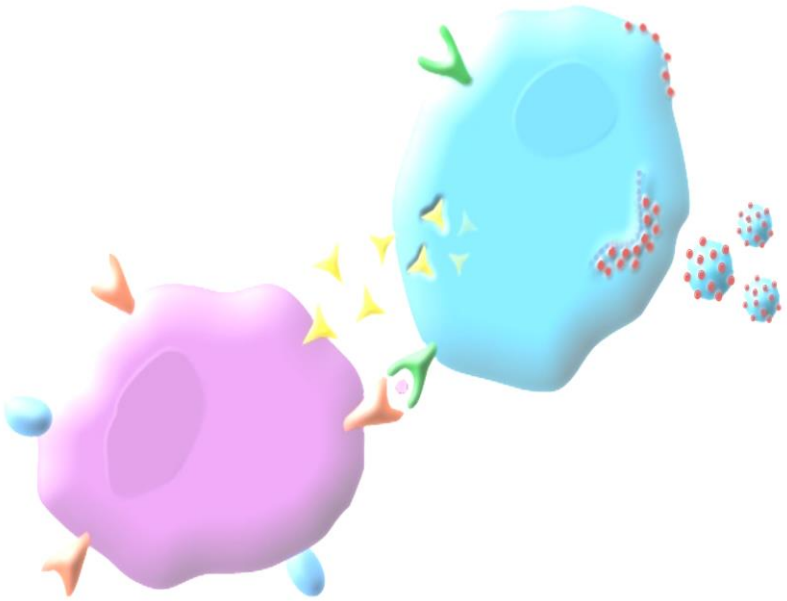
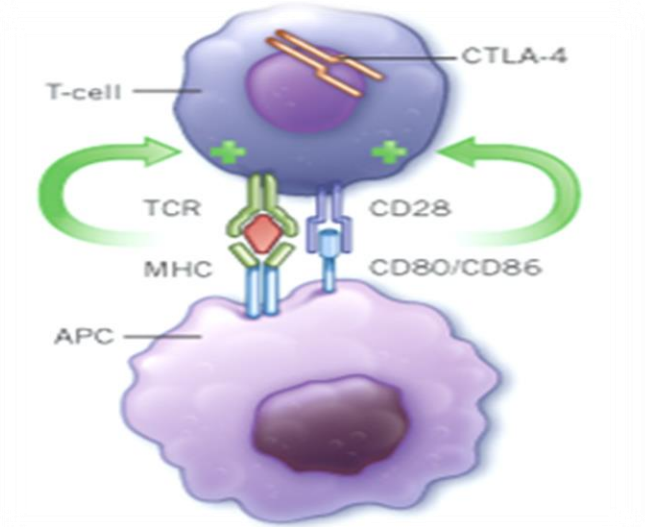
Lecture 3



Cellular immune response

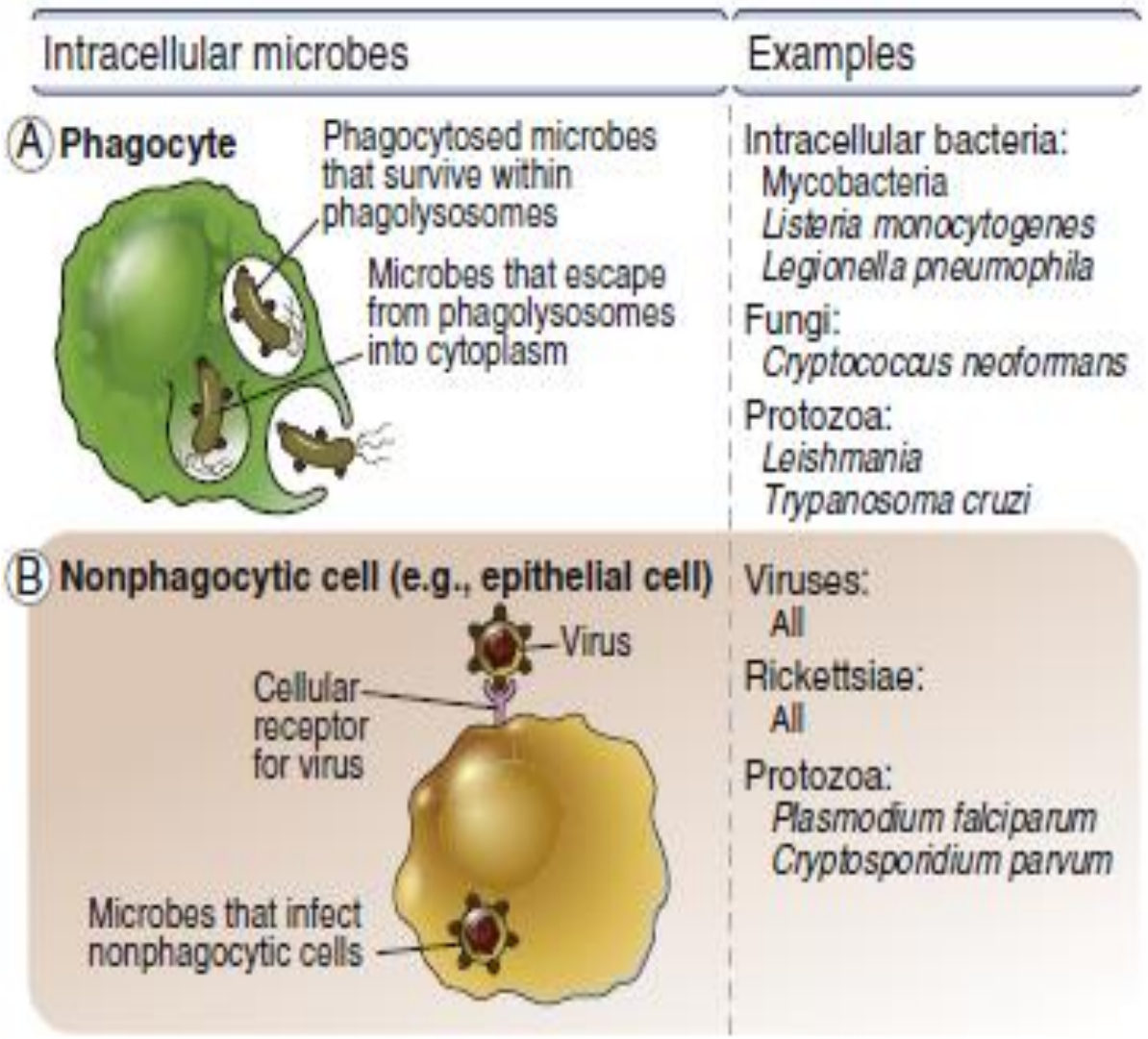
Effector mechanisms of cellular immunity

Cellular immune response



Activation of T lymphocytes by intracellular microorganisms

… let us remind ourselves



Cellular immunity protects us from intracellular microorganisms

T lymphocytes play a major role in this type of acquired immunity

There are two types of intracellular infections

Phases of T-cell response

The response of T lymphocytes to antigens of intracellular microorganisms takes place in several successive stages.

During this response:

- ✓ The number of T lymphocytes **specific** for the given antigen increases.

- ✓ The transformation of **naive** into **effector** and **memory** T lymphocytes.

… let us remind ourselves

Naive T lymphocytes...

...recirculate constantly...

...before eliminating antigens, they must additionally differentiate from naive to effector lymphocytes...

...that process begins with antigen recognition.

T lymphocytes **recognize** peptide fragments of protein antigens...

...and that as part of the products of the MHC on the APC that bring processed antigens from the periphery to the secondary lymphatic organs...

...the most effective in this process are dendritic cells because they provide an additional (second) signal for activation.

… let us remind ourselves

...after activation of T lymphocytes (antigen-specific)
they begin to synthesize and secrete cytokines
... Cytokines also stimulate **clonal expansion**

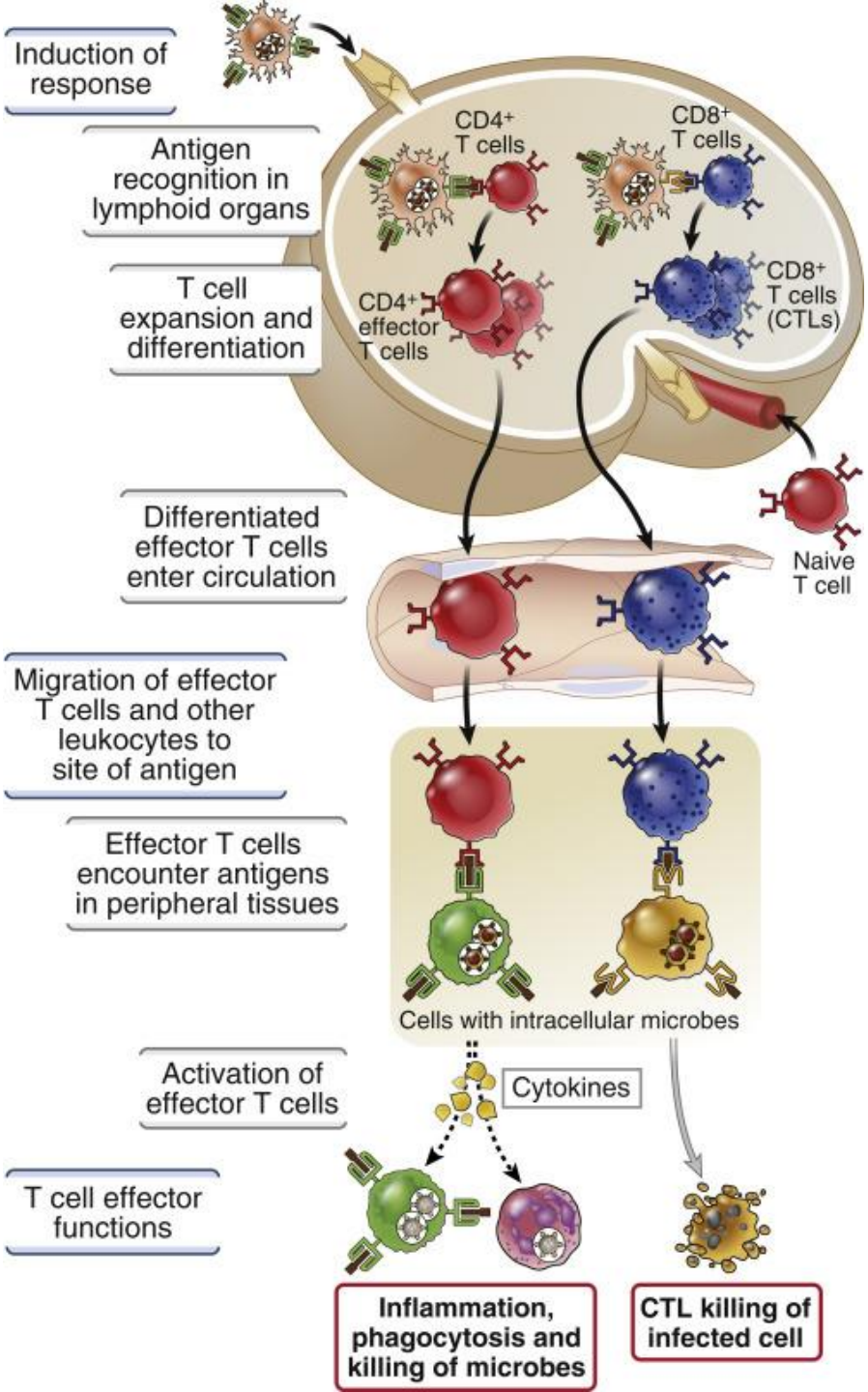
...lymphocytes activated in this way
further **differentiate** into effector and memory lymphocytes

...some of these cells remain in the lymph node
to participate in the elimination of the infected
cells and to help B lymphocytes

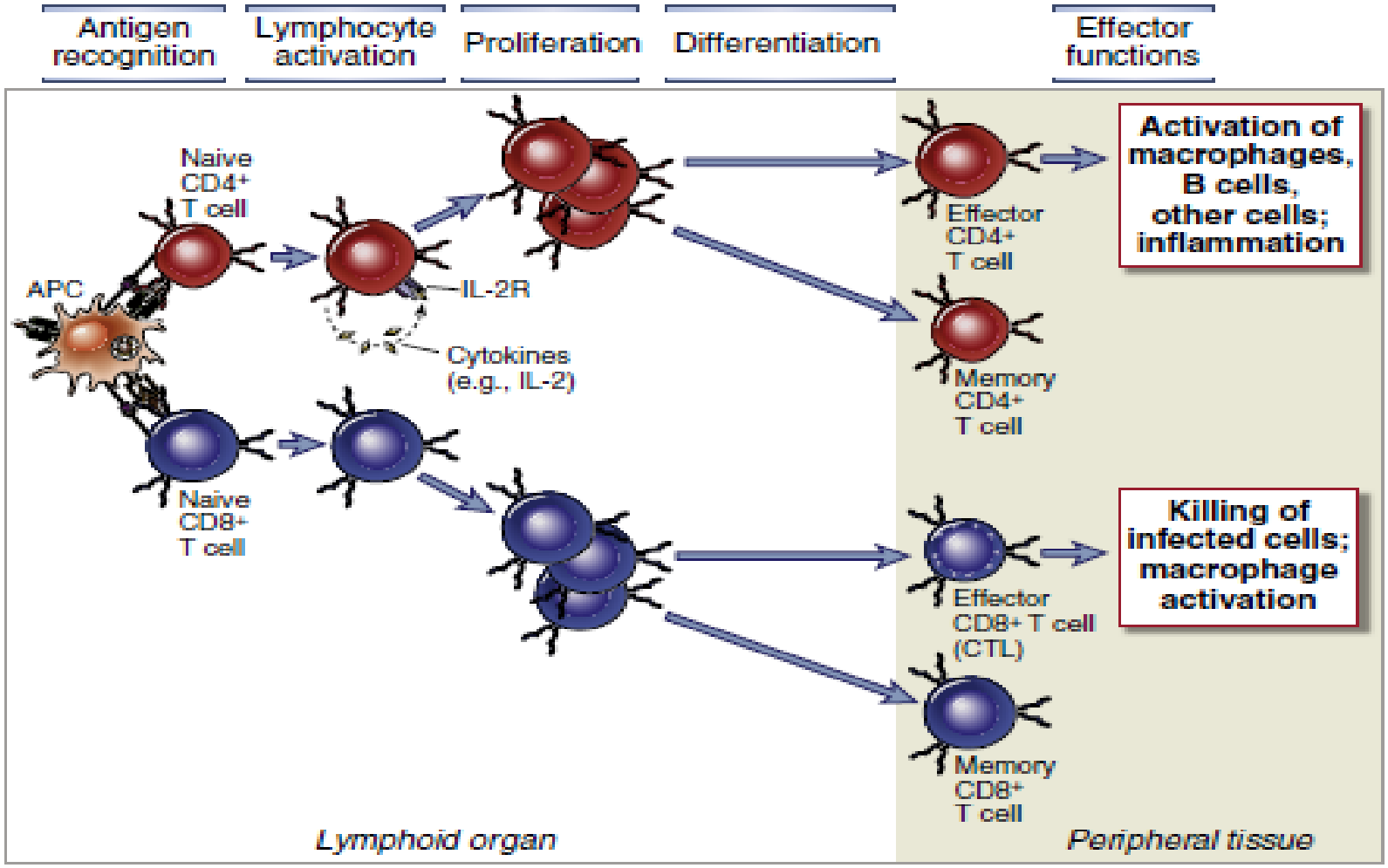
...most other effector T lymphocytes migrate to the site of infection...

...after antigen elimination, some of these lymphocytes become memory T lymphocytes

Initiation and effector phases of cellular immunity

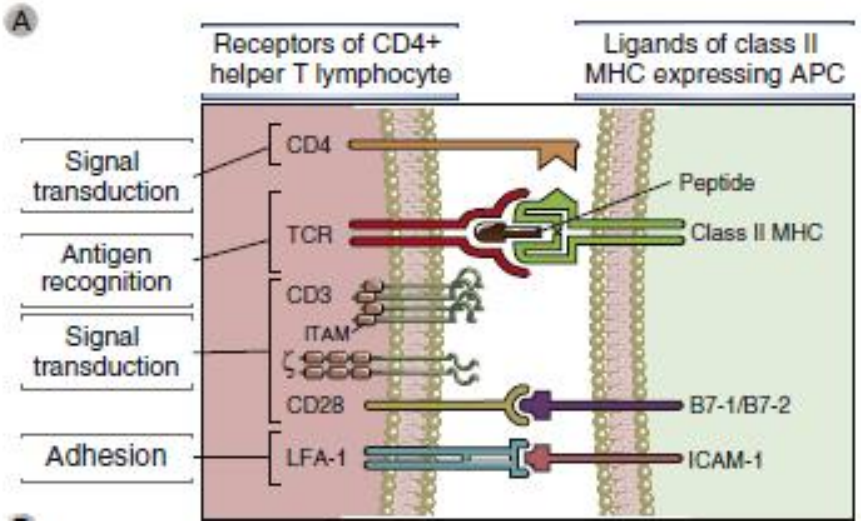


Phases of T lymphocyte activation: from naive to effector T lymphocytes



Antigen recognition and costimulation

Initiating a T-cell response requires multiple molecules on T lymphocytes to recognize the appropriate ligands on APC.

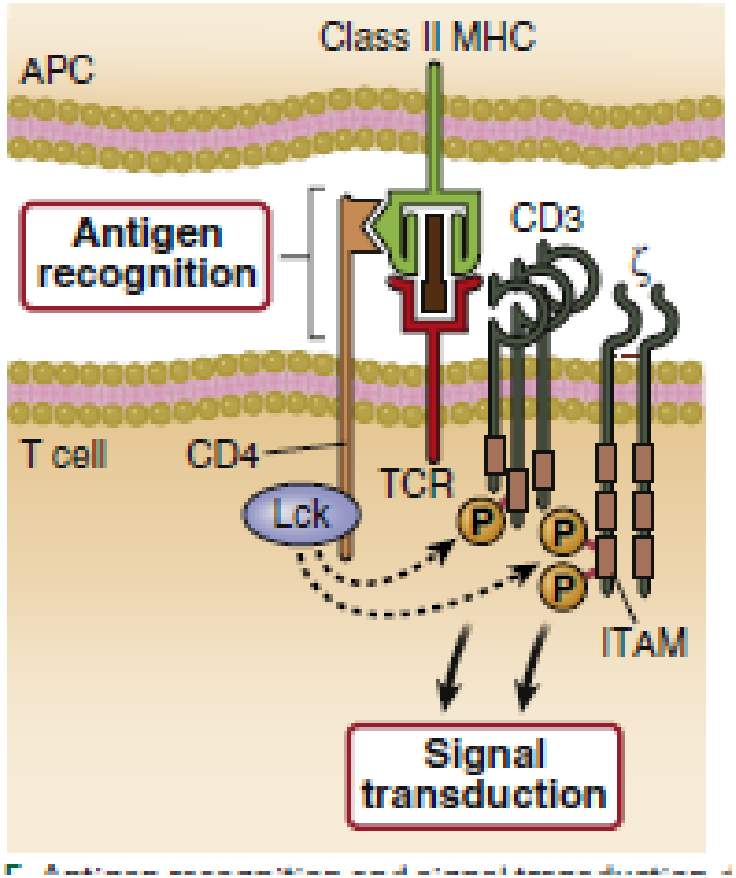


T cell accessory molecule	Function	Ligand	
		Name	Expressed on
CD3	Signal transduction by TCR complex	None	
ζ	Signal transduction by TCR complex	None	
CD4	Signal transduction	Class II MHC	Antigen presenting cells
CD8	Signal transduction	Class I MHC	All nucleated cells
CD28	Signal transduction (costimulation)	B7-1/B7-2	Antigen presenting cells
CTLA-4	Signal transduction (negative regulation)	B7-1/B7-2	Antigen presenting cells
PD-1	Signal transduction (negative regulation)	PD-L1/PD-L2	Antigen presenting cells, tissue cells, tumor cells
LFA-1	Adhesion	ICAM-1	Antigen presenting cells, endothelium

1. Recognition of peptides within the MHC molecule

This is the first signal for the activation of T lymphocytes. Receptor (TCR complex and coreceptors).

Coreceptors are **CD4** or **CD8** molecules.

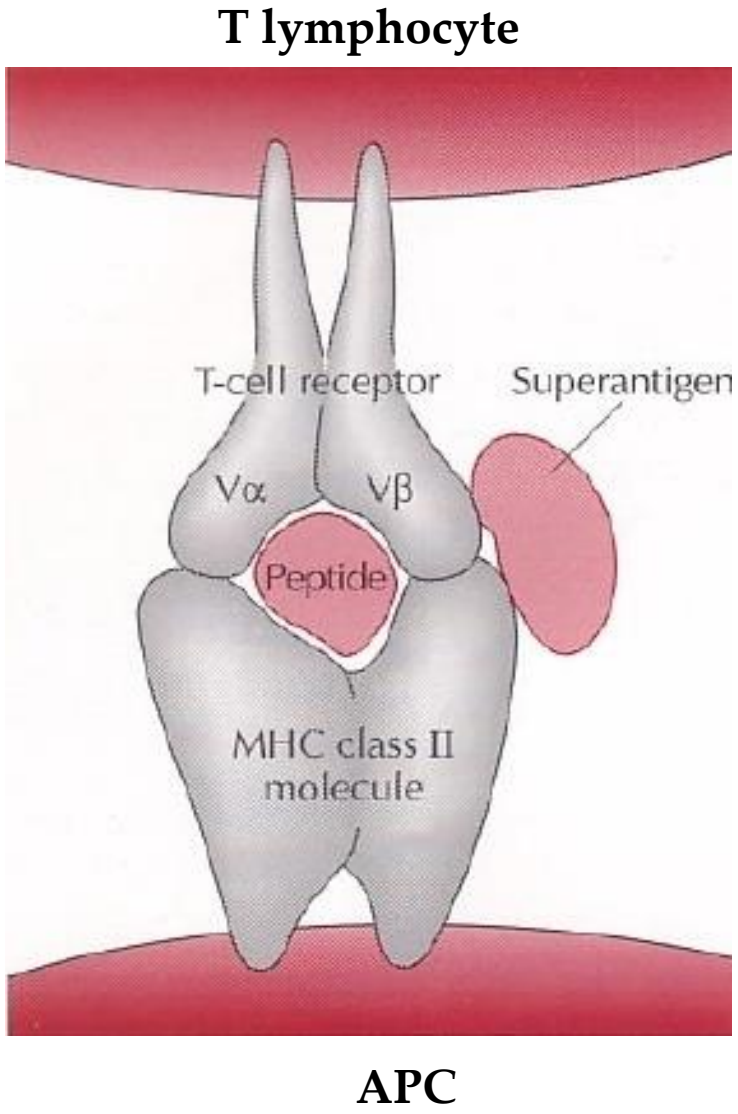


In the TCR complex,
Recognition of antigens
perform
variable regions of
α and β chains of TCR molecules,
while the invariable function
of signalling
perform
proteins CD3 and ζ.

Superantigens

Superantigens - some exotoxins of Gram-positive bacteria (S. aureus and S. pyogenes) stimulate a large number of CD4+ T lymphocytes by directly binding to class II MHC molecules on APC and to regions of VβTCR on T lymphocytes that are not part of active site.

By nonspecifically activating large numbers of CD4+ T lymphocytes, superantigens stimulate the production of large amounts of cytokines, resulting in a systemic reaction similar to septic shock.



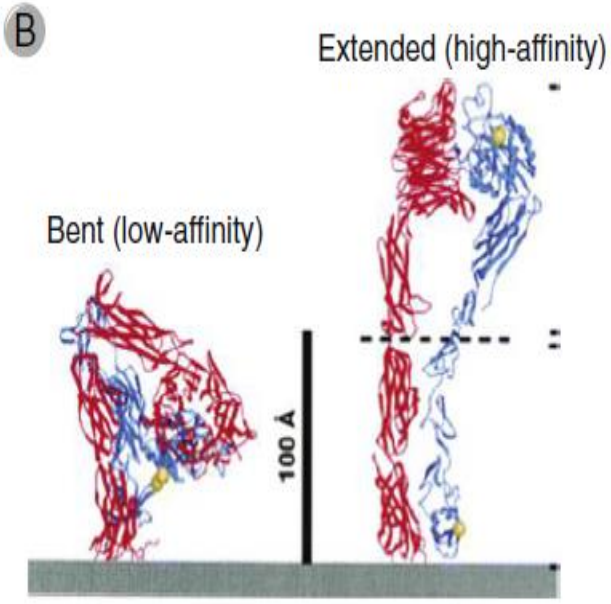
2. **Adhesive molecules in T lymphocyte activation**

Adhesive molecules are expressed on T lymphocytes, recognize their ligands on APC and thus stabilize the binding of T lymphocytes to APC.

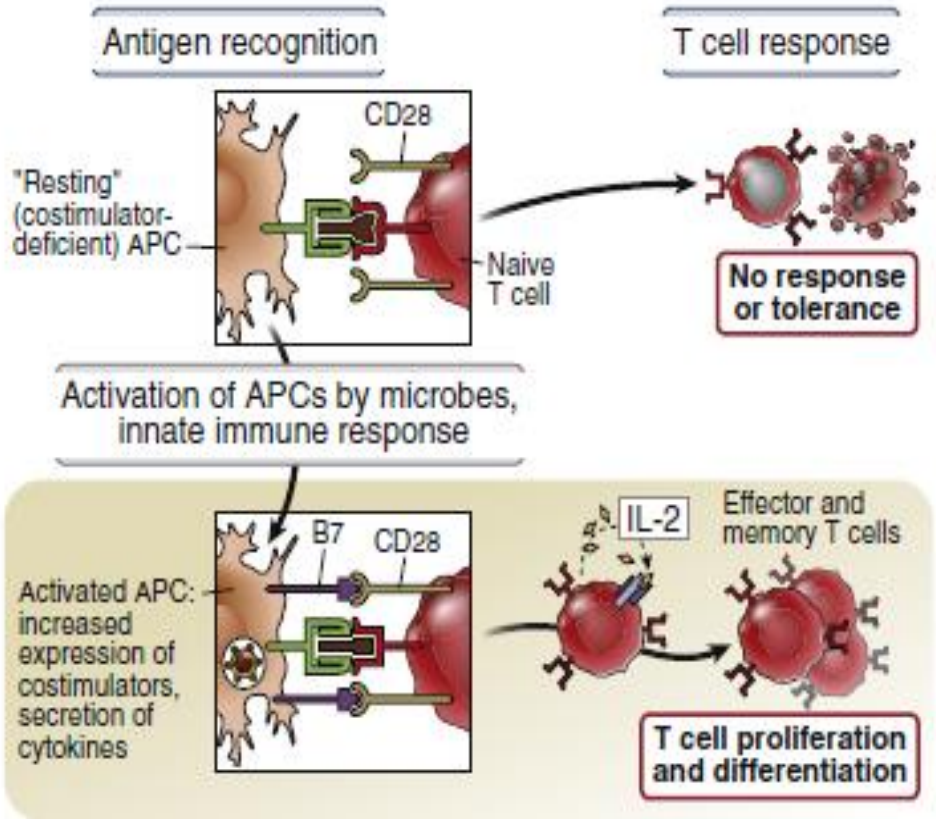
The most important adhesive molecules belong to a family of heterodimeric proteins called integrins. The main integrin on T cells is **LFA-1** (Leukocyte Function Associated Antigen -1). Its ligand is ICAM-1 (Intercellular adhesion molecule-1).

Adhesive molecules in T lymphocyte activation

- The integrins on blood leukocytes are normally in a low-affinity state.
- ***An important feature of integrins is their ability to respond to intracellular signals by rapidly increasing their affinity for their ligands***
- Chemokine and antigen receptor engagement in cells lead to increased affinity of the integrins
- Integrins are also important in directing the migration of effector T lymphocytes to the site of infection.



3. Costimulators in the activation of T lymphocytes



Costimulators are molecules expressed on **APCs** and provide a **second signal**.

The best studied **B7-1(CD80)** and **B7-2(CD86)** are expressed on professional APC.

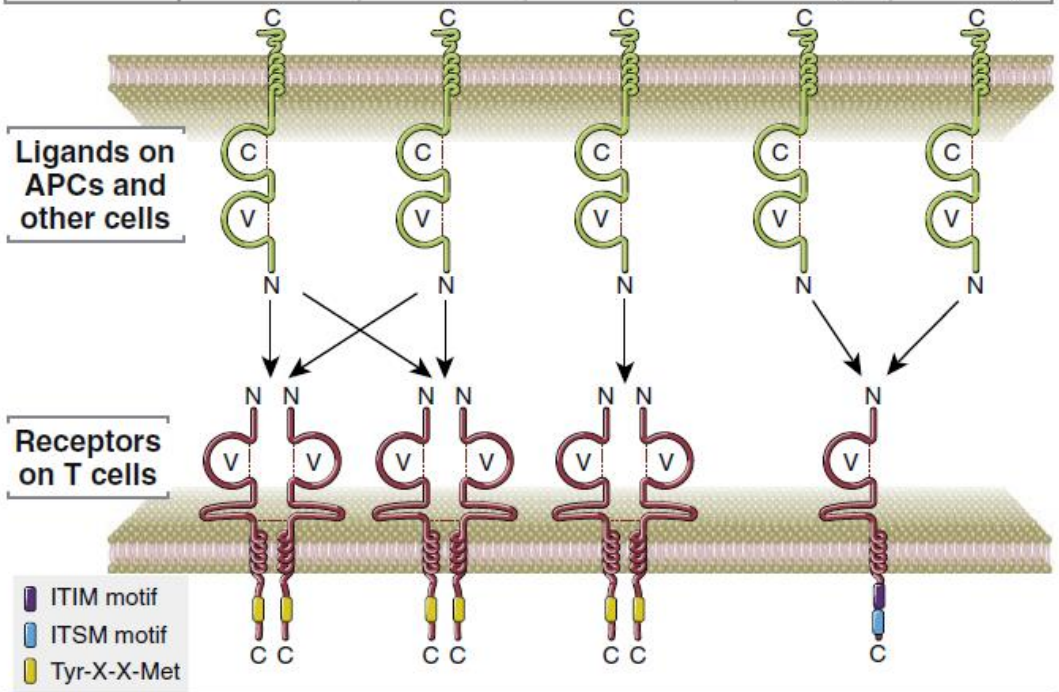
The expression of these molecules increases significantly when APC comes into contact with microorganisms.

The ligand for these molecules is **CD28** expressed on T lymphocytes.

In the absence of CD28 and B7 interaction, not only that there is no lymphocyte activation, but the lymphocyte can be disabled for a long time.

Members of the B7 and CD28 protein families

Expression	DCs; macrophages, B cells		DCs; macrophages, B cells, other cells	DCs; macrophages, B cells; endothelial, epithelial and tumor cells (PD-L1 only)	
Name	**B7-1 (CD80)**	**B7-2 (CD86)**	**ICOS-L (CD275)**	**PD-L1 (B7-H1, CD274)**	**PD-L2 (B7-DC, CD273)**



Name	**CD28**	**CTLA-4**	**ICOS**	**PD-1**
Expression	T cells; constitutive	T cells; inducible	T cells; inducible	T cells, B cells, myeloid cells; inducible
Major function	Costimulation of naive T cells; generation of regulatory T cells	Negative regulation of immune responses; self-tolerance	Costimulation of effector and regulatory T cells; generation of follicular helper T cells	Negative regulation of T cells

Another group of costimulatory molecules consists of **CD40** on APC and its **CD40 ligand** (CD154) on T lymphocytes.

The contact of these molecules does not directly enhance the activation of T lymphocytes. Instead, this binding increases the expression of B7 molecules on APCs and prompts them to secrete IL-12, which stimulates T lymphocyte differentiation.

Protein antigens (e.g. those used in vaccines are inert and cannot induce a T cell immune response on their own, but it is necessary to give them substances that activate ARS (dendritic cells, macrophages, and probably also B lymphocytes). These substances are **adjuvants**.

Adjuvants work by inducing the expression of costimulators on APCs and prompting them to secrete activating cytokines.

Different members of the CD28 family participate in the activation, but also in the inhibition of T lymphocytes.

To limit or end the immune response are important:

...**CTLA4** which also binds to B7 on APC, but transmits an inhibitory signal and prevents the immune response to some tumors.

…**PD-1** which binds to similar ligands and inhibits the response to infection allowing chronicity.

Receptor: TCR recognizes the peptide within the APC

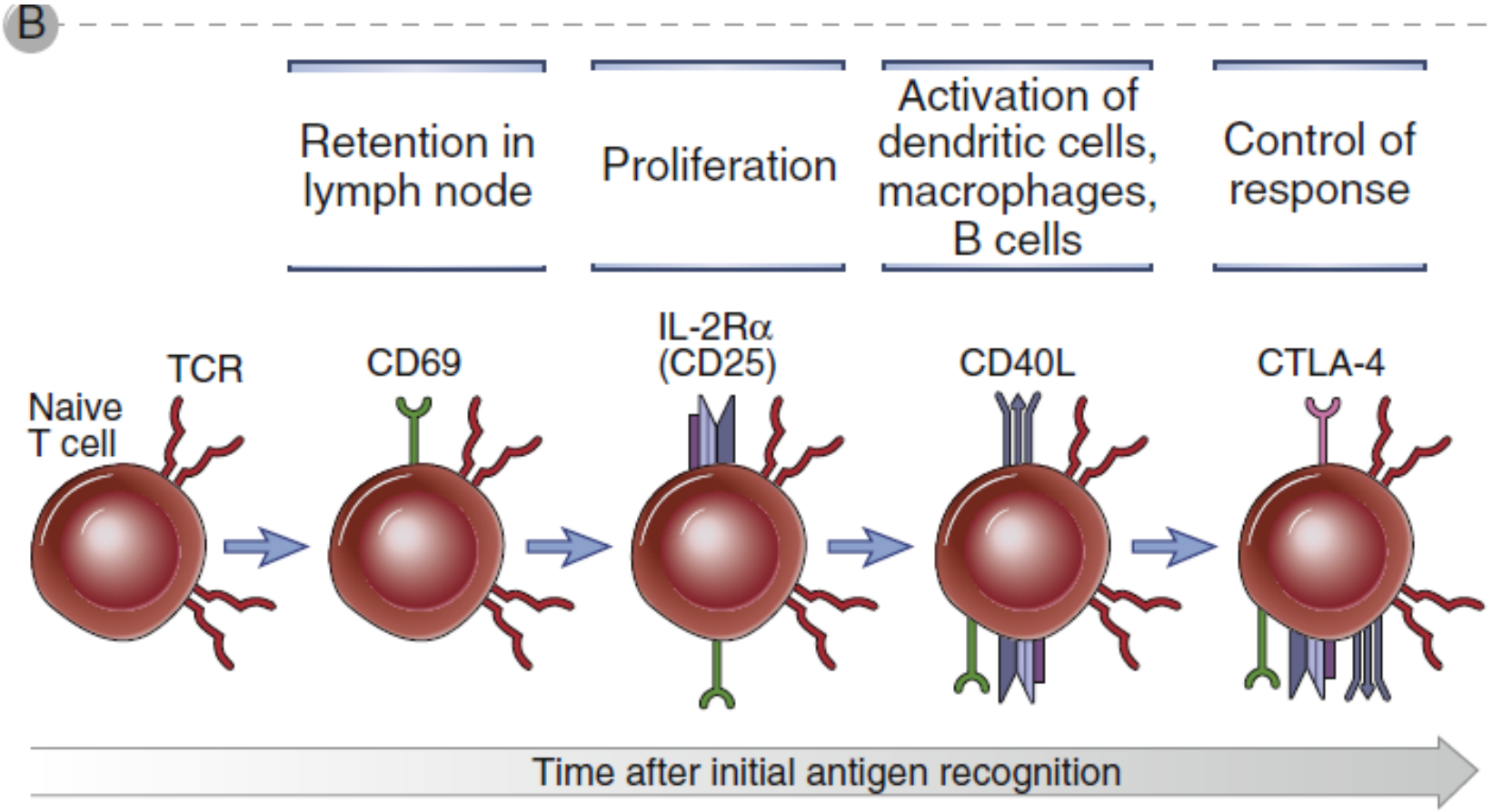
ACCESSORY MOLECULES :

CO-RECEPTORS (expressed on T lymphocytes): CD4 and CD8

ADHESIVE MOLECULES (expressed on T lymphocytes): LFA-1

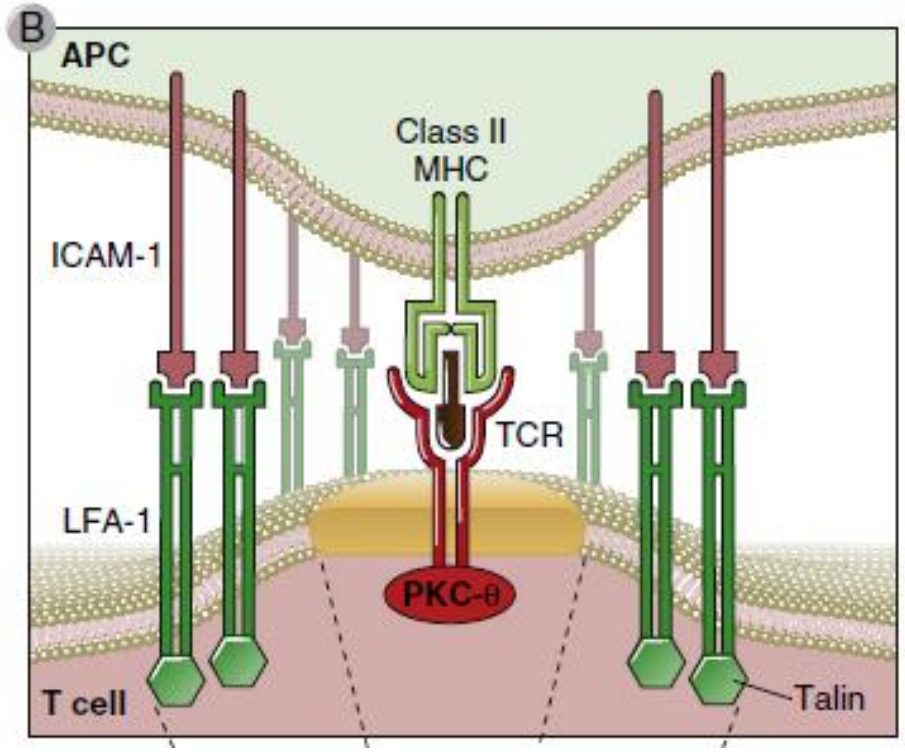
COSTIMULATORS (expressed on APC): B7-1, B7-2, CD40

Proteins produced by antigen-stimulated T lymphocytes

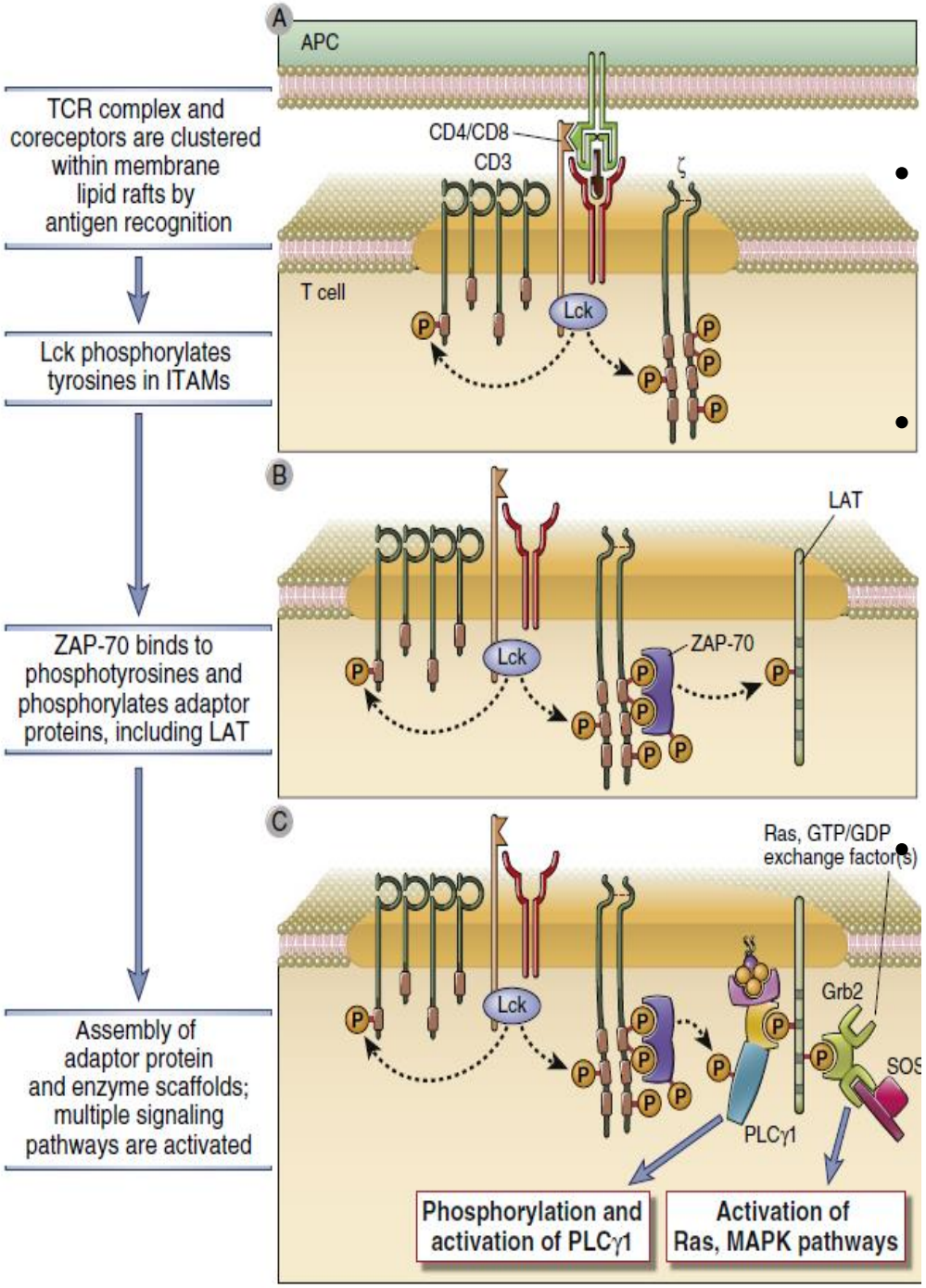


After the initiation of activation by antigen recognition and costimulator binding, there are characteristic changes in the expression of various surface molecules in T cells. These proteins are typically expressed at low levels in naive T cells and are induced by activating signals.

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 forms structure that is called an immunologic synapse

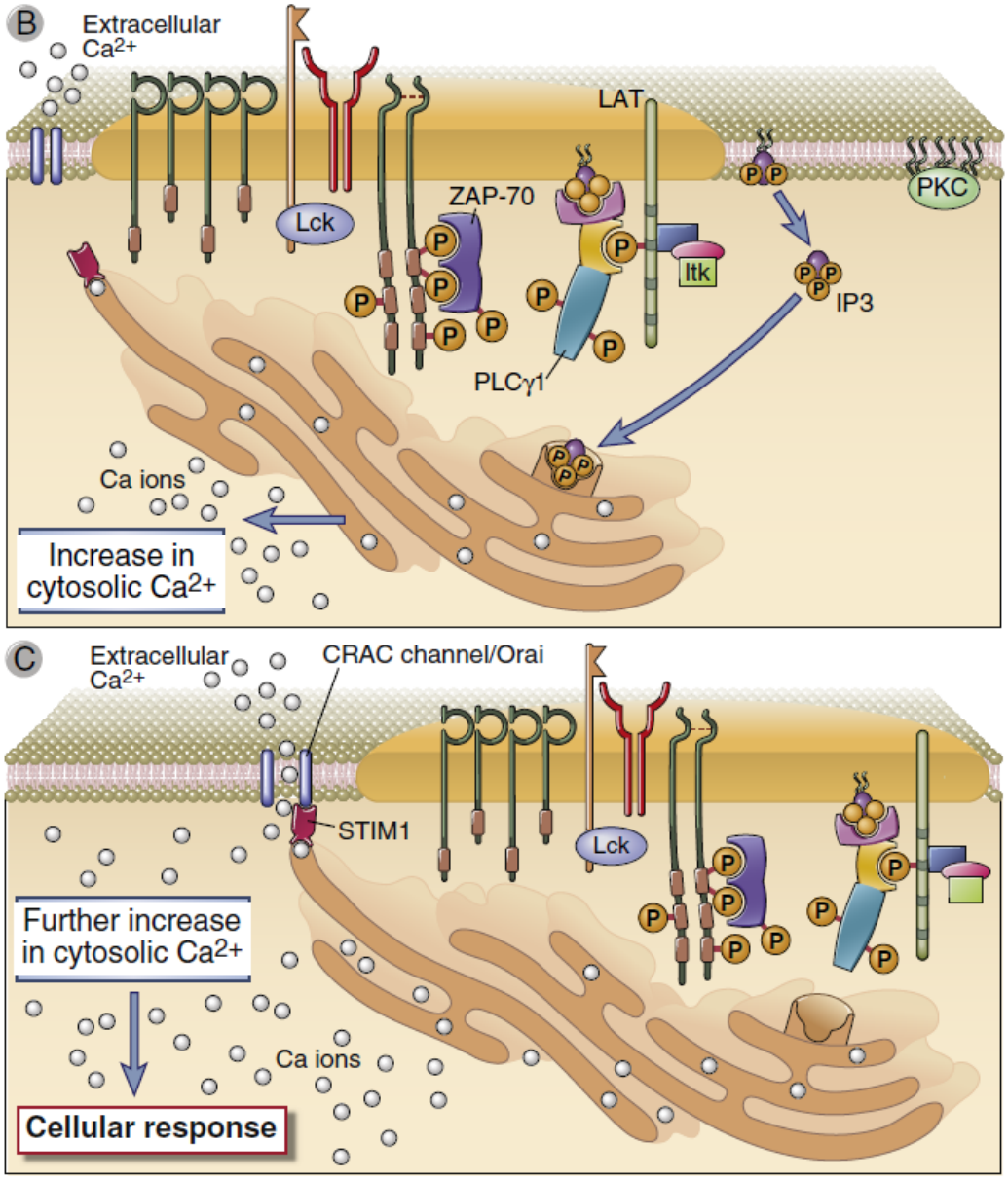


Early tyrosine phosphorylation events in T cell activation.



- ***Phosphorylation of proteins and lipids plays a central role in the transduction of signals from the TCR complex and coreceptors***
- On antigen recognition, there is clustering of TCR complexes with coreceptors (CD4/CD8). Coreceptor-associated Lck becomes active and phosphorylates tyrosines in the ITAMs of CD3 and ζ chains.
- ZAP-70 binds to the phosphotyrosines of the ζ chains and is itself phosphorylated and activated. Active ZAP-70 then phosphorylates tyrosine's on various adaptor molecules that results activating multiple signaling pathways.

1. NFAT cells signaling pathway



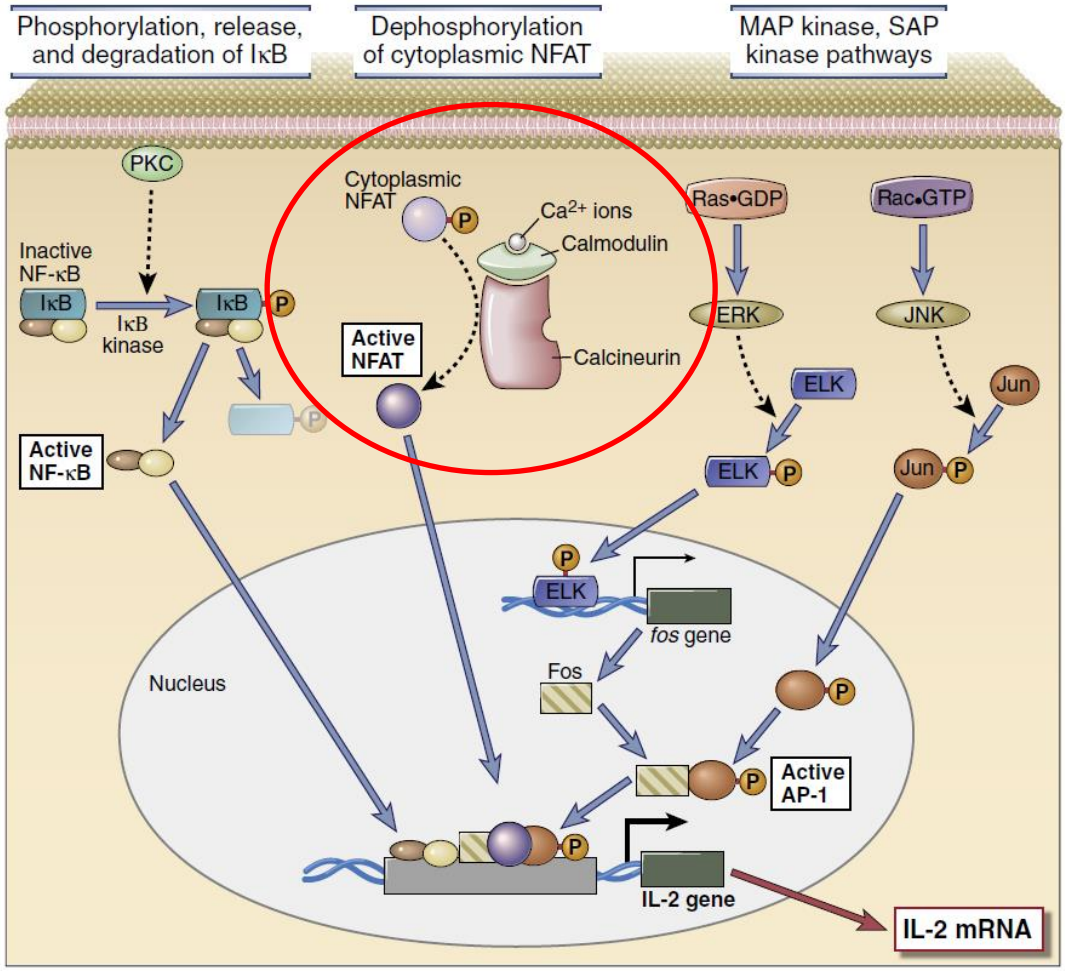
NFAT is a transcription factor required for the expression of genes encoding IL-2, IL-4, TNF, and other cytokines.

The LAT adaptor protein that is phosphorylated on T cell activation binds the cytosolic enzyme PLCγ1, which is phosphorylated by ZAP-70 and activated.

Active PLCγ1 hydrolyzes membrane PIP2 to generate IP3.

IP3 induces the opening of the CRAC channel that facilitates entry of extracellular calcium into the cytosol.

1. NFAT cells signaling pathway



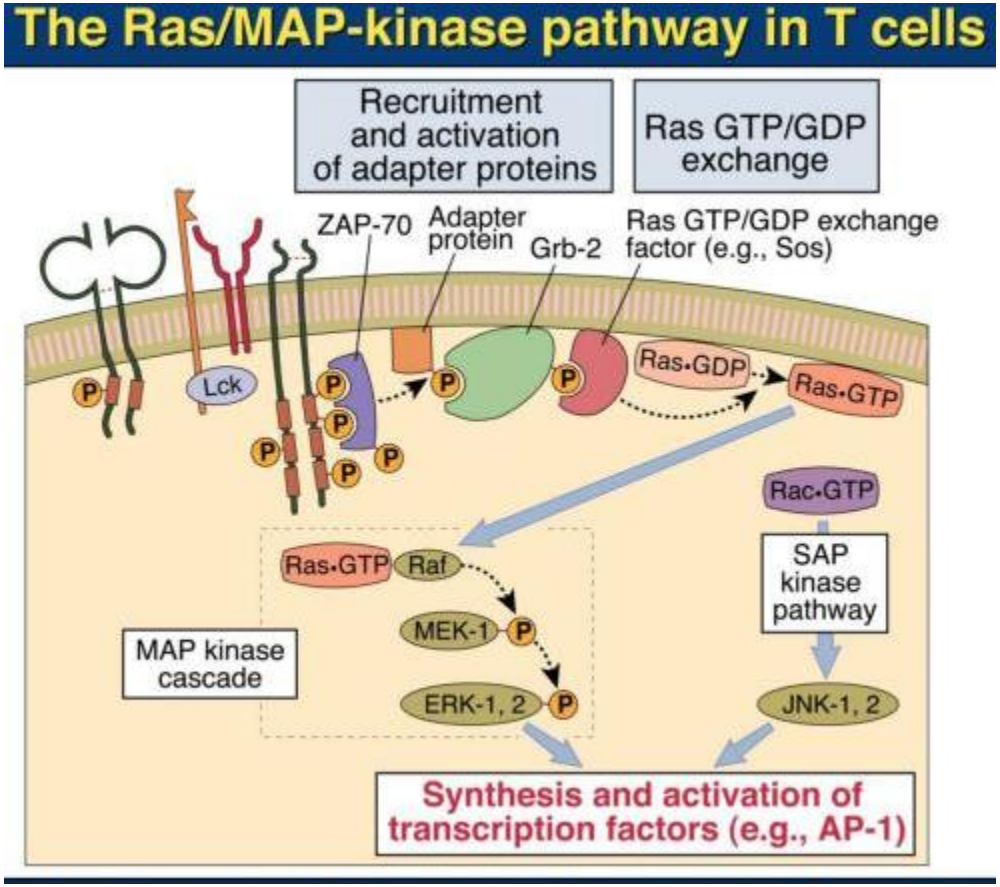
NFAT is present in an inactive phosphorylated form in the cytoplasm of resting T lymphocytes.

Ca^{++} binds to the protein calmodulin, and this complex activates the calcineurin phosphatase, which removes phosphate groups from NFAT.

NFAT translocate into the nucleus.

In the nucleus, NFAT binds to the regulatory regions of IL2 and other cytokine genes and initiates transcription of the IL-2 gene

2. The Ras-MAP kinase pathway



ZAP-70 phosphorylates membrane-associated adaptor proteins, which then bind another adaptor, Grb-2.

Grb-2 provides a docking site for the GTP/GDP exchange factor SOS.

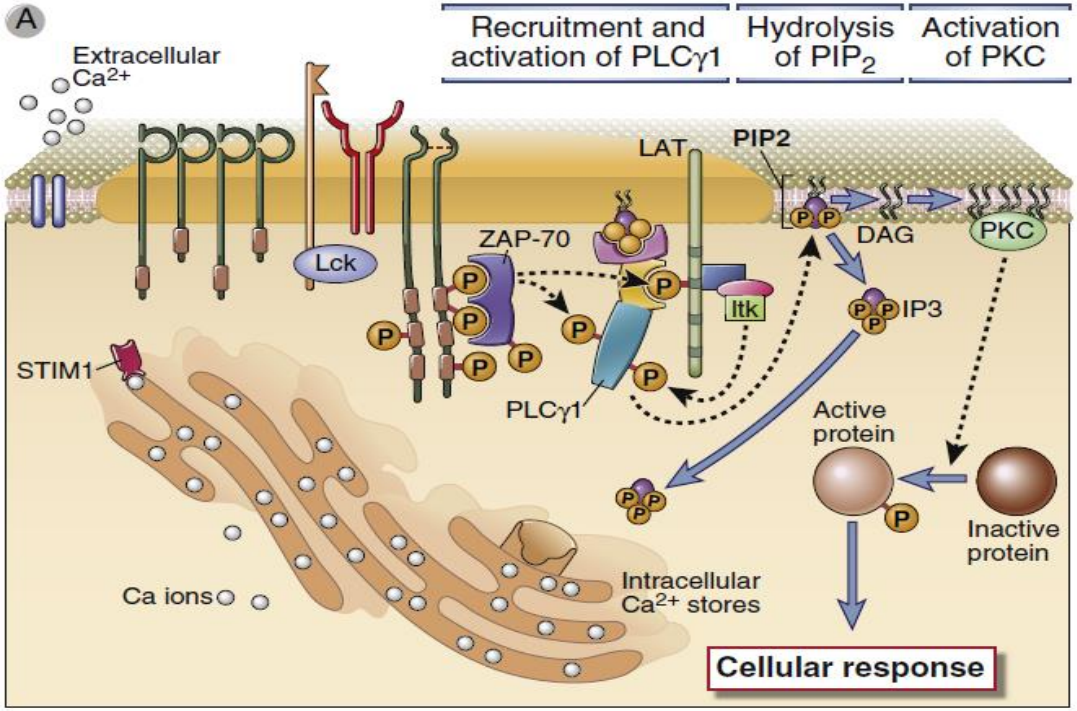
SOS converts Ras·GDP to Ras·GTP. Ras·GTP activates a cascade of enzymes, which results in the activation of the MAP kinase

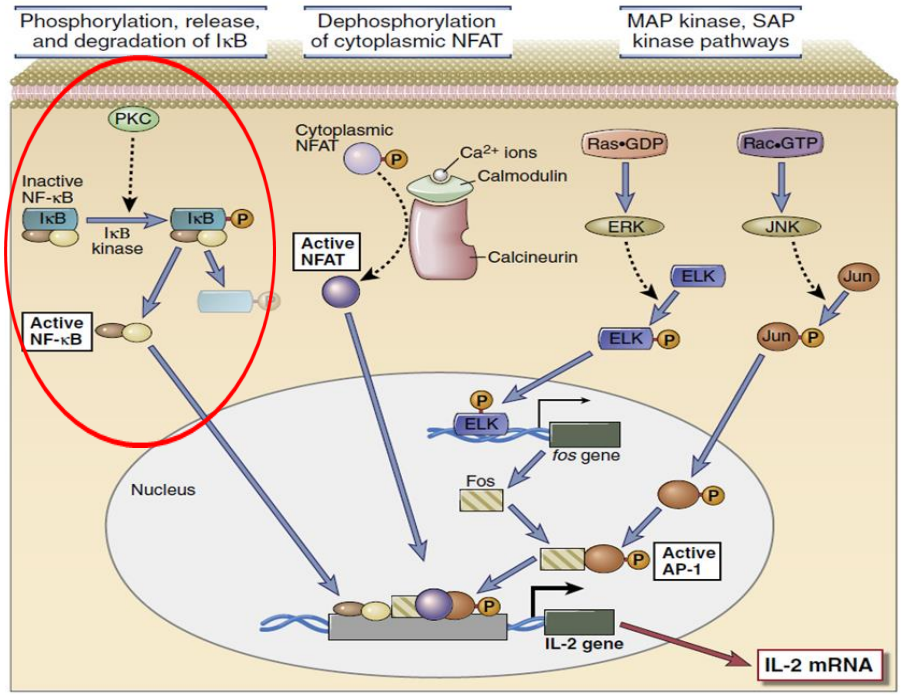
ERK.

A parallel Rac-dependent pathway generates another active MAP kinase, JNK

These kinases stimulate:
the expression of the protein c-Fos
the phosphorylation of the protein c-Jun
c-Fos and c-Jun together form the transcription factor AP-1 (activating protein – 1)

3. PKCΘ-NF-κB signal pathway :



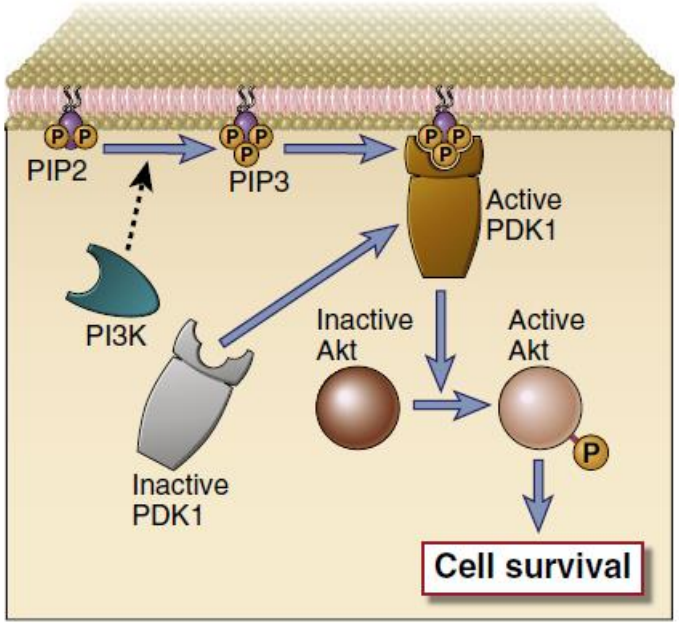


PLC γ hydrolyzes the membrane inositol phospholipid to IP3 and diacylglycerol (DAG).

DAG activates PKCΘ (protein kinase C).

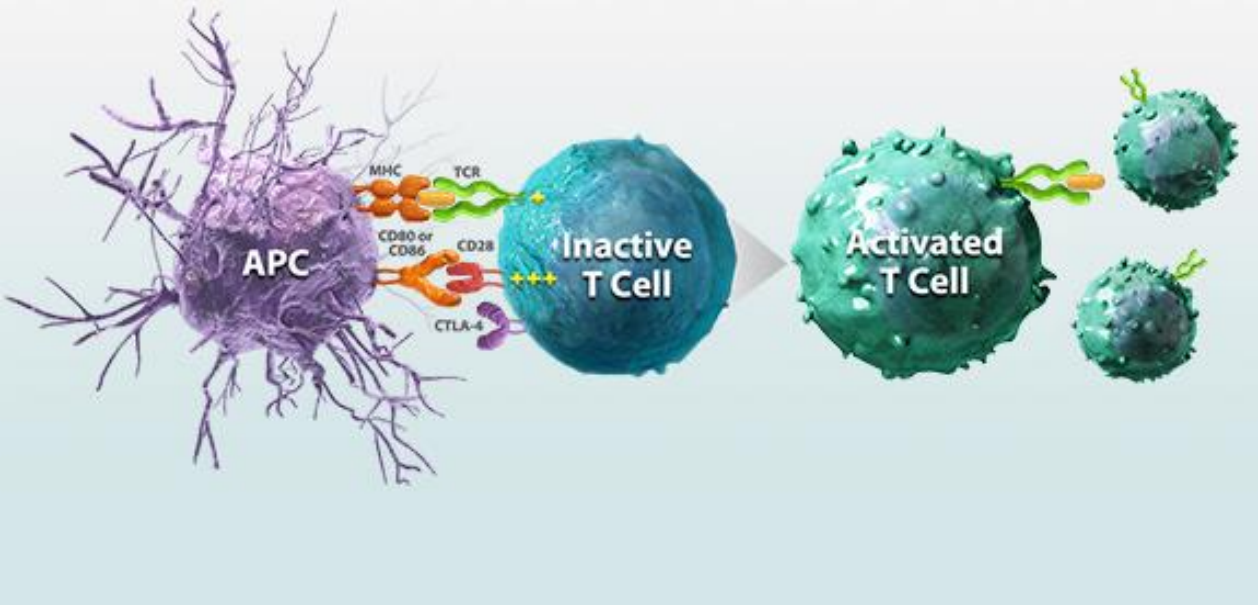
PKCΘ activates NF-κB by phosphorylating its inhibitor IκB, so the activated NF-κB moves into the nucleus where it stimulates the transcription of several genes.

4. PI3-kinase signaling pathway



- Phosphatidylinositol 3-kinase **PI3-kinase**, phosphorylates a specific phosphatidylinositol bisphosphate (PIP2) and generates phosphatidylinositol trisphosphate (PIP3).
- PIP3 activates Akt kinase.
- Activated Akt phosphorylates crucial targets and contributes to cell survival in a number of ways, including the inactivation of pro-apoptotic members of the Bcl-2 family.

After antigen recognition and costimulators bind to their ligands, gene transcription for cytokines, their receptors, cell cycle activators and effector molecules (eg CD40 ligand) begins.



The final result of the activation of T lymphocytes is the proliferation (expansion) of the antigen-specific clone and the differentiation of naive into effector lymphocytes.

Functional response of T lymphocytes to antigens and costimulation

1. Cytokine secretion and expression of their receptors

In a non-specific immune response, the main source of cytokines is the **macrophage**.

In the specific immune response it is **CD4+ T lymphocyte**.

Cytokines secreted by helper CD4+ T lymphocytes

General properties of T cell cytokines

Property	Significance
Produced transiently in response to antigen	Provides cytokine only when needed
Usually acts on same cell that produces the cytokine (autocrine) or nearby cells (paracrine)	Systemic effects of cytokines usually reflect severe infections or autoimmunity
Pleiotropism: each cytokine has multiple biological actions	Provides diversity of actions but may limit clinical utility of cytokines because of unwanted effects
Redundancy: multiple cytokines may share the same or similar biological activities	Blocking any one cytokine may not achieve a desired effect

Biologic actions of selected T cell cytokines

Cytokine	Principal action	Cellular source(s)
IL-2	T cell proliferation; regulatory T cell survival	Activated T cells
Interferon-γ (IFN-γ)	Activation of macrophages (classical pathway)	$CD4^+$ Th1 and $CD8^+$ T cells, natural killer (NK) cells
IL-4	B cell switching to IgE; alternative macrophage activation	$CD4^+$ Th2 T cells, mast cells
IL-5	Activation of eosinophils	$CD4^+$ Th2 T cells, mast cells, innate lymphoid cells
IL-13	B cell switching to IgE; alternative macrophage activation	$CD4^+$ Th2 T cells, mast cells, innate lymphoid cells
IL-17	Stimulation of acute inflammation	$CD4^+$ Th17 T cells, other cells
IL-21	B cell activation; Tfh differentiation	$CD4^+$ Tfh T cells
IL-22	Maintenance of epithelial barrier function	$CD4^+$ Th17 T cells, NK cells, innate lymphoid cells

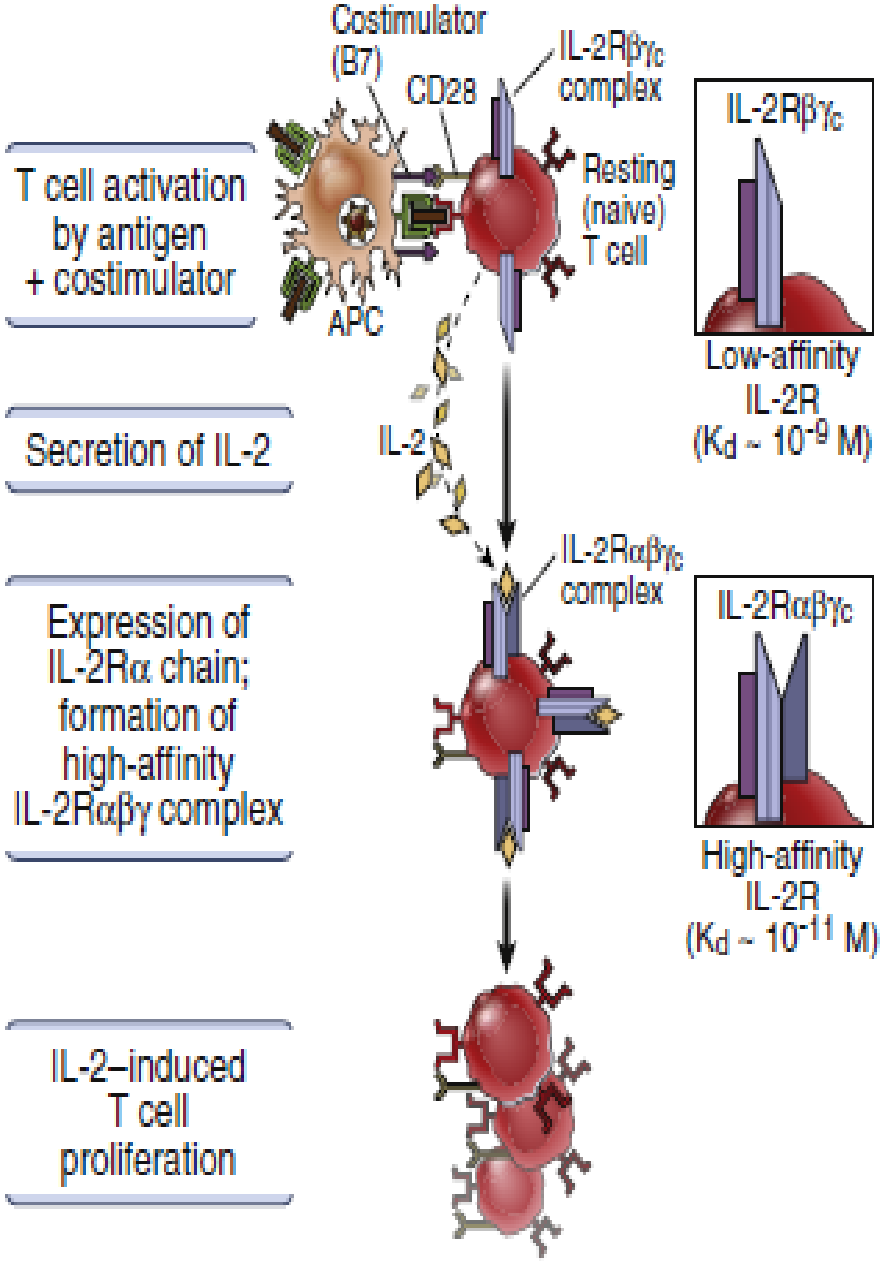
IL-2 is the first cytokine secreted immediately (one to two hours) after activation. Activation also stimulates **IL-2 receptor expression.**

The IL-2 receptor (IL-2R) consists of three non-covalently associated proteins

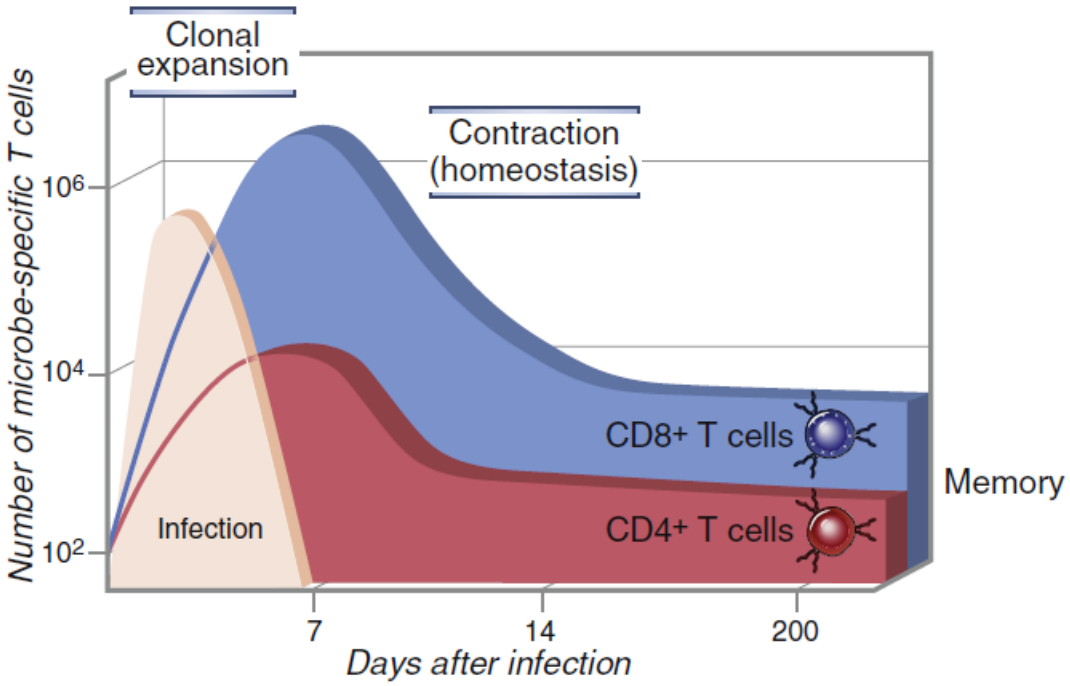
Resting (naive) T lymphocytes express the IL-2Rβγc complex which has a low affinity for IL-2

Activation of the T cells and IL-2 itself leads to expression of the IL-2Rα chain and increased levels of the high-affinity IL-2Rαβγ complex.

IL-2 is a growth (proliferation) and survival factor of T lymphocytes.



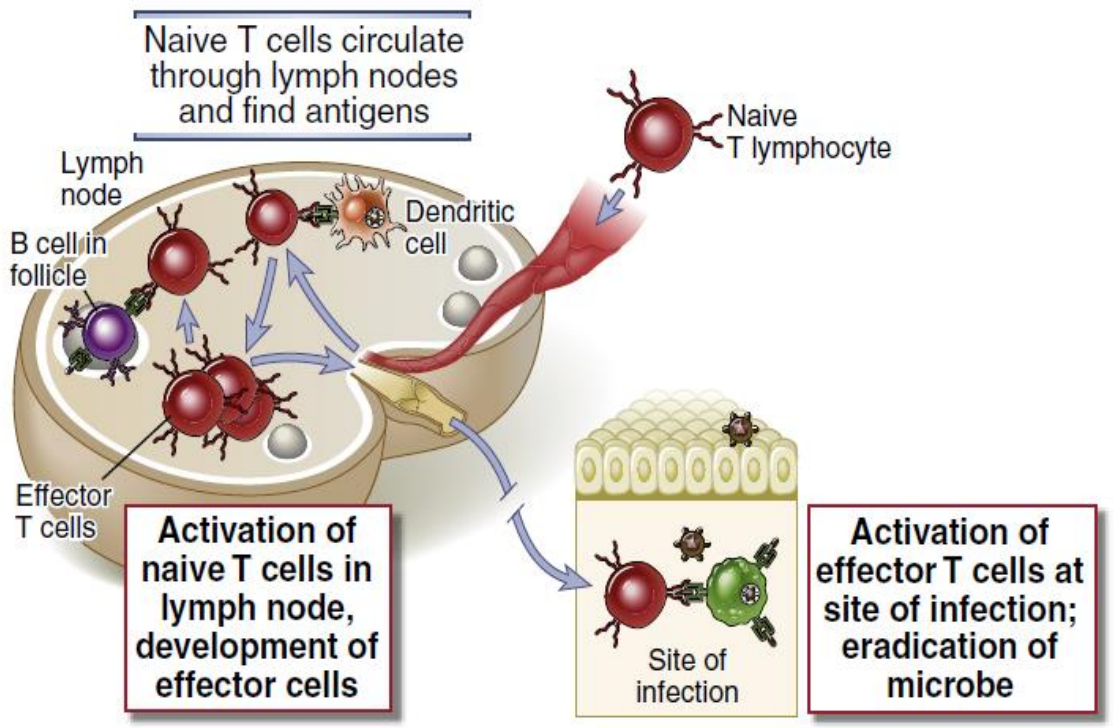
2. Clonal expansion



In response to some viruses, the number of antigen-specific T lymphocytes can increase

more than 10,000-fold with an estimated doubling time of about 6 hours (especially for CD8+ T lymphocytes).

3. Differentiation of naive into effector T lymphocytes

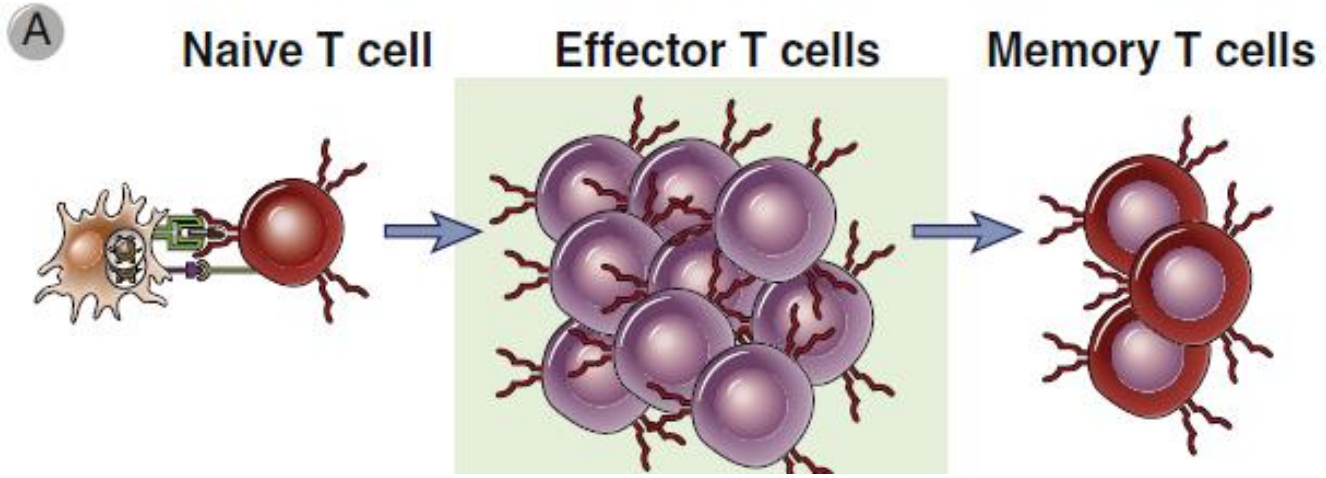


- After antigen recognition T cells activate and differentiate into effector cells, which may remain in the lymphoid organs to help B lymphocytes or migrate to sites of infection, macrophage activation.

These **effector** lymphocytes produce **membrane molecules** and **cytokines** in response to antigen.

These products mainly activate **macrophages** and **B lymphocytes**.

Development of memory T lymphocytes

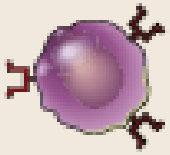
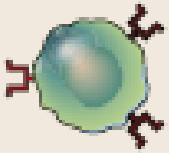
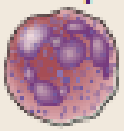


Some antigen-activated T lymphocytes differentiate into long-lived memory lymphocytes

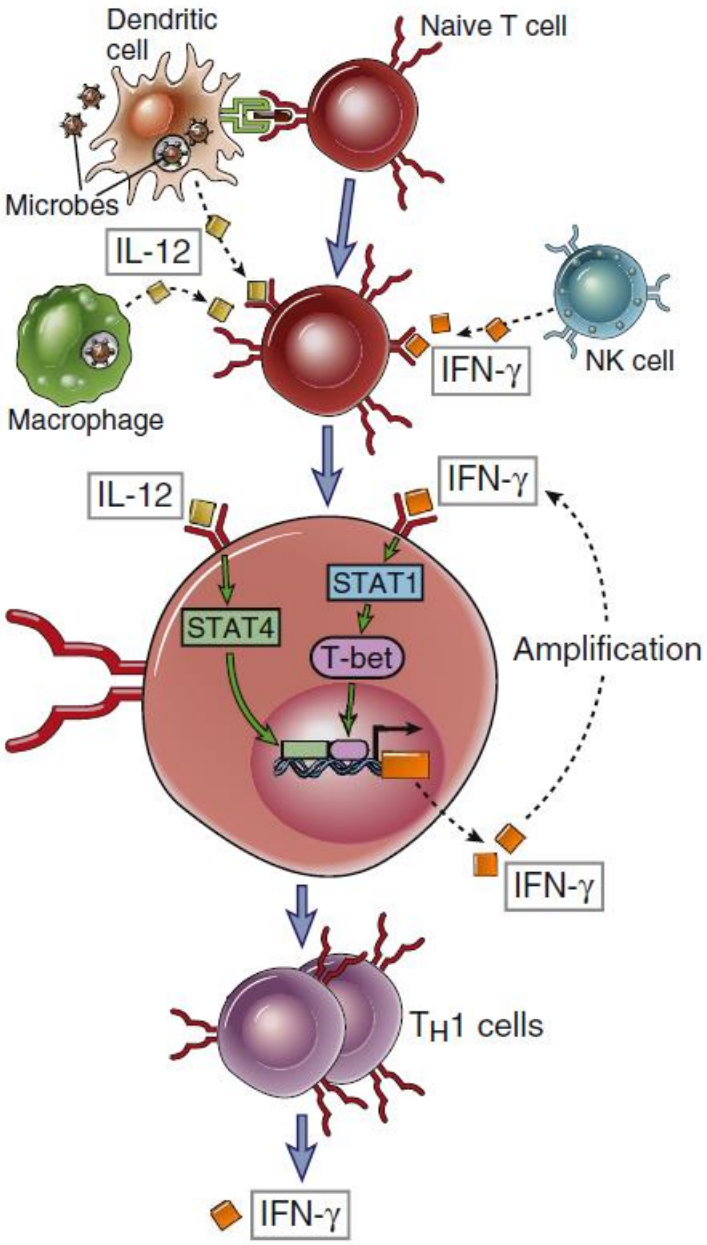
IL-7 is important for the survival of memory T lymphocytes

There are central and effector memory lymphocytes

Naive CD4+T lymphocytes differentiate into different effector cells that secrete different sets of cytokines and perform different functions

Effector T cells	Defining cytokines	Principal target cells	Major immune reactions	Host defense	Role in disease
Th1 	IFN-γ	Macrophages 	Macrophage activation	Intracellular pathogens	Autoimmunity; chronic inflammation
Th2 	IL-4 IL-5 IL-13	Eosinophils 	Eosinophil and mast cell activation; alternative macrophage activation	Helminths	Allergy
Th17 	IL-17 IL-22	Neutrophils 	Neutrophil recruitment and activation	Extracellular bacteria and fungi	Autoimmunity; inflammation

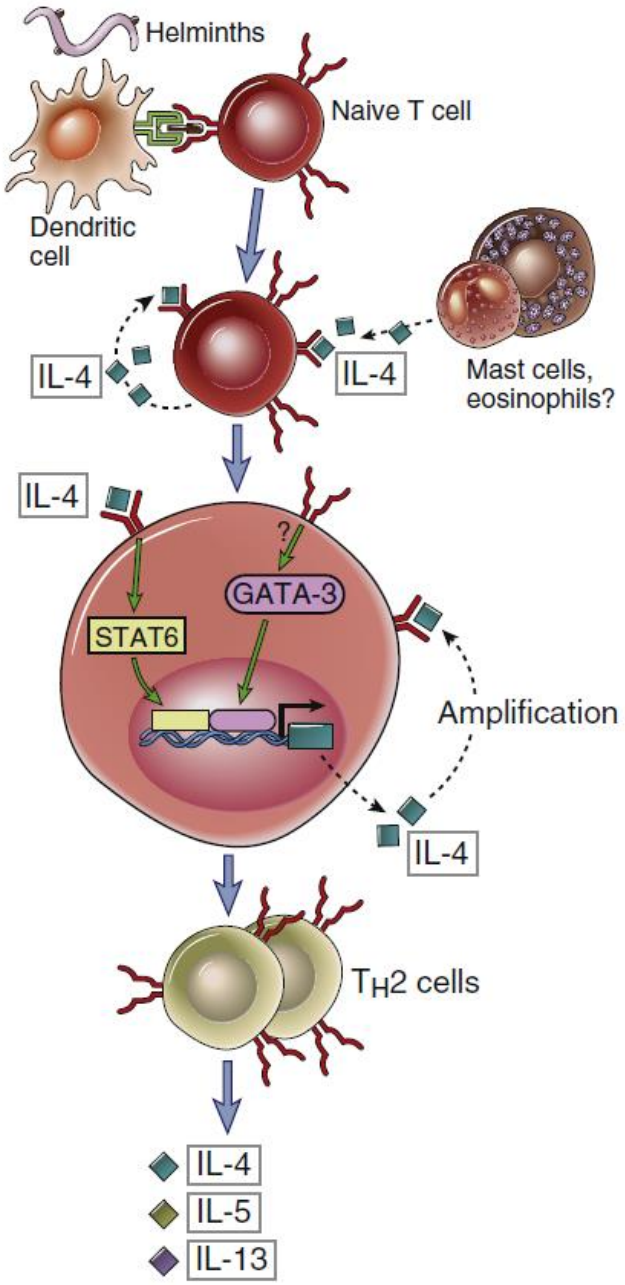
The emergence of effector Th1, Th2, Th17 from naive CD4+ T(Th0) lymphocytes is not a random process, but the direction of differentiation depends on the signals that arise after the contact of Th0 with the antigen. And the type of signal will depend on the characteristics of the pathogen, as well as on the genetic predisposition.



Development of Th1 cells.

IL-12 produced by dendritic cells and macrophages in response to microbes and IFN-γ produced by NK activate the transcription factors T-bet, STAT1, and STAT4, which stimulate the differentiation of naive CD4+ T cells to the Th1 subset.

IFN-γ produced by the Th1 cells amplifies this response and inhibits the development of Th2 and Th17 cells

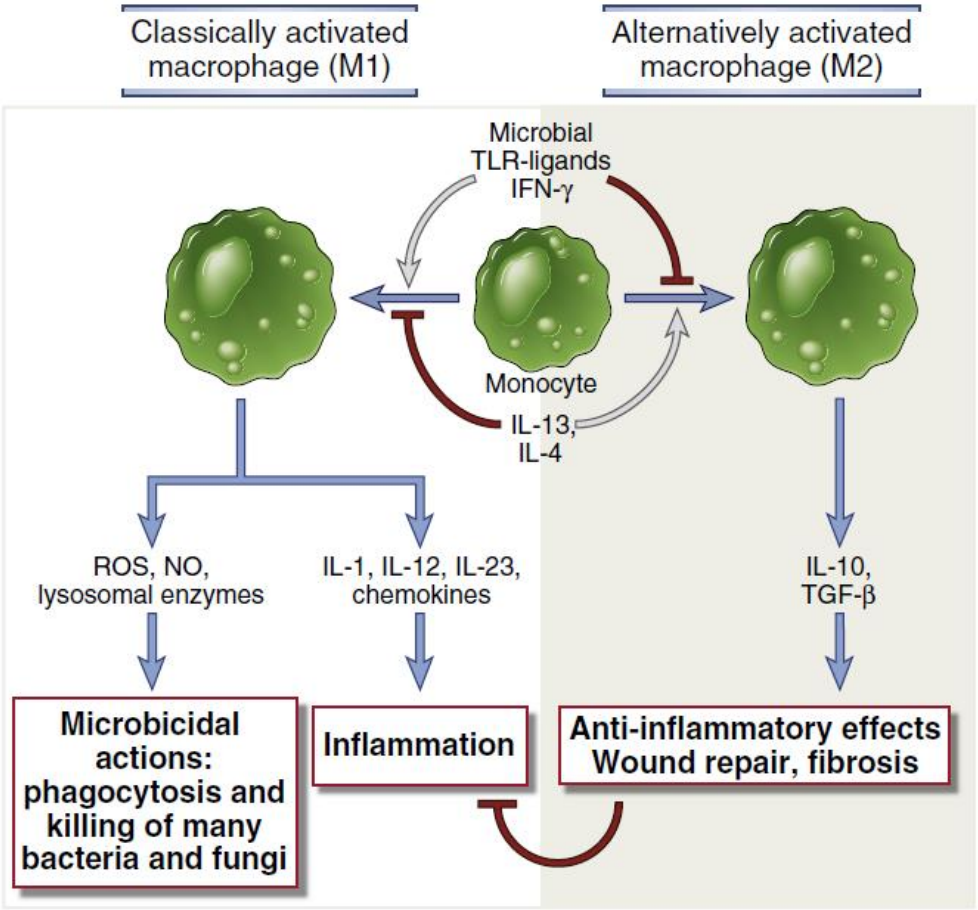


Development of TH2 cells.

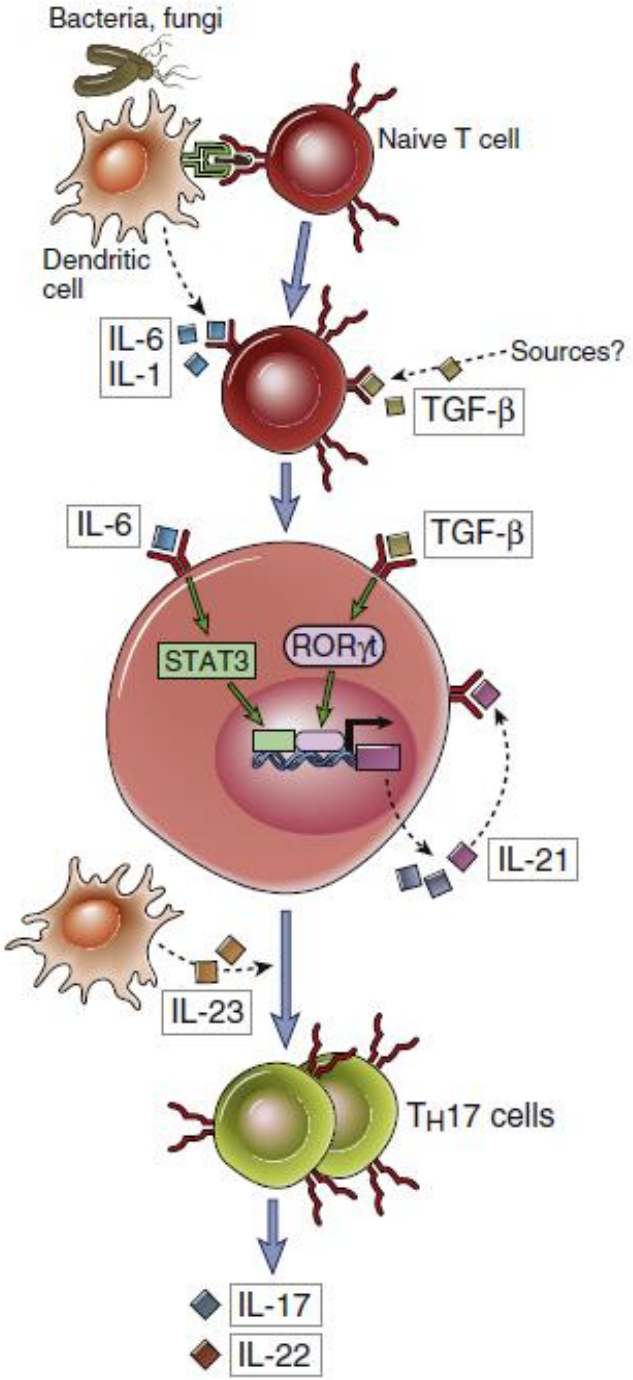
IL-4 produced by activated T cells themselves or by mast cells and eosinophils, especially in response to helminths, activates the transcription factors GATA-3 and STAT6, which stimulate the differentiation of naive CD4+ T cells to the Th2 subset.

IL-4 produced by the Th2 cells amplifies this response and inhibits the development of Th1 and Th17 cells.

Classical and alternative macrophage activation



- Different stimuli activate monocytes-macrophages to develop into functionally distinct populations.
- Classically activated macrophages are induced by microbial products and cytokines (IFN-γ). They are microbicidal and involved in inflammation.
- Alternatively activated macrophages are induced by IL-4 and IL-13 produced by TH2 cells. They control inflammation and promote tissue repair and fibrosis.

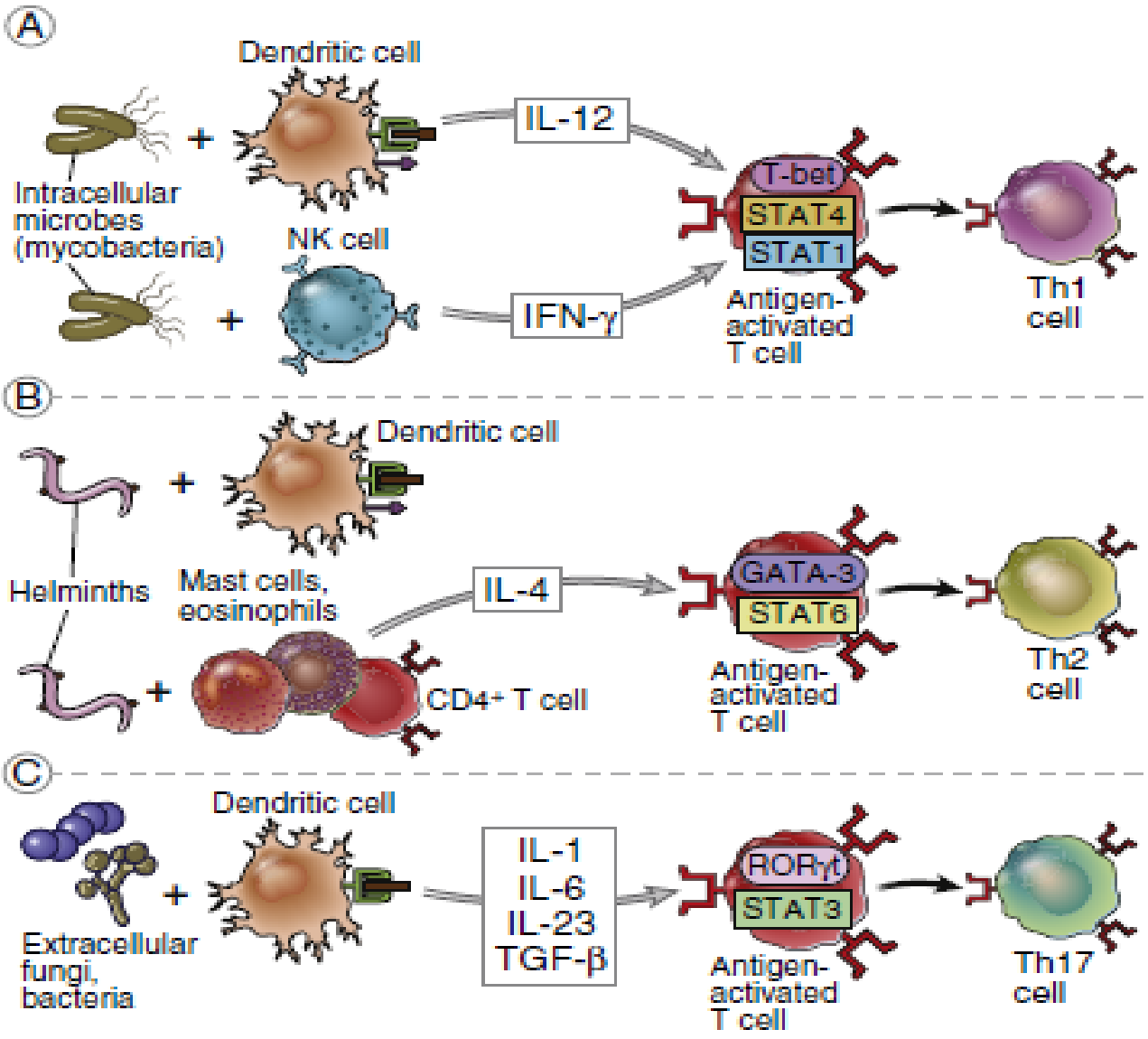


Development of TH17 cells.

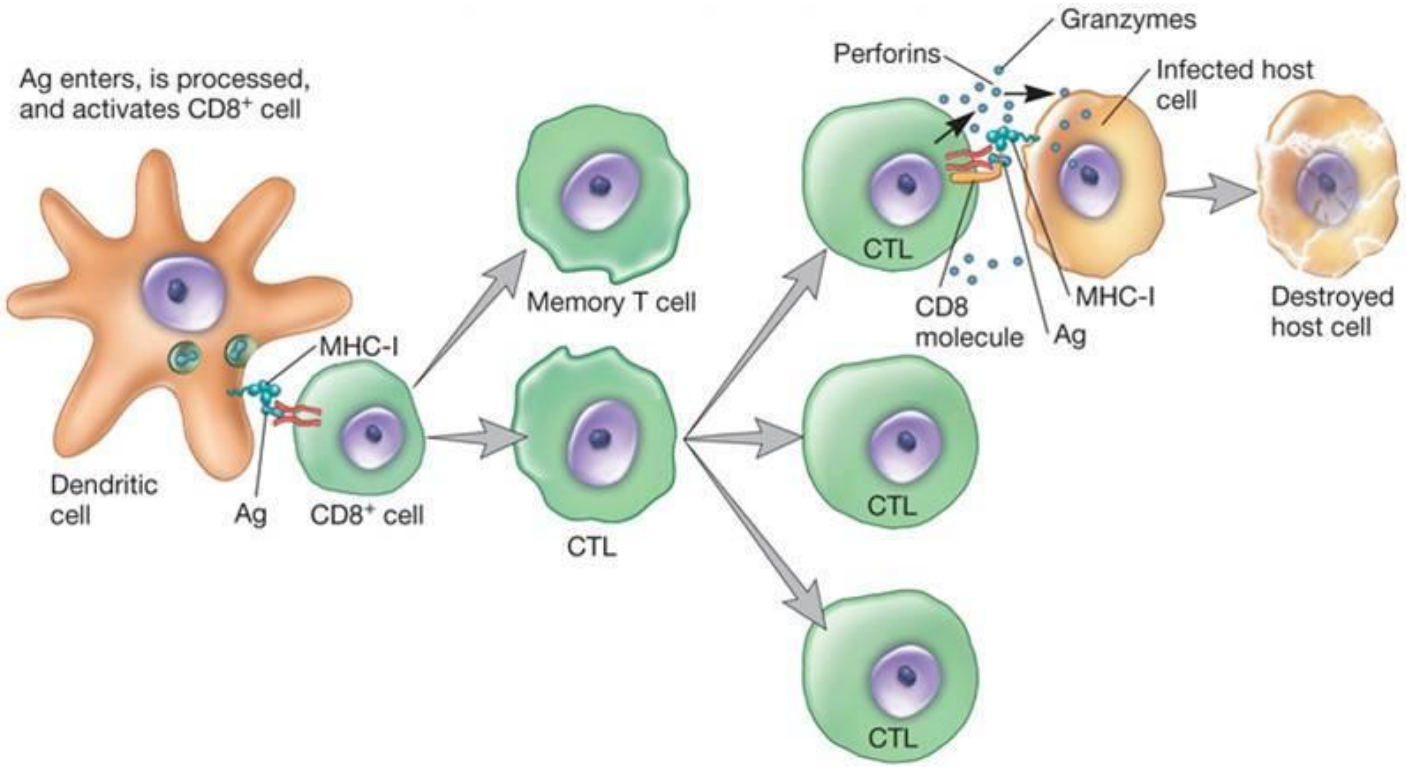
IL-1 and IL-6 produced by APCs and transforming growth factor-β (TGF-β) produced by various cells activate the transcription factors RORγt and STAT3, which stimulate the differentiation of naive CD4+ T cells to the Th17 subset.

- IL-23, which is also produced by APCs stabilizes the TH17 cells.
- IL-21 produced by the TH17 cells amplifies this response.

The development of Th1, Th2 and Th17 effector lymphocytes



After activation, CD8+ T lymphocytes differentiate into CTL



Effector mechanisms of cellular immunity

Elimination of intracellular microorganisms

It remains for us to learn :

How do effector T lymphocytes find infected cells (intracellular microorganisms) anywhere in the body?

How do T lymphocytes eliminate intracellular infections?

Microorganisms:

Extracellular: they multiply outside our cells

Staphylococcus, Streptococcus, Escherichia, Clostridium…

Intracellular: they multiply inside our cells

- in APC:

  Mycobacterium spp. (M. tuberculosis, M. leprae…), Listeria monocytogenes, Legionella pneumophila…

  Leishmania spp, Tripanosoma spp, …

  Cryptococcus neoformans,…

- in other cells:

  Vuruses

  Rickettsiae

  Plasmodium, Cryptosporidium

Types of cellular immunity

CD4+ T lymphocytes

recognize the peptide in the context of MHC class II products. They are the main source of interleukins.

Function: **helper T lymphocyte**.

They activate macrophages to efficiently destroy phagocytosed microbes.

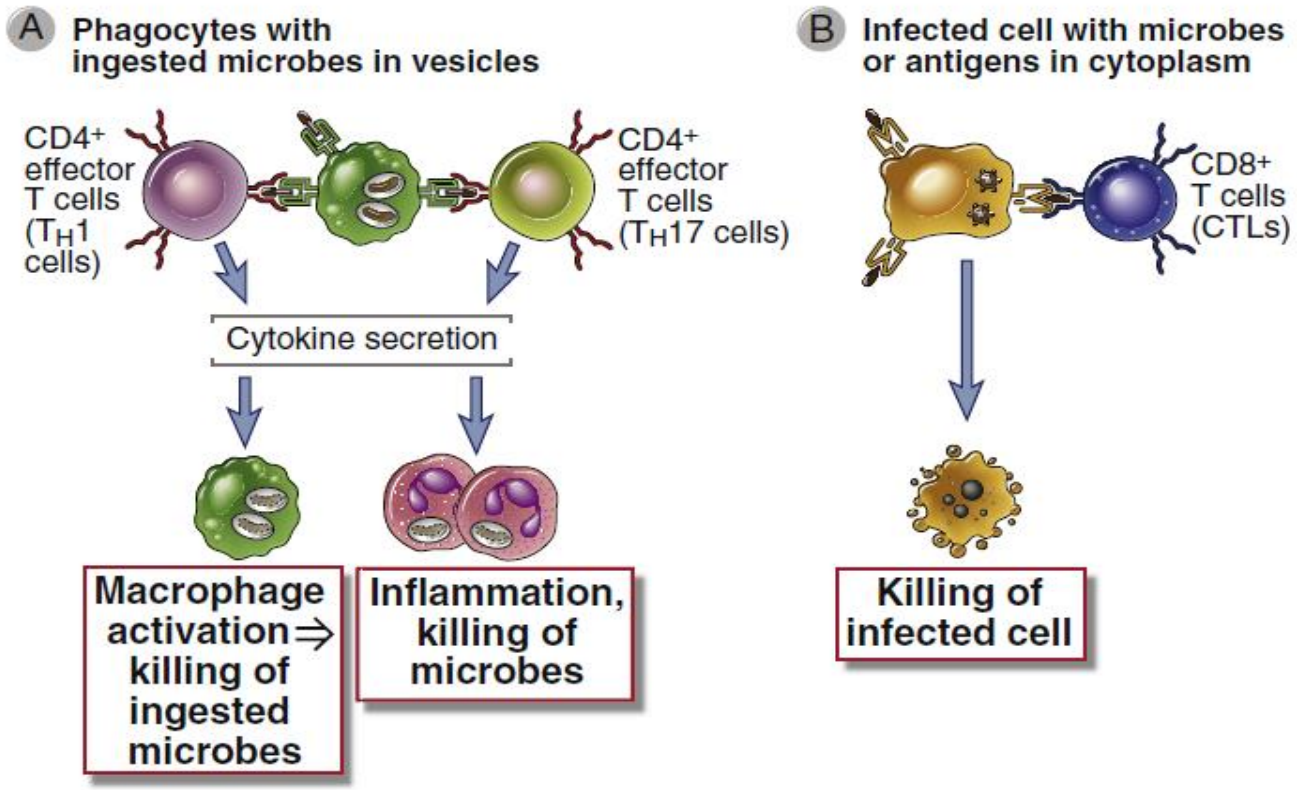
CD8+ T lymphocytes

recognize the peptide in the context of MHC class I products.

Function: **cytotoxic T lymphocyte.**

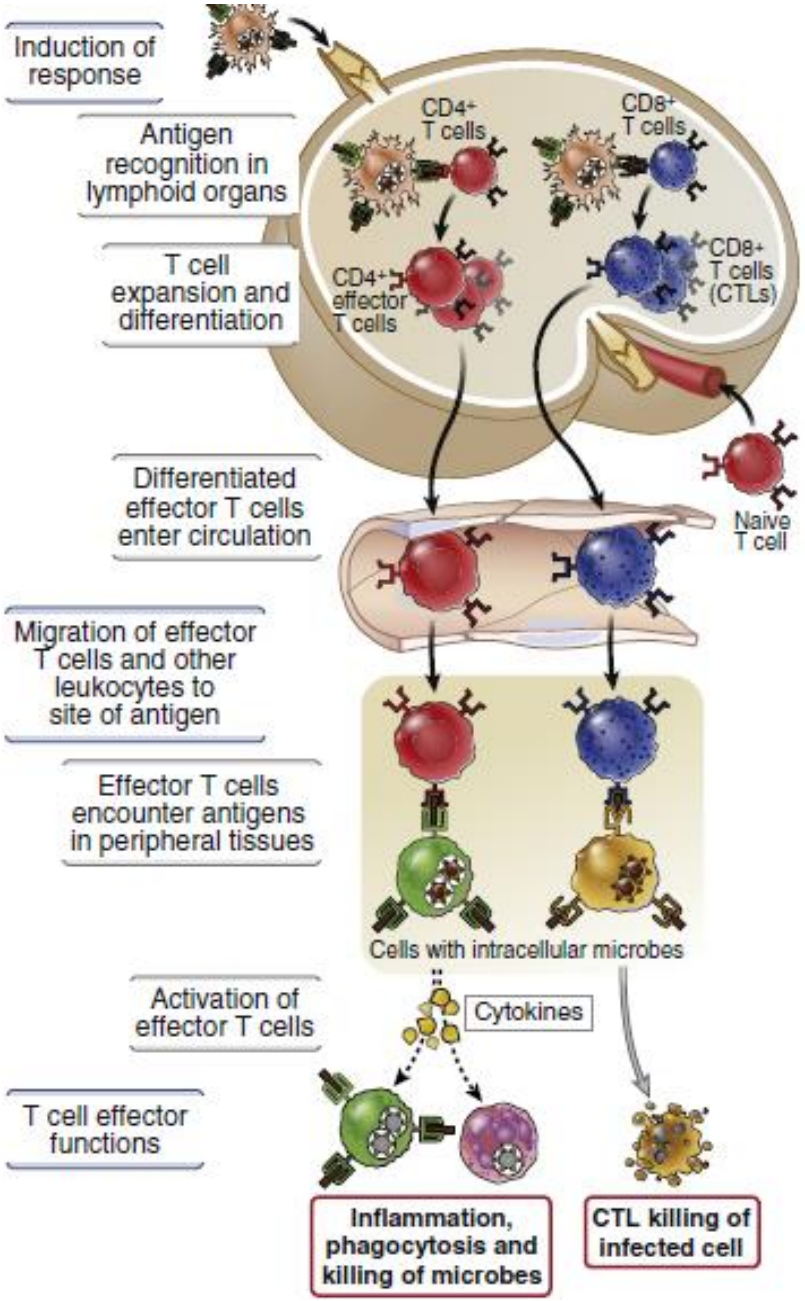
They kill all cells that contain microbes or their proteins in the cytoplasm.

Role of T cells in eradicating infections



CD4+ T cells recognize antigens of phagocytosed and extracellular microbes and produce cytokines that activate the phagocytes to kill the microbes and stimulate inflammation.

CD8+ cytotoxic T lymphocytes (CTLs) recognize antigens of microbes residing in the cytosol of infected cells and kill the cells.



NAIVE T LYMPHOCYTES

- ✓ recognition,
- ✓ activation,
- ✓ proliferation and
- ✓ differentiation in

EFFECTOR T LYMPHOCYTE

- ✓ migration,
- ✓ recognition,
- ✓ activation and
- ✓ effector functions

Effector CD8+T: CTL

Effector CD4+T: Th1, Th2, Th17, Treg

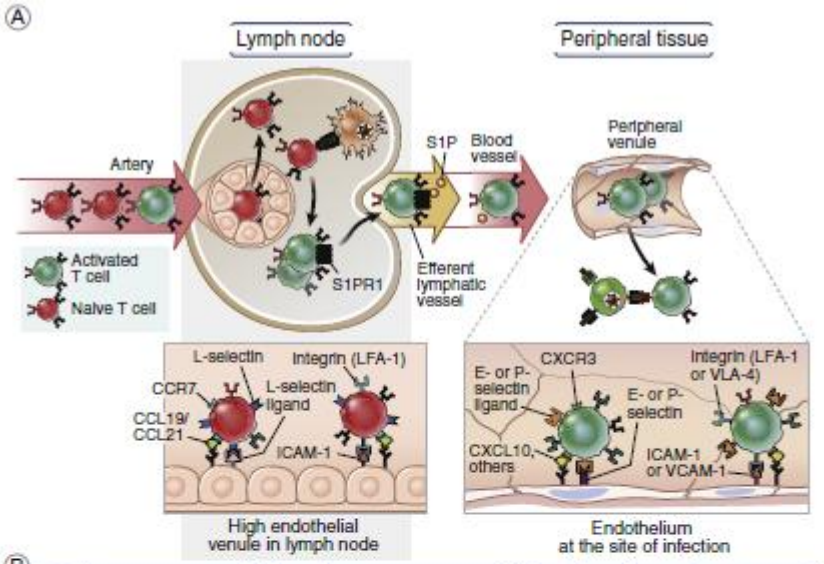
Effector lymphocytes became that thanks to the **calling of new PROGRAMS:**

- programs needed **FOR FINDING THE SITE OF INFECTION** - applies to both CTL and Th1 and Th2

  - ✓ expression of adhesive molecules and chemokine receptors. Those molecules need to find ligands on the endothelial cells of the infected tissue. These ligands are expressed only on the endothelium of the infected tissue and are the result of a new program of these endothelial cells programmed by cytokines of non-specific immunity.

- programs needed **FOR ELIMINATION OF MICROORGANISMS** - specific for each type of effector lymphocytes

Migration of effector lymphocytes to the site of infection



B

T cell homing receptor	Ligand on endothelial cell	Function of receptor: ligand pair
Naive T cells		
L-selectin	L-selectin ligand	Adhesion of naive T cells to high endothelial venule (HEV) in lymph node
LFA-1 (β_2-integrin)	ICAM-1	Stable arrest on HEV
CCR7	CCL19 or CCL21	Activation of integrins and chemotaxis
Activated (effector and memory) T cells		
E- and P-selectin ligand	E- or P-selectin	Initial weak adhesion of effector and memory T cells to cytokine-activated endothelium at peripheral site of infection
LFA-1 (β_2-integrin) or VLA-4 (β_1 integrin)	ICAM-1 or VCAM-1	Stable arrest on cytokine-activated endothelium at peripheral site of infection
CXCR3, others	CXCL10, others	Activation of integrins and chemotaxis

- ✓ Activated T lymphocytes reduce the expression of receptors for chemokines that are created in the T cell zones of lymph nodes, and increase the expression of receptors for chemokines present in the circulation. That's how they leave lymph node and reach the circulation.
- ✓ Entry into infected tissues is regulated by the same mechanisms that regulate the migration of other leukocytes into tissues.
- ✓ Activated lymphocytes increase the expression of ligands for **E or P selectins**, followed by high-affinity forms of integrins **LFA-1 and VLA-4**.
- ✓ At the same time, the endothelium at the site of infection is exposed to high concentrations of TNF and IL-1 and under this effect increases the expression of **E- and P-selectin**, as well as **ligands for integrins ICAM-1** (ligand for LFA-1) and **VCAM-1** (ligand for VLA -4).
- ✓ After activation, **lymphocytes** express re**ceptors for chemokines** produced by macrophages and endothelial cells located on the surface of the endothelium.

Rolling - selectins

Tight binding – integrins

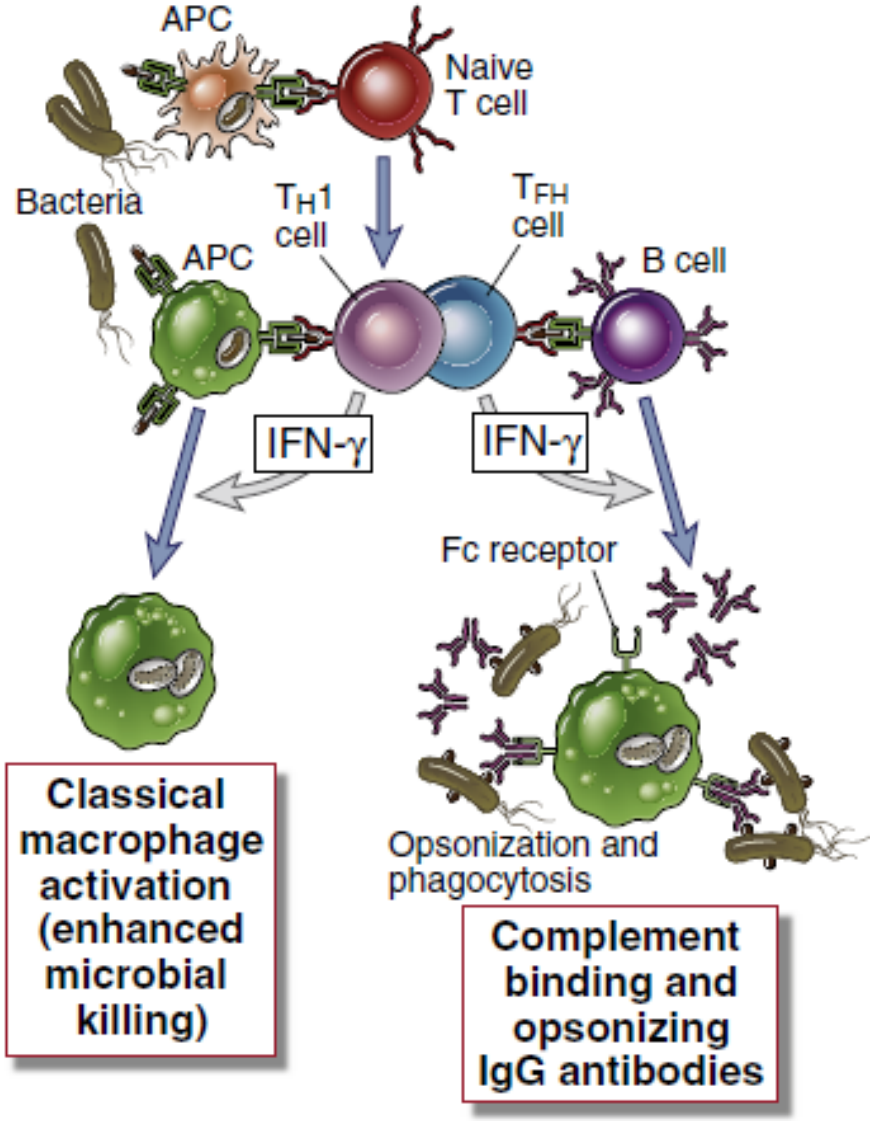
Motility - chemokines

Passage through the endothelium - PECAM-1 (CD31)

- ✓ Settlement of T lymphocytes in infected tissues does not depend on specificity (antigen recognition) but on adhesive molecules and chemokines, so that all circulating effector T lymphocytes formed in response to other infectious agents enter the focus of any infection.

- ✓ Those that are specific for a given current infection recognize the antigen and are additionally activated.

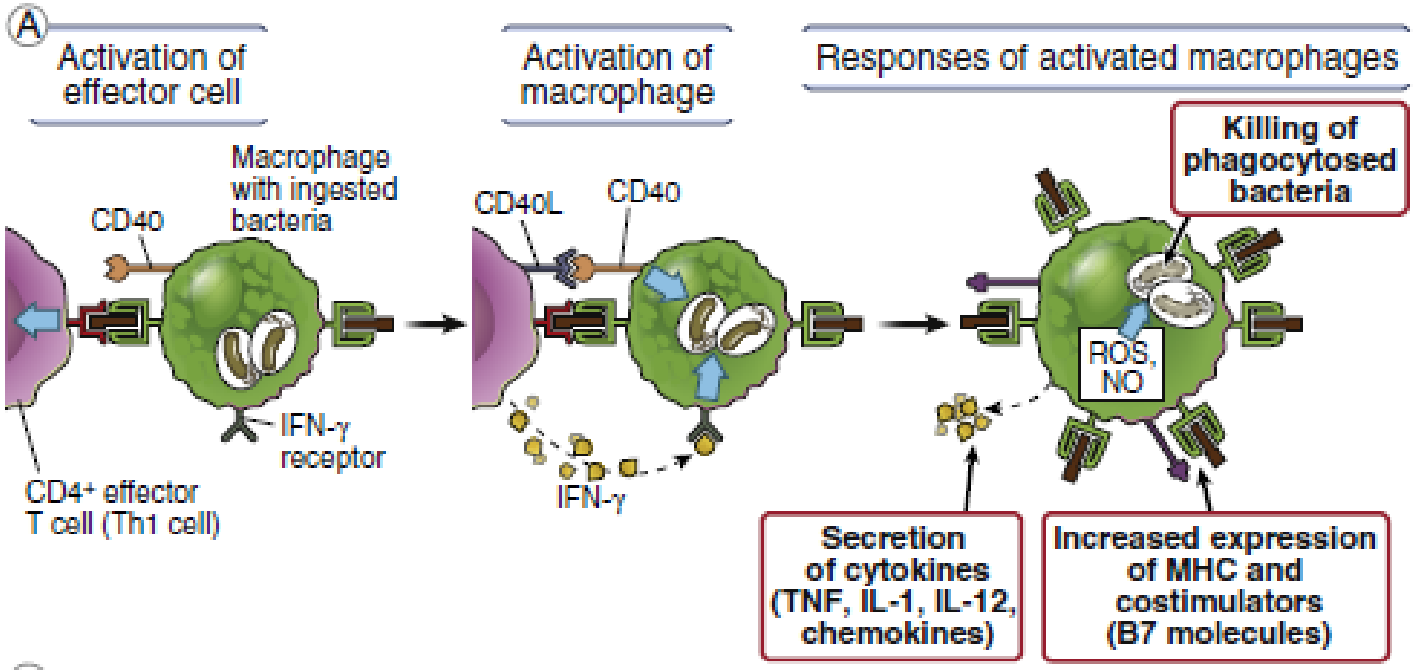
- ✓ Thus, VLA integrins are also expressed more strongly, some of which enable adhesion to fibronectin and hyaluronic acid, which stops specific lymphocytes in the infected tissue, while the others continue on.



Functions of TH1 cells.

Th1 cells secrete IFN-γ, which acts on macrophages to increase phagocytosis and killing of microbes in phagolysosomes and on B lymphocytes to stimulate production of IgG antibodies that opsonize microbes for phagocytosis.

Th1 lymphocytes help CD8+ T lymphocytes to differentiate into CTLs

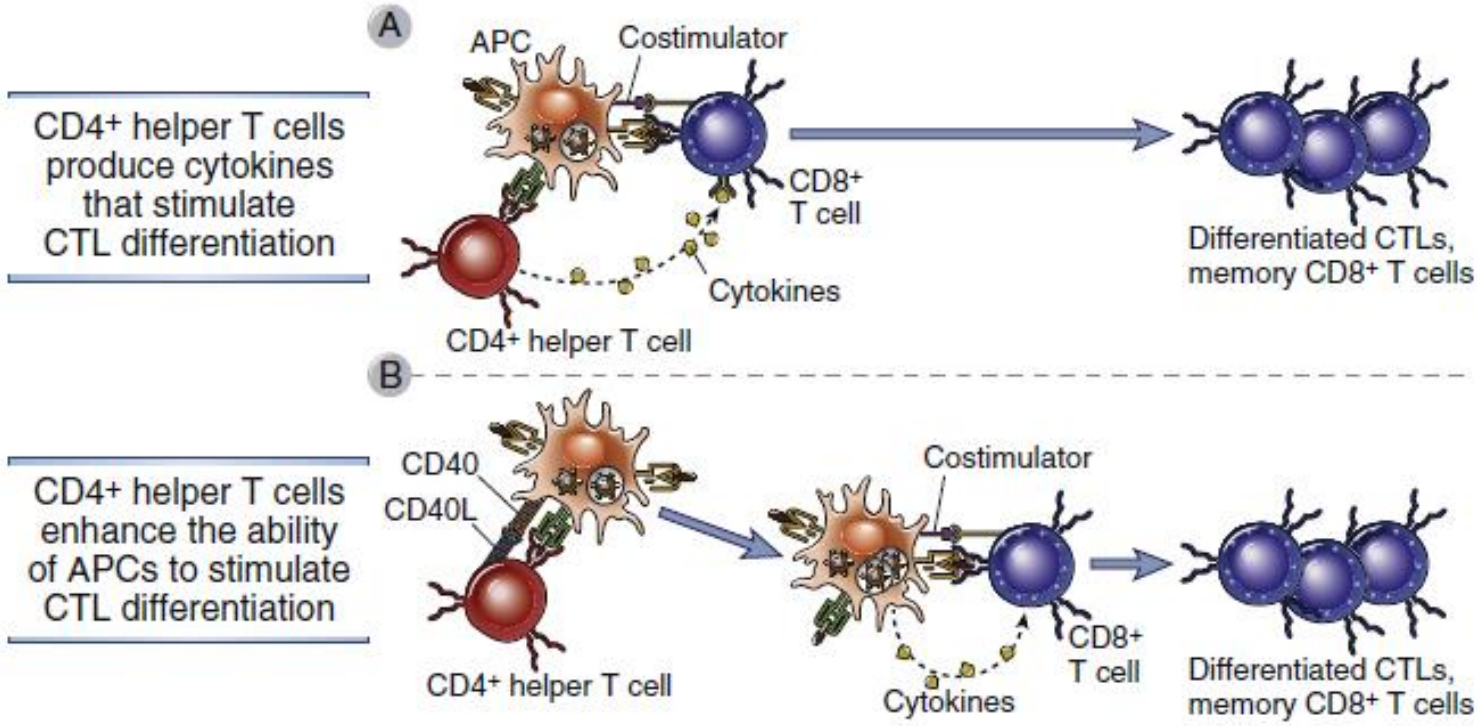


B

Macrophage response	Role in cell-mediated immunity
Production of reactive oxygen species, nitric oxide, increased lysosomal enzymes	Killing of microbes in phagolysosomes (effector function of macrophages)
Secretion of cytokines (TNF, IL-1, IL-12) and chemokines	TNF, IL-1, chemokines: leukocyte recruitment (inflammation) IL-12: Th1 differentiation, IFN-γ production
Increased expression of B7 costimulators, MHC molecules	Increased T cell activation (amplification of T cell response)

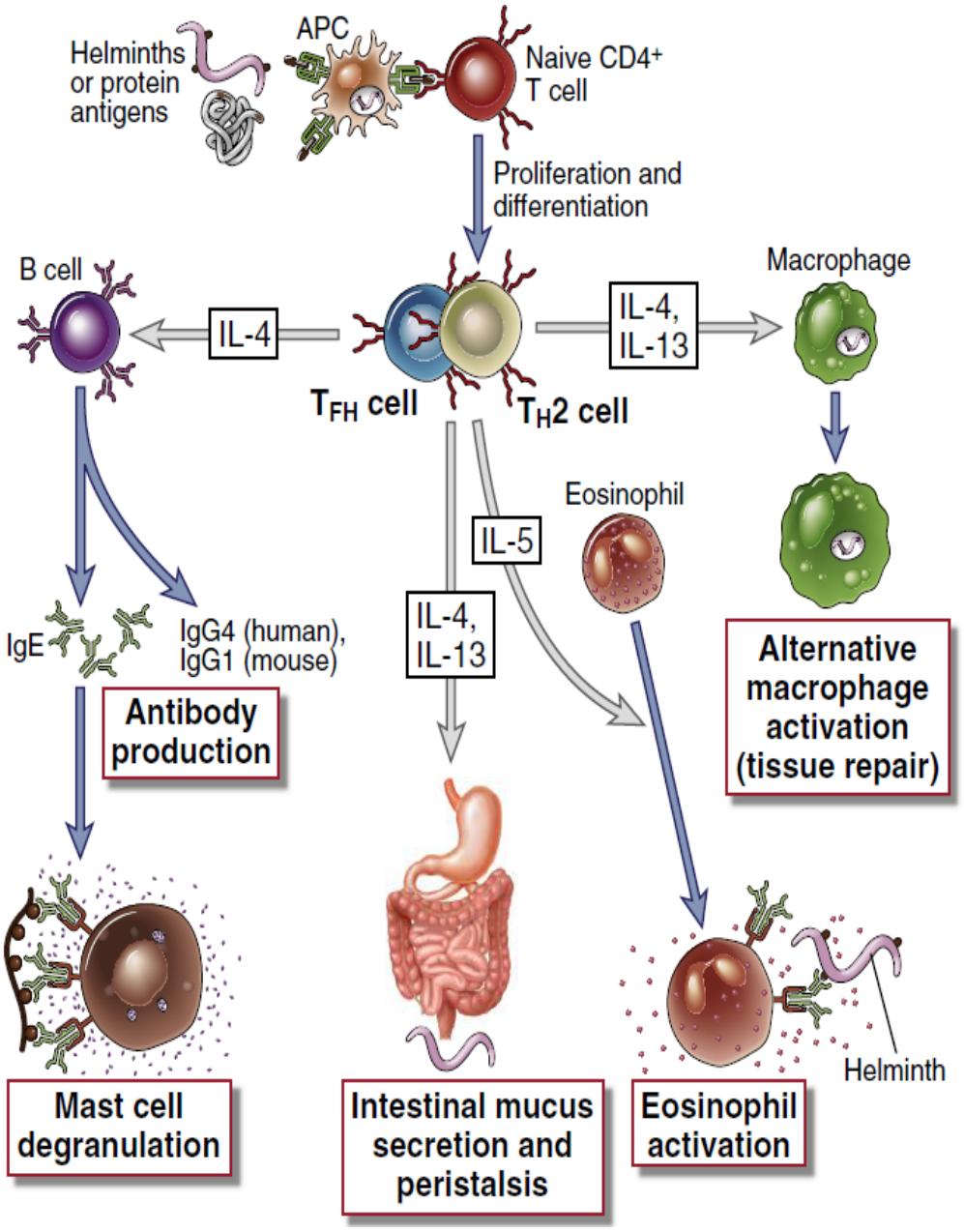
Macrophage activation by TH1 cells Macrophages are activated by CD40L-CD40 interactions and by IFN-γ expressed by TH1 cells and perform several functions that kill microbes, stimulate inflammation, and enhance the antigen-presenting capacity of the cells.

Role of helper T cells in the differentiation of CD8+ T lymphocytes.



CD4+ helper T cells promote the development of CD8+ CTLs and memory cells by secreting cytokines that act directly on the CD8+ cells or by activating APCs to become more effective at stimulating the differentiation of the CD8+ T cells

Function of Th2 lymphocytes



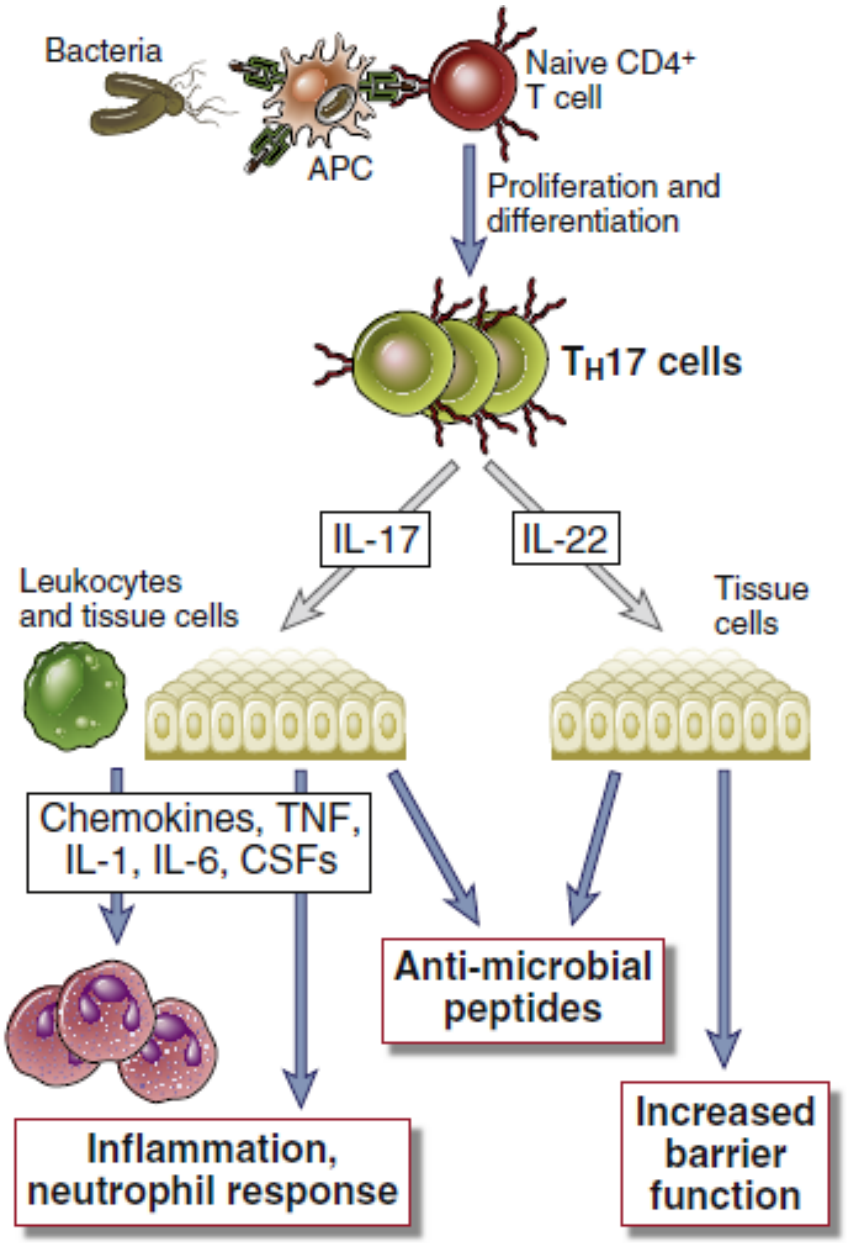
Th2 cells secrete IL-4, IL-5, and IL-13.

IL-4 acts on B cells to stimulate production of antibodies that bind to mast cells, such as IgE.

IL-4 is also an autocrine growth and differentiation cytokine for Th2 cells.

IL-5 activates eosinophils

IL-4 and IL-13 are involved in immunity at mucosal barriers, induce an alternative pathway of macrophage activation, and inhibit classical Th1-mediated macrophage activation.

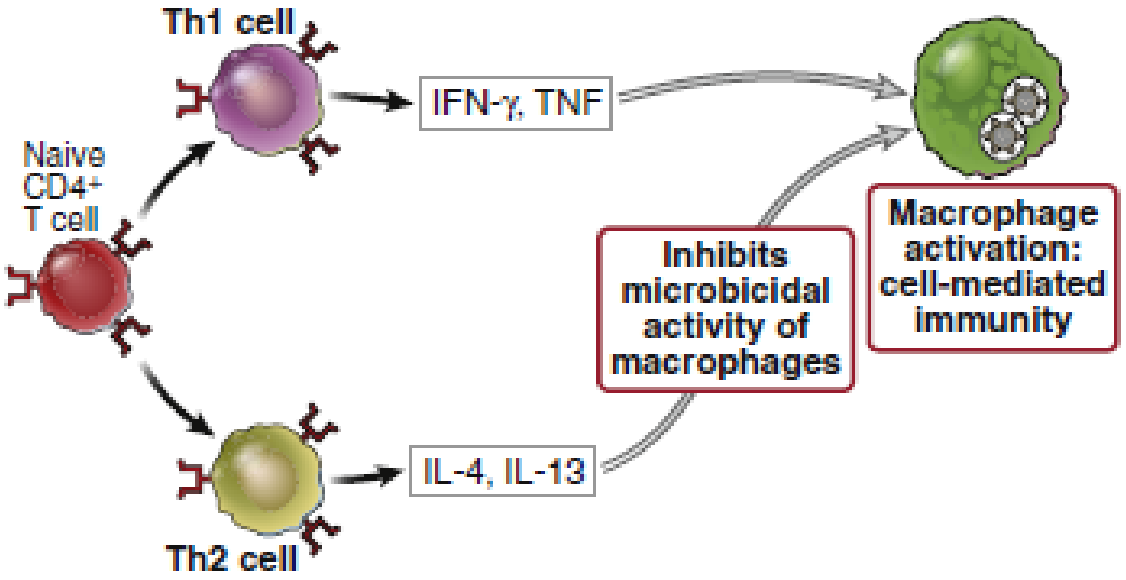


Function of Th17 lymphocytes

Cytokines produced by Th17 cells:

- stimulate local production of chemokines that recruit neutrophils and other leukocytes
- increase production of antimicrobial peptides (defensins)
- promote epithelial barrier functions.

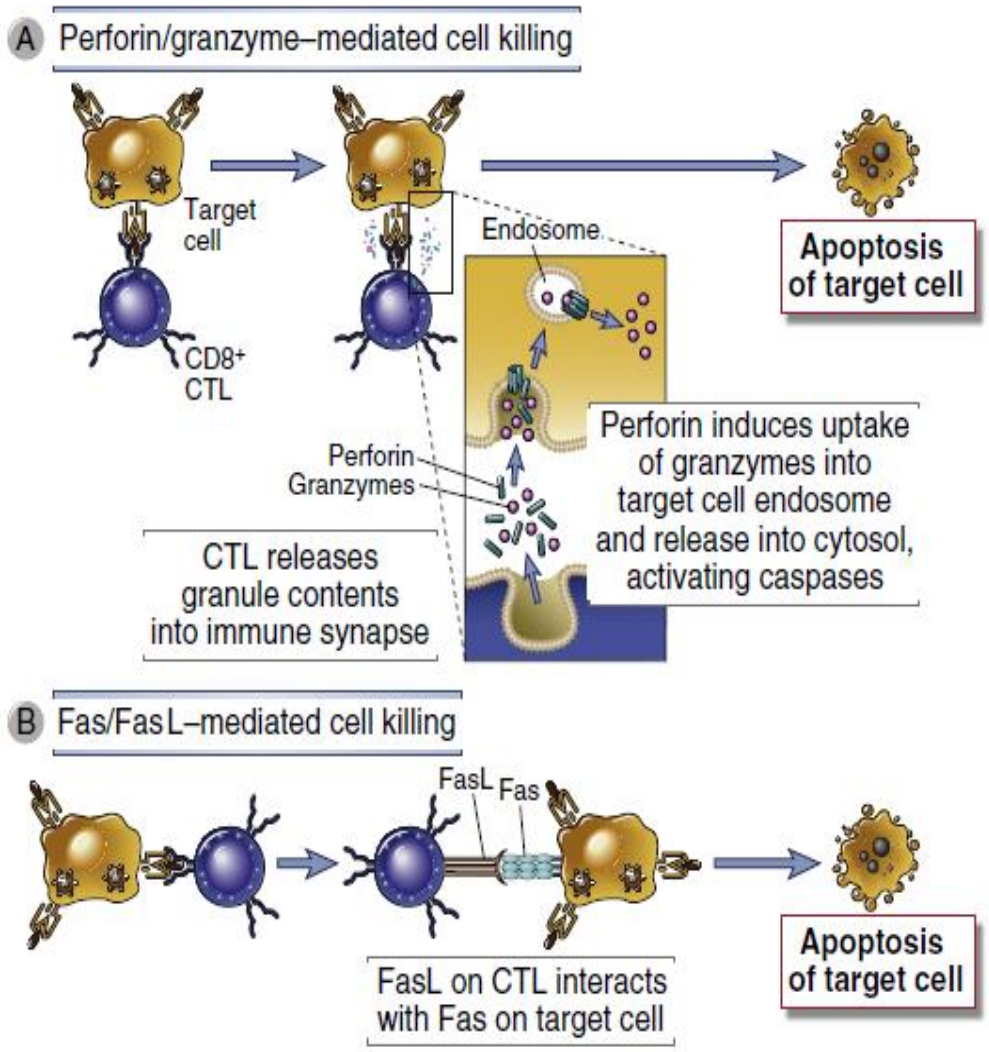
Pathogenesis of tuberculosis and leprosy



Infection	Response	Outcome
Leishmania major	Most mouse strains: Th1 ⇒	Recovery
	BALB/c mice: Th2 ⇒	Disseminated infection
Mycobacterium leprae	Some patients: Th1 ⇒	Tuberculoid leprosy
	Some patients: Defective Th1 or dominant Th2 ⇒	Lepromatous leprosy (high bacterial count)

The ratio between the activation of Th1 and Th2 lymphocytes determines the outcome of the infection

Effector functions of CD8+ CTL



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