

DOCTOR 2020 | JU



IMMUNOLOGY

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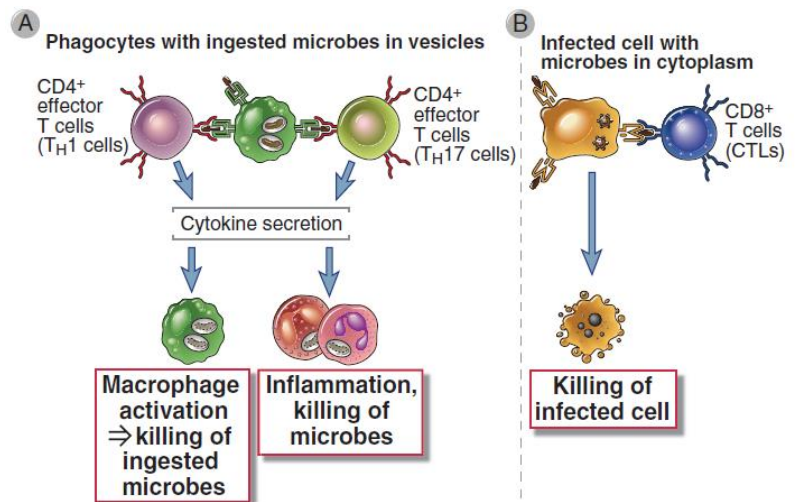
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In this lecture we'll concentrate more on the effector functions of T lymphocytes "part of adaptive immune system" how do they function and how to stimulate them starting by an **overview**↓ of what we have learned in some previous lectures.

The binding of MHC molecule from an APC (Antigen Presenting Cell) like a macrophage with the **T cell receptors** (**$\alpha\beta$ receptors**) will lead to secretion of cytokines that aid in the killing of microbe by the macrophages or recruitment of other inflammatory cells like **neutrophils** or **eosinophils**.

- this is what we learned about the function of CD4+ T cells (helper T cells)



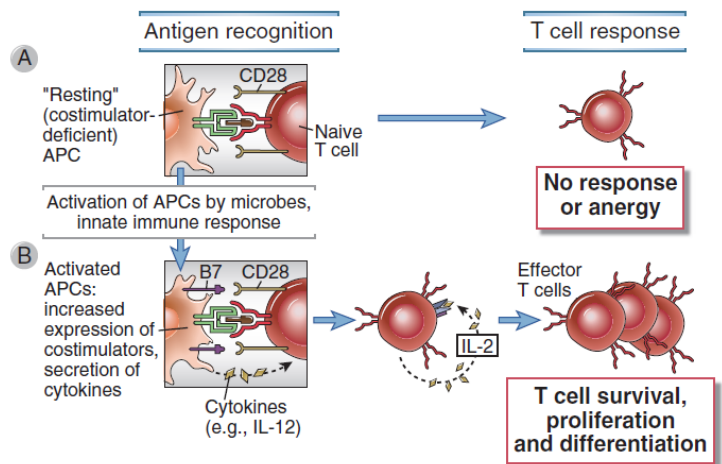
While in CD8+ T cells (Cytotoxic T cells) the binding of the MHC molecule of an infected cell with the T cell receptors will lead to killing of that infected cell.

Signals for T lymphocyte activation:

The first signal required for the activation of T cell is the binding of T cell receptors with an MHC molecule (whether it's class 1 or 2) but this signal is not enough, in B cells' activation for example in addition to the binding of the antigen with its receptor on B cell (immunoglobulin) they require additional signaling from Toll-like receptors or the complement receptors.

A similar thing happens here with T cells, they need **costimulatory signals** because they're binding to a cell presenting the antigen not directly to the antigen, one of the important costimulatory signals is the signal that happen when binding **B7** (a protein on an APC) with its receptor on T cell **CD28** with the help of cytokines like **IL-12** from an activated APC.

This process is crucial to make sure that it's a foreign antigen, we don't want T cells to react towards a self antigen.



[more explanation of the previous diagram]

A) So if the APC presented the antigen to the T cell without the costimulatory signals two things might happen either:

1- The T cell will do nothing, it won't initiate a response towards that antigen

Or 2- It will enter a state of **Anergy**, it will become non-functional.

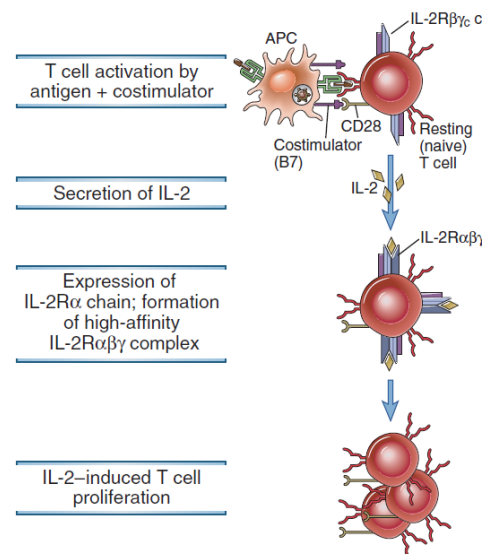
* What induces the production of costimulatory signal is the recognition of the microbe by an APC through pattern recognition receptors like toll-like receptors.

B) Antigen recognition → Costimulatory signal(B7 ⇌ CD28) + cytokines (like IL-2) → all will lead to T cell survival, proliferation and differentiation.

- After that will come the role of **IL-2**. It's the most important cytokine produced by T cells early after activation, often within 2~4 hrs after recognition of antigen and costimulators.

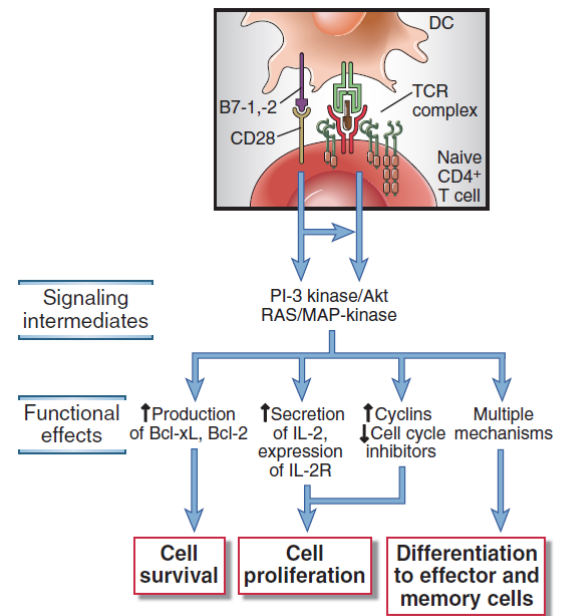
IL-2 will work on the T lymphocytes themselves (there's a receptor on T cells for IL-2) to induce the
1)proliferation of T cells "clonal expansion",
2)survival and 3)differentiation.

cell proliferation in response to antigen recognition is mediated primarily by a combination of signals from the antigen receptor, costimulators, and autocrine growth factors, **primarily IL-2**



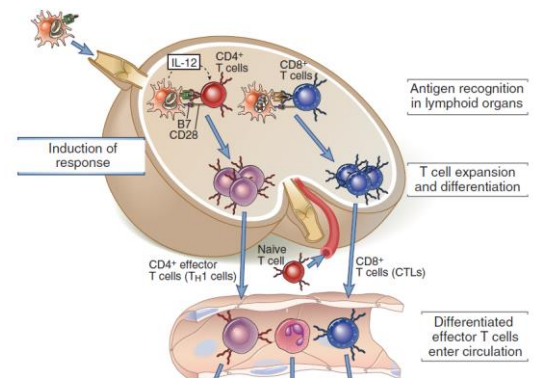
So again what IL-2 do along with other signals:

- increase the production of BCL2 (anti-apoptotic protein) → cell survival.
- Increase of certain proteins that will finally lead to cell proliferation and differentiation into **effector cells** (Helper T cells and Cytotoxic T cells) and **memory cells**, so memory is a characteristic of **adaptive immunity** all lymphocytes will have memory not only B cells.



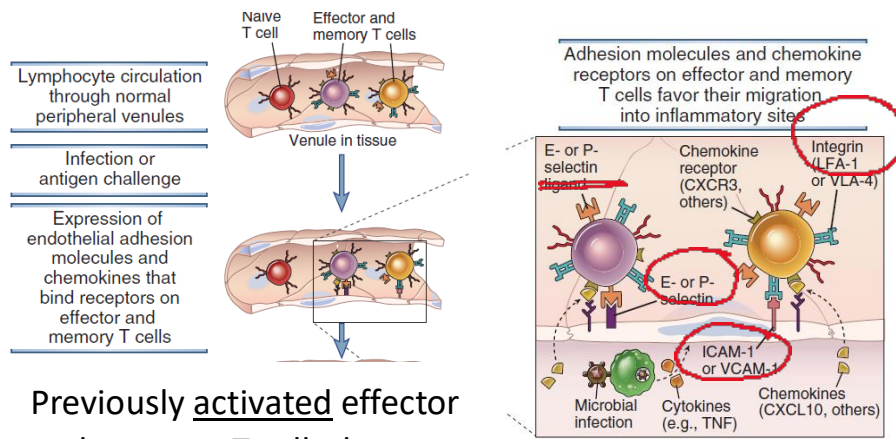
Migration of effector T cells to sites of infection

This is also a thing that we've come through previously, an APC(dendritic cell in this case) carrying antigen to a lymph node → then it will go to the **parafoallicular cortex** where T cells reside along with antigen presentation , costimulatory signals and cytokines → activation of T cells→ proliferation with the help of **IL-2**.



**** in the lecture the doctor said that the "medulla" is where T cells reside but I asked him about that and he said that he got mistaken them with the sub-capsular sinus, so T cells mainly reside in the parafoallicular cortex**

Later on these effector T cells will leave to the circulation towards the site of the infection (unlike B cells which after their activation and differentiation will go to the bone marrow) following chemokines, then selectins and integrins will slow down their movement (they **roll**) and stop them near the site of the infection.



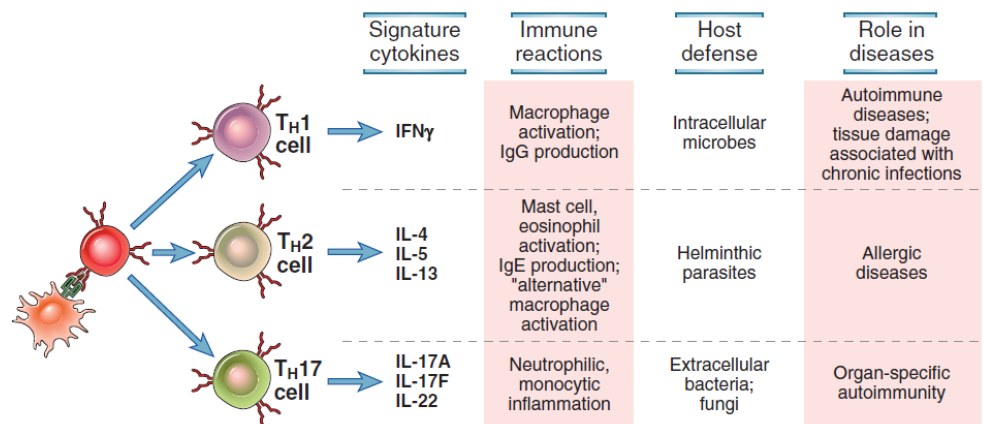
Selectin ligand - on T cell - will interact with selectin for weak adhesion then T cells will express integrin to interact with ICAM-1 for strong adhesion

Previously activated effector and memory T cells, but not naive cells (because they don't express selectins' ligands and integrins), migrate through endothelium that is activated by cytokines (e.g., TNF) produced at a site of infection, once the strong adhesion molecules are connected, the T lymphocyte can transmigrate and go to perform its function at the site of the infection whether its CD4+ or CD8+ T cell.

*Suppose that some memory and effector T cells migrated to an infection by another antigen they don't recognize what will happen? They either die in the tissue or get resorbed by lymphatics and go back to lymph nodes waiting for their specific antigen.

Effector functions of CD4+ T Cells

The main function of CD4+ T cells is **producing cytokines** but the action of these cytokines differs depending on the type (subtype) of Helper T cell that is formed after activation.



APCs produce cytokines that drive the development of CD4+ T cells. There are three distinct subsets of CD4+ T cells called **TH1, TH2, and TH17**, the differentiation of these subsets depends on the **type of the microbe**.

- **TH1** produce mainly **IFN γ** that activate M1(classical) pathway of macrophages for fighting phagocytosed intracellular microbes and help B cells to class switch to IgG production.

* recall that there are also type 1 interferons (α and β) which play distinctive role during viral infection, they stimulates the infected cell to enter antiviral state by blocking viral protein synthesis, send signals to the neighboring cells, produce RNases that degrade the nucleic acid of the virus+ mRNA and increase production of MHC1.

- **TH2** produce cytokines **IL-4** and **IL-13** which will 1) help B cells to class switch to IgE production, 2) recruitment of eosinophils and mast cells 3) they have a role in allergic diseases and 4) they activate M2(alternative) pathway of macrophages.
- **TH17** produce mainly **IL-17** that recruits neutrophils and monocytes in response to extracellular bacteria and fungi.


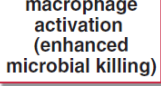

IFN- γ is the principal **macrophage-activating cytokine**, it induces the production of ROS (reactive oxygen species) + NO (nitric oxide) all are part of the oxidative burst and increase lysosomal enzymes to finish the killing of the pathogen, it increases the production of cytokines like IL-1, TNF...etc and it will increase the production of **B7(costimulatory molecule)** to activate more and more T cells.

-Activation of macrophages requires another signal (in addition to $\text{IFN-}\gamma$) which is the binding of CD40 (on the macrophage) with its ligand on T lymphocyte CD40L.

* recall that B cells also have CD40 that binds to CD40L on T lymphocyte during *T cell dependent antibody response to protein antigens*.

And as we stated previously **IFN- γ** works on B cells to promote switching to certain **IgG subclasses** which help in opsonization and complement binding. Also, it promotes the differentiation of CD4+ T cells to TH1 and inhibits the differentiation of TH2 & TH17 cells.

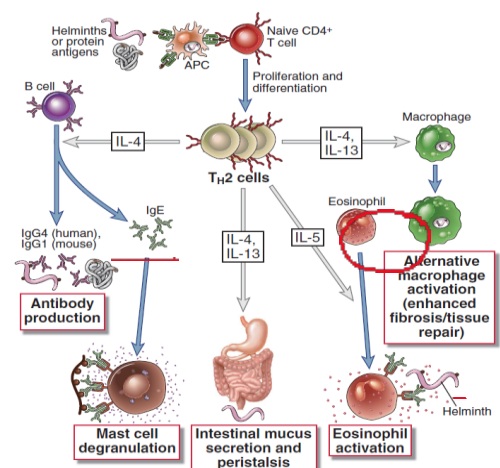
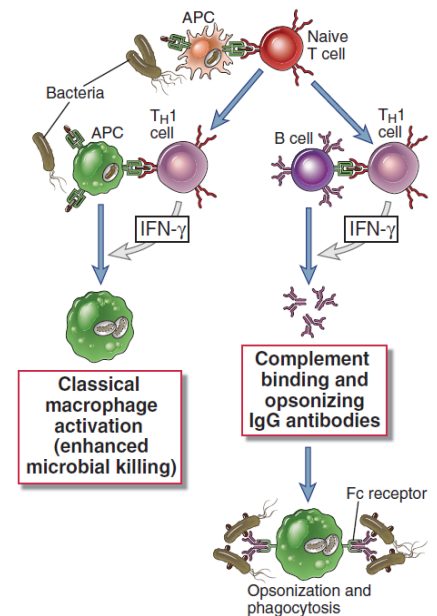
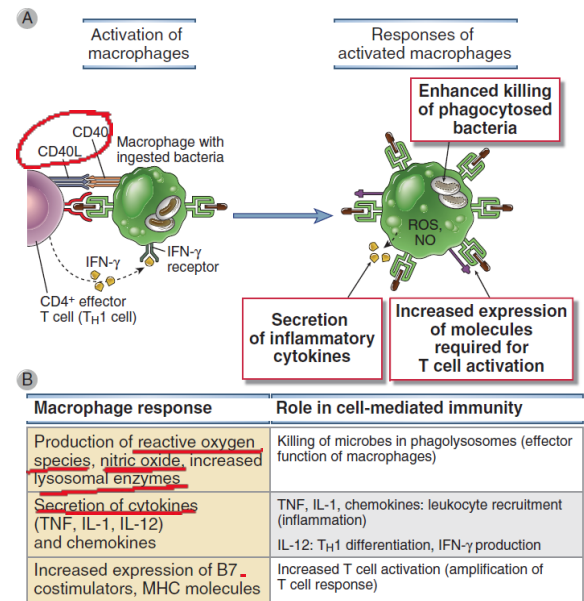
IFN- γ stimulates expression of several different proteins that contribute to **enhanced MHC- associated antigen presentation** and the initiation and amplification of T cell- dependent immune responses.



Functions of Th2 cells:

The principal function of TH2 cells is **stimulate IgE- and eosinophil-mediated reactions** that serve to eradicate helminthic infections.

- Their cytokines are IL-4, IL-5 and IL-13.



In the diagram naïve CD4⁺ T cell got activated by dendritic cell presented an antigens that came from a worm or helminthic parasite along with the right cytokines this naïve T cell will differentiate into T_H2 cells.

TH2 will produce many cytokines including **IL-4** which induces **IgE antibody responses** (IgEs have receptor called **FcεR1** on eosinophils and mast cells), **IL-5** which **activates eosinophils** and **IL-13** which has diverse actions.

>> Now we have an eosinophil bounds to IgE antibody through **FcεR1** and whenever the antigen binds to that IgE this will stimulate the eosinophil to degranulate to kill the helminth. The same mechanism happens during **allergic reactions** (will be discussed later on)

* **IL-4 and IL-13** both increase intestinal mucus secretion and peristalsis that will help in expulsion of the parasite and activate alternative pathway of macrophages which will induce matrix deposition and healing.

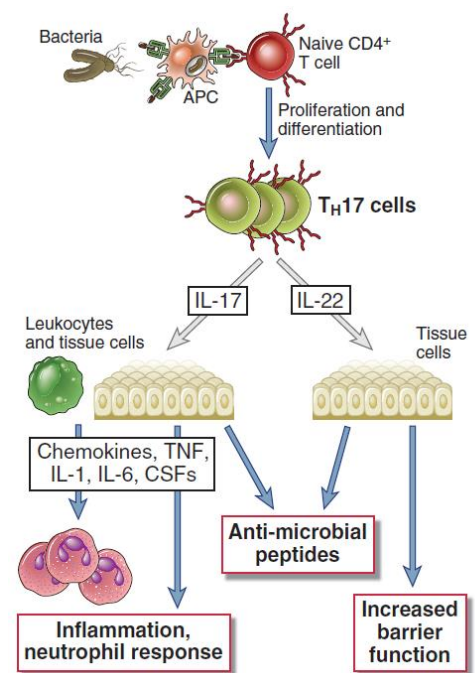
Functions of T_H17 cells:

-In this scenario an extracellular bacteria will get captured by a dendritic cell → processing of the antigen and presentation to naïve CD4⁺ T cell along with cytokines will aid in the formation of T_H17 cells.

They will secrete IL-17 that will recruit leukocytes and will induce the tissue cells for example epithelial cells to produce pro-inflammatory cytokines like (IL-1, IL-6, TNF).

[Neutrophils are a major defense mechanism against extracellular pathogens]

*recall that initially the first signals of presence of a foreign antigen are produced by tissue cells through the recognition of PAMPs and DAMPS by PRRS (pattern recognition receptors) and later on by the help of adaptive immune system there will be more signalling. It's a sort of a **loop**.



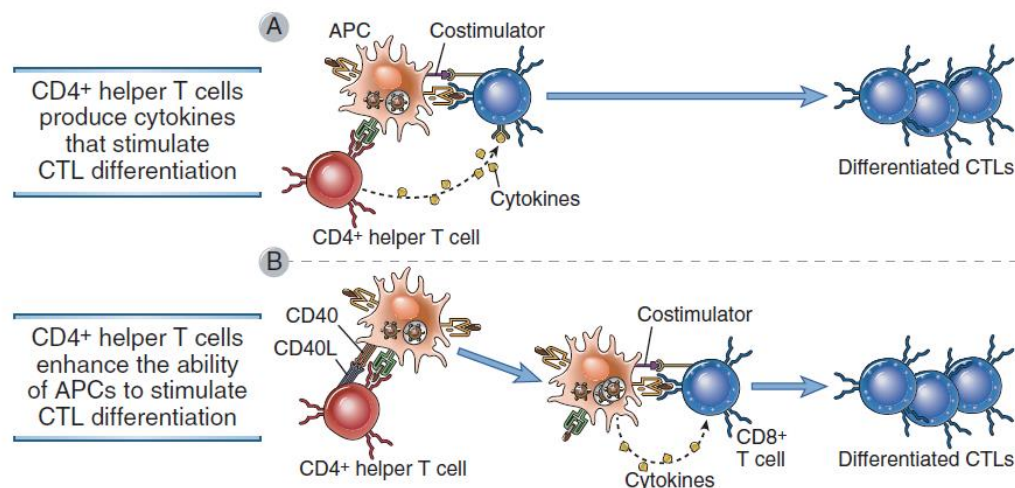
Innate and adaptive immunity are not separated they stimulate each other so there is an overlap between them.

-Cytokines produced by T_H17 (IL-17 and IL-22) can help in the production of **anti-microbial peptides (cathelicidins and defensins)**. Antimicrobial peptides possessing a net positive charge are attracted and incorporated into negatively charged bacterial membranes thus disturbing them.

So they increase barrier functions in general.

Effector functions of CD8+ T cells

CD8+ T cells also require a costimulatory signal ($B7 \Leftrightarrow CD28$) along with antigen presented on MHC1 molecule then they will proliferate and differentiate into effector Cytotoxic T cells and memory cells → migrate to the site of infection start their function which is killing if infected cells.



cross presentation process happen with Cytotoxic T cells where antigens that got taken up from the extracellular environment which usually should be presented by MHC2 but in this case the APC especially dendritic cells can switch this pathway into MHC class 1 to stimulate cytotoxic T lymphocytes to go and kill the virus infected cell without killing the dendritic cell.

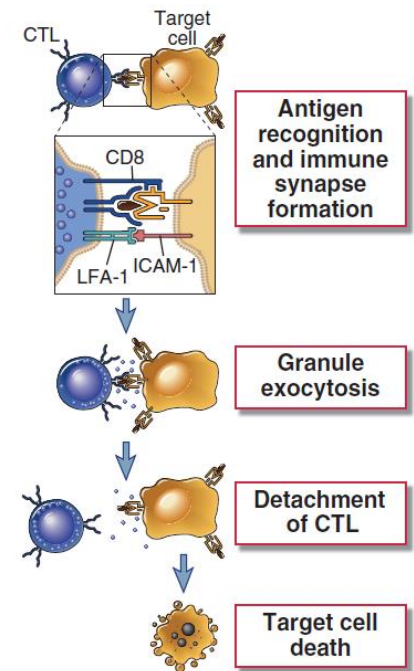
CD4+ T cells will secrete cytokines help cytotoxic T cells in their differentiation and proliferation, most probably T_H1 cells producing **IFN- γ** since they're the ones that can control intracellular antigens

Also ($CD40 \Leftrightarrow CD40L$) signal between CD4+ T cell and dendritic cell can aid as a costimulatory signal it will fully activate dendritic cells and as a result dendritic cells will produce cytokines that will continue stimulating CTLs (Cytotoxic T Lymphocytes).

Cytotoxic T cell capture the infected cell by **integrins** to ensure a strong binding then they will induce apoptosis through producing **perforins** that will form pores in the infected cell [similar to C9 proteins in the complement system] and **granzymes** that induce apoptotic pathway.

These two proteins will be released in a synapse to protect neighbouring non infected cells,

after the release of perforins and granzymes cytotoxic T cell will get detached and finally death of the target cell



Another mechanism of killing infected cells by CD8+ T cells

By engaging with death receptor **Fas** (on infected cell) when it bind to **FasL** (on CTL) the infected cell will undergo apoptosis.

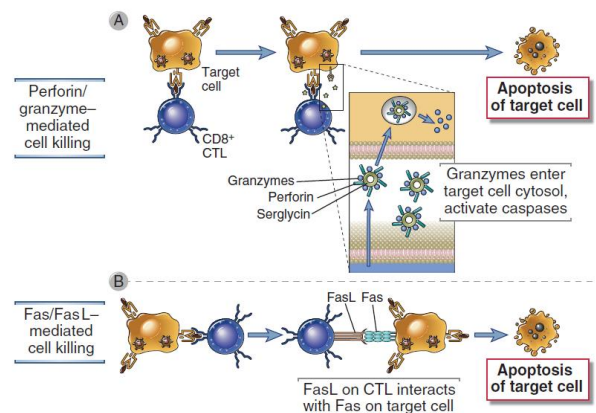


FIGURE 10-13 Mechanisms of CTL-mediated killing of target cells. CTLs kill target cells by two main mechanisms. **A.** Complexes of perforin and granzymes are released from the CTL by granule exocytosis and enter target cells. The granzymes are delivered into the cytoplasm of the target cells by a perforin-dependent mechanism, and they induce apoptosis. **B.** FasL is expressed on activated CTLs, engages Fas on the surface of target cells, and induces apoptosis.

EFFECTOR FUNCTIONS OF Regulatory T (TReg) cells

- * Treg cells express the biomarkers **CD4**, **FOXP3**, and **CD25** and are thought to be derived from the same lineage as naïve CD4+ cells.
- * Regulatory T (TReg) cells are essential for maintaining **peripheral tolerance**, preventing autoimmunity and limiting chronic inflammatory diseases. However, they also limit beneficial responses by suppressing sterilizing immunity and limiting anti-tumour immunity.
- * TReg cells have multiple mechanisms at their disposal to mediate their suppressive effects.
- * Suppression by inhibitory cytokines: interleukin-10 (IL-10), transforming growth factor- β (TGF β) and the newly identified IL-35 are key mediators of TReg-cell function.