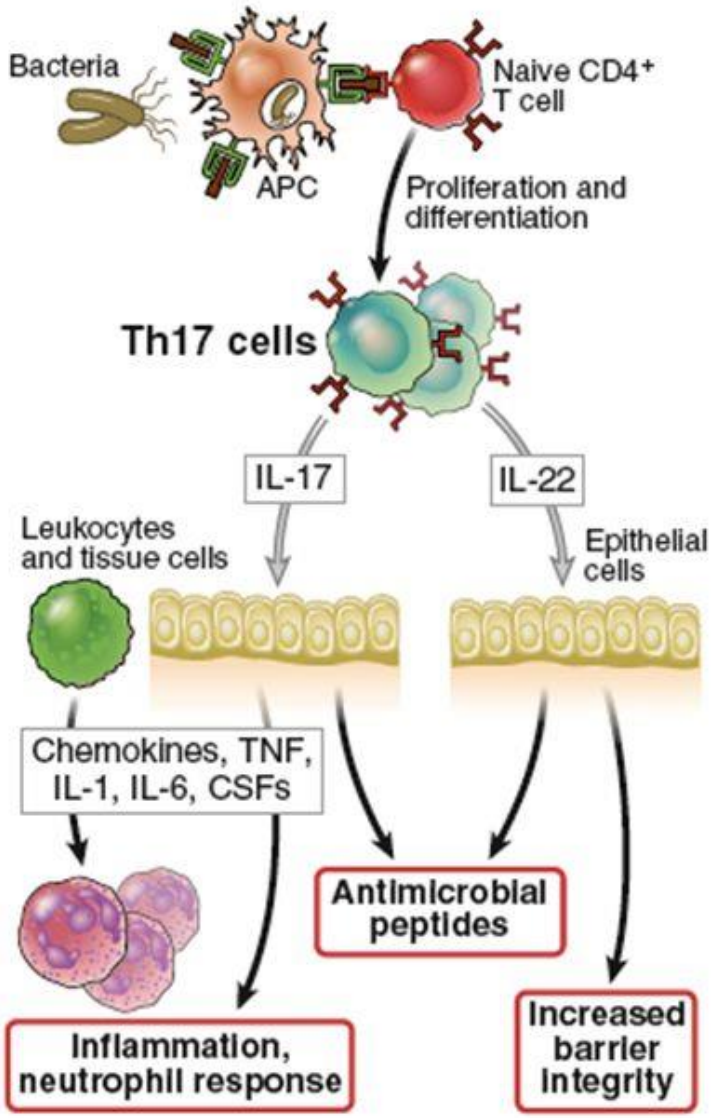
- TH1 function
  - Activate CD8, macrophages and NK to do direct killing of infected cell (by secreting IFN gamma)
  - do neutrophil activation
  - Activate B cell to secret opsonizing antibodies belonging to certain IgG subclasses (IgG1 and IgG3 in humans that increase phagocytosis
  - Help in cell mediated immunity


Naive CD4+
T cell
APC
Microbes
Proliferation and
differentiation
IFN-γ
B cell
TH1 cells
Macrophage
activation
(enhanced
microbial killing)
IFN-γ
LT, TNF
Complement-binding
and opsonizing
antibodies
Fc receptor
Opsonization and
phagocytosis
Neutrophil activation
(enhanced microbial
killing)

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.
- Also produce IL22 that help in tissue repair

Effector functions of T_H17 Cells



The immunologic synapse.

- When the TCR complex recognizes MHC-associated peptides on an APC, several T cell surface proteins and intracellular signaling molecules are rapidly mobilized to the site of T cell–APC contact
- This region of physical contact between the T cell and the APC is called an immunologic synapse or a supramolecular activation cluster (SMAC).
- The T cell molecules that are rapidly mobilized to the center of the synapse include the TCR complex (the TCR, CD3, and ζ chains), CD4 or CD8 coreceptors, receptors for costimulators (such as CD28), enzymes, and adaptor proteins that associate with the cytoplasmic tails of the transmembrane receptors.

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, IFN gamma and IL12 respectively from TH1 and infected DC
- 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

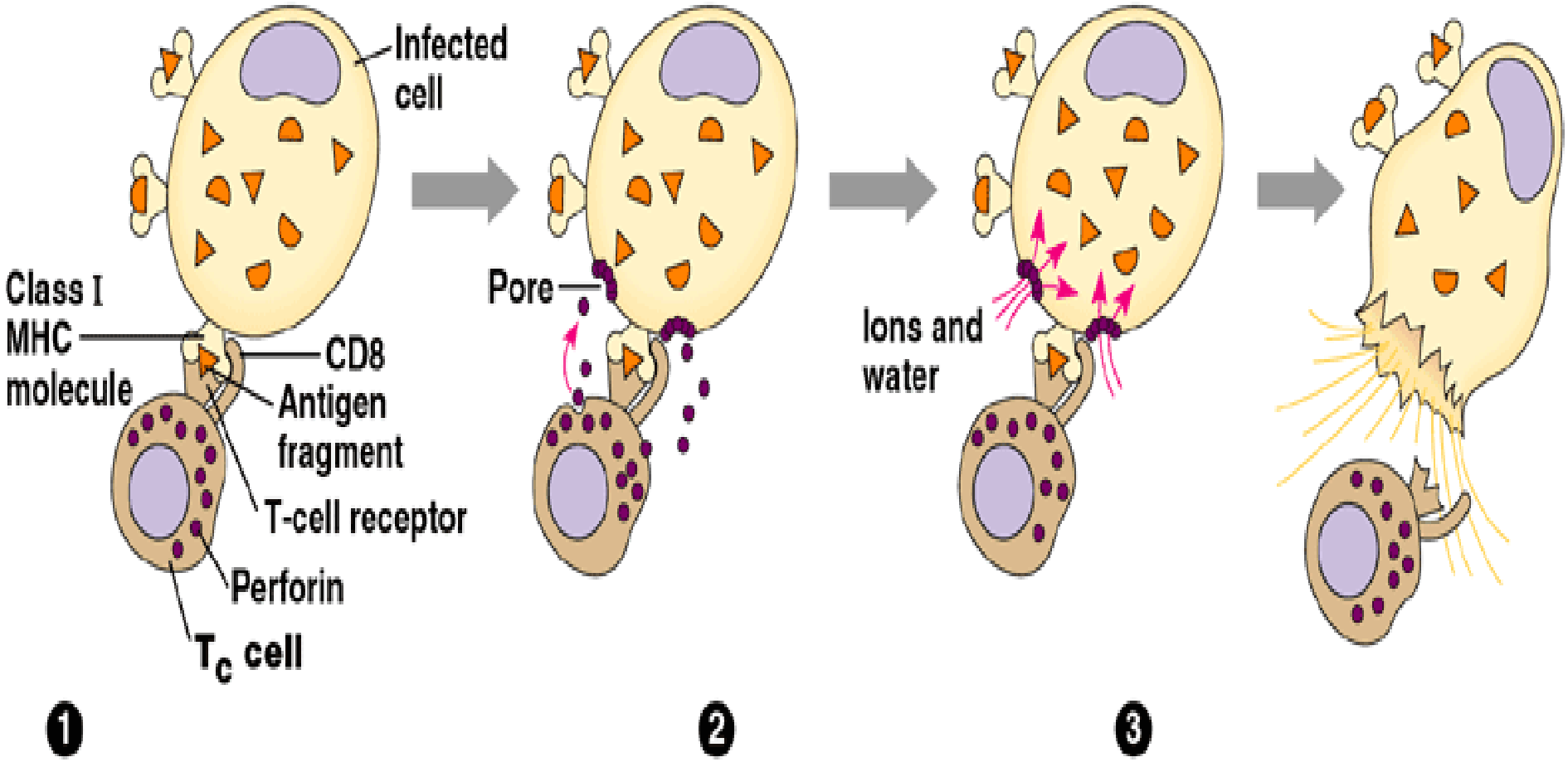
1-Directly.

2-indirectly by TH1 cells that secret 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

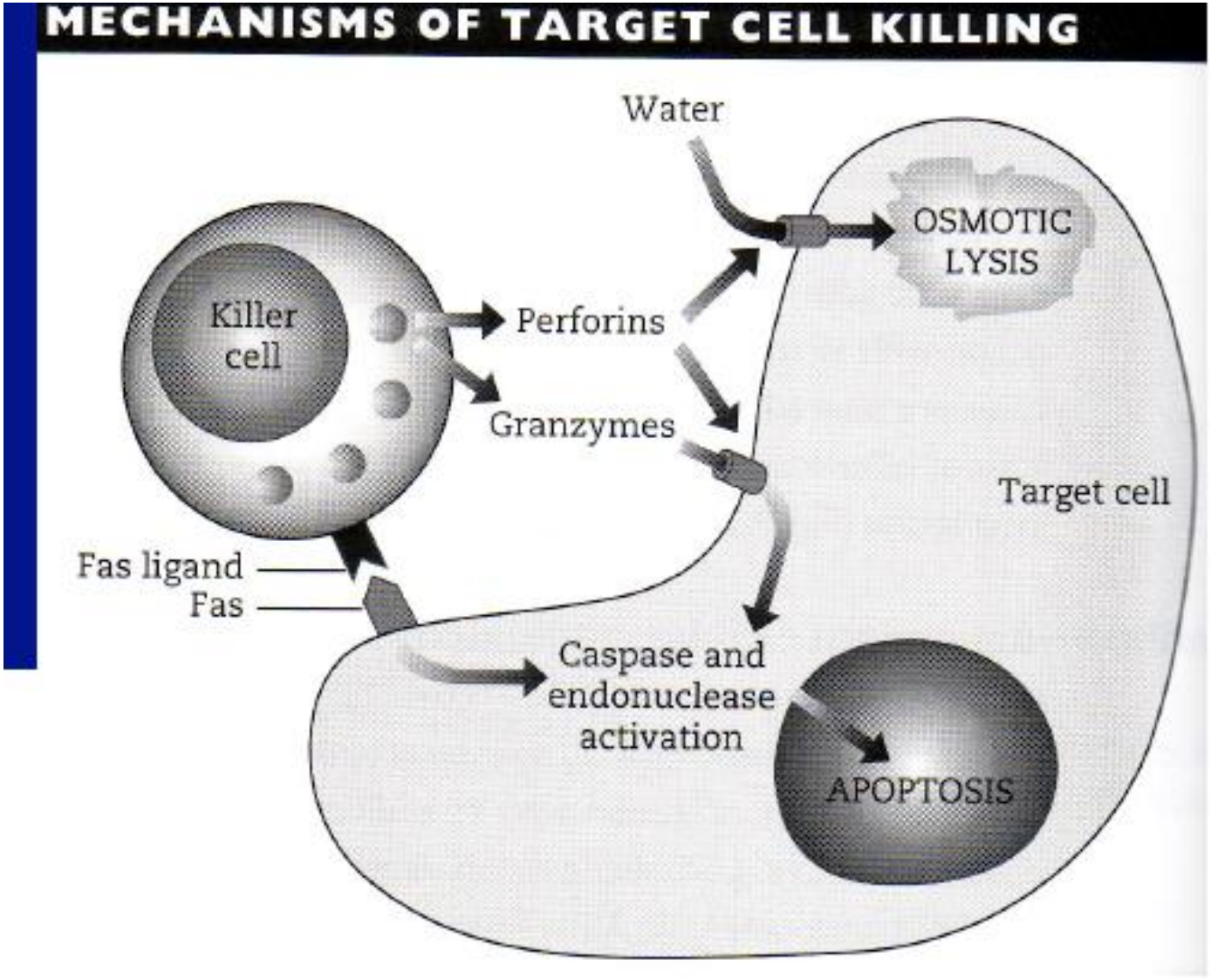


(a)

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



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. the immune system deals with this problem by the process of cross presentation.
- In this process; dendritic cells ingest intracellular 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**
- **Target: to augment activation of immune cells against tumors and intracellular infection>**

Memory T cells

- Both CD4+ and CD8+ memory T cells are CD44 + T cells and CD45RO+ while naïve T cells have CD45RA.) 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 CD27+ and home mainly to lymph nodes.
- Effector memory T cells, on the other hand, do not express CCR7 or L-selectin and CD27- cells 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 fasL on Tc cells and natural killer cells with the fas on target T cell

-elimination of Ag result in passive cell death

-CD4 reg T cells peripheral differentiation 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.

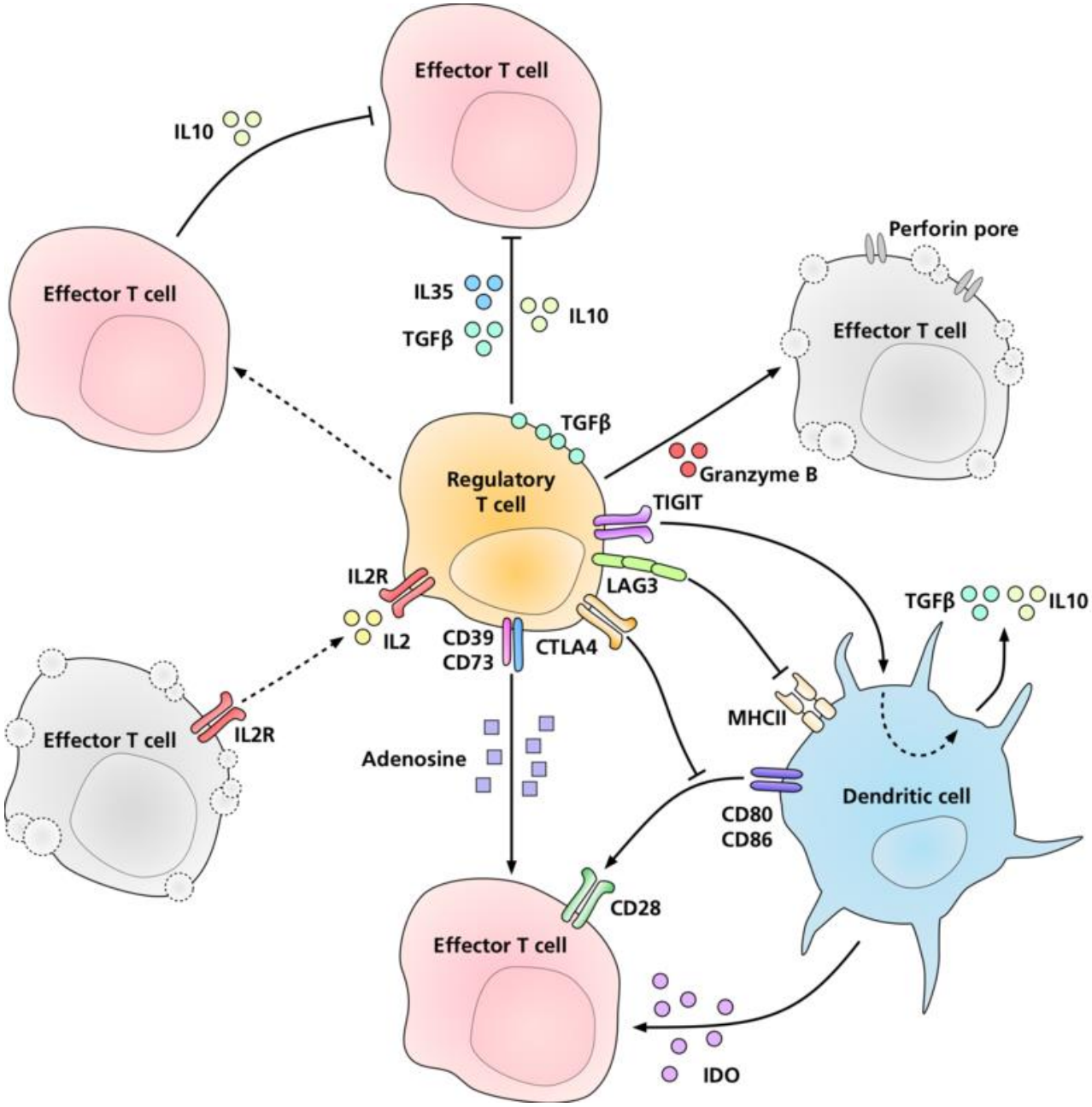
.

New T cell phenotypes

- Regulatory T cells
  - Subset of CD4 T cells
  - Naturally occurring (FoxP3, CD25 and CD4 positive) CD25 is a component of the IL-2 receptor
  - Induced peripherally in the presence of (IL-2 and TGF-β)
  - • FoxP3 is crucial for maintaining suppression of the immune system. Naturally occurring mutations in the FOXP3 gene can result in self-reactive lymphocytes that cause a rare but severe disease IPEX (Immune Dysregulation, Polyendocrinopathy, Enteropathy, X-Linked) in humans and scurfy in mice.

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) requires the cytokine TGF-β. And IL-2***
- ***Differentiated from CD4***
- ***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 high affinity of binding of CTLA-4 on regulatory cells to B7 molecules on APCs,
- Secret granzyme B act on activated T cells


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

- Autoimmune-preventive CD4+ T cells revealed the CD25 molecule (the IL-2 receptor α chain) as a candidate.
- • Removal or reduction of CD25+CD4+ Tregs also provokes effective tumor immunity and augments microbial immunity in chronic infection, leading to eradication of tumors or microbes, respectively
- • Conversely, CD25+CD4+ T cells enriched from normal mice suppress allergy, establish tolerance to organ grafts, prevent graft-versus-host disease after bone marrow transplantation, and promote feto-maternal tolerance

- Increase activation of T reg to inhibit allergy and autoimmunity
- Treat any mutation in foxp3 in autoimmunity
- Anti-CTLA4 in tumors
- T reg direction to site of graft transplantation or allergy

T reg cytokines

- TGF-β inhibits T cells and macrophages
- Interleukin-10.
  - IL-10 is an inhibitor of an 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

Privileged sites

- Immune response do not normally occur in these sites
- Anterior chamber of eye and testes, brain, cornea and placenta
- Some privileged; articular cartilage, adrenal cortex, hair follicles, and the pregnant uterus.
- 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 that are not processed and bind MHC2 with common region on TCR as bridge 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 Streptococcus pyogenes leading to toxic shock-like syndrome, 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 toxic shock syndrome (TSS).

MECHANISM OF ACTION

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