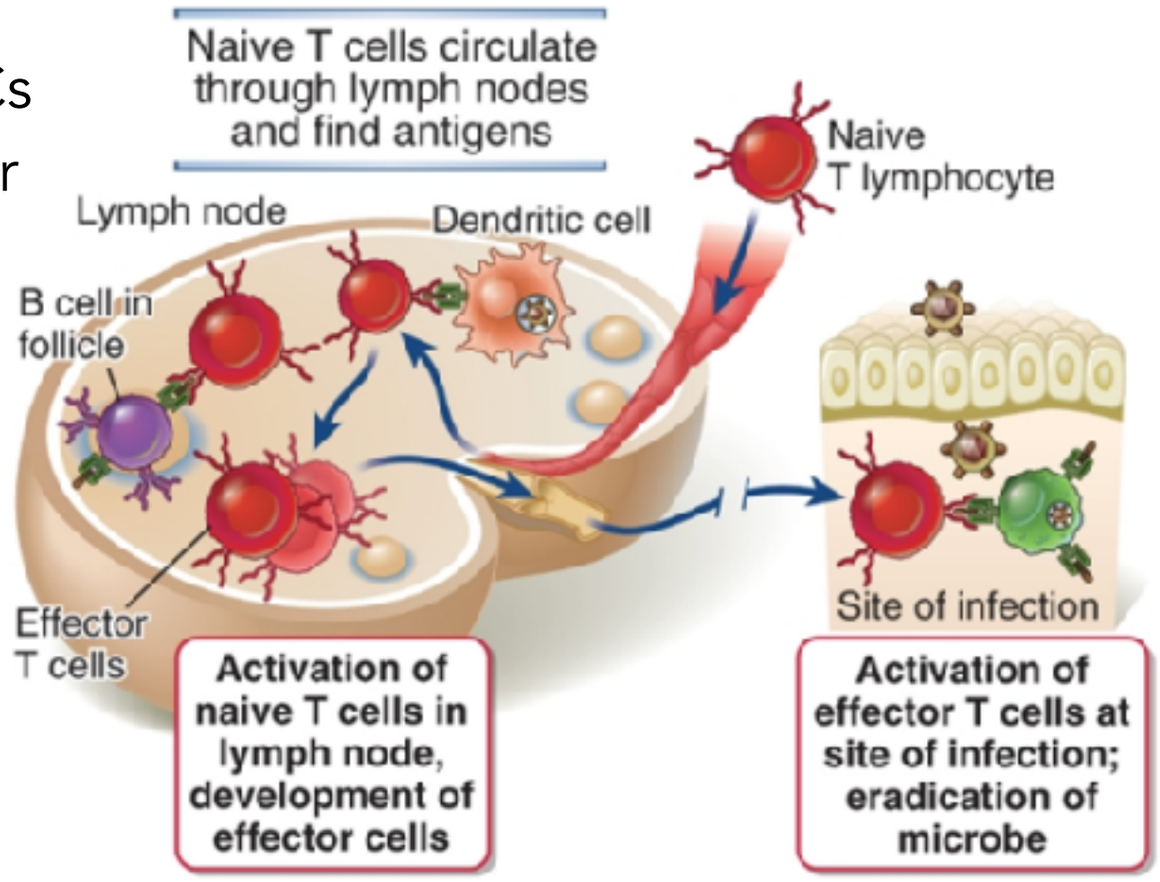
Activation of T Lymphocytes

Activation of naive T cells by antigen

Naive T lymphocytes: move around *within lymphoid organs*, transiently interact with DCs and stop when they recognise the antigen for which they express specific receptors



- **Antigen recognition + activating stimuli** induce biological responses in T cells:
  - *Cytokine* secretion
  - *Proliferation* allowing for clonal expansion
  - *Differentiation* into effector and memory cells.

- **Positive feedback loops** regulate proliferation and differentiation of T cells (e.g. signals between T cells and APCs)

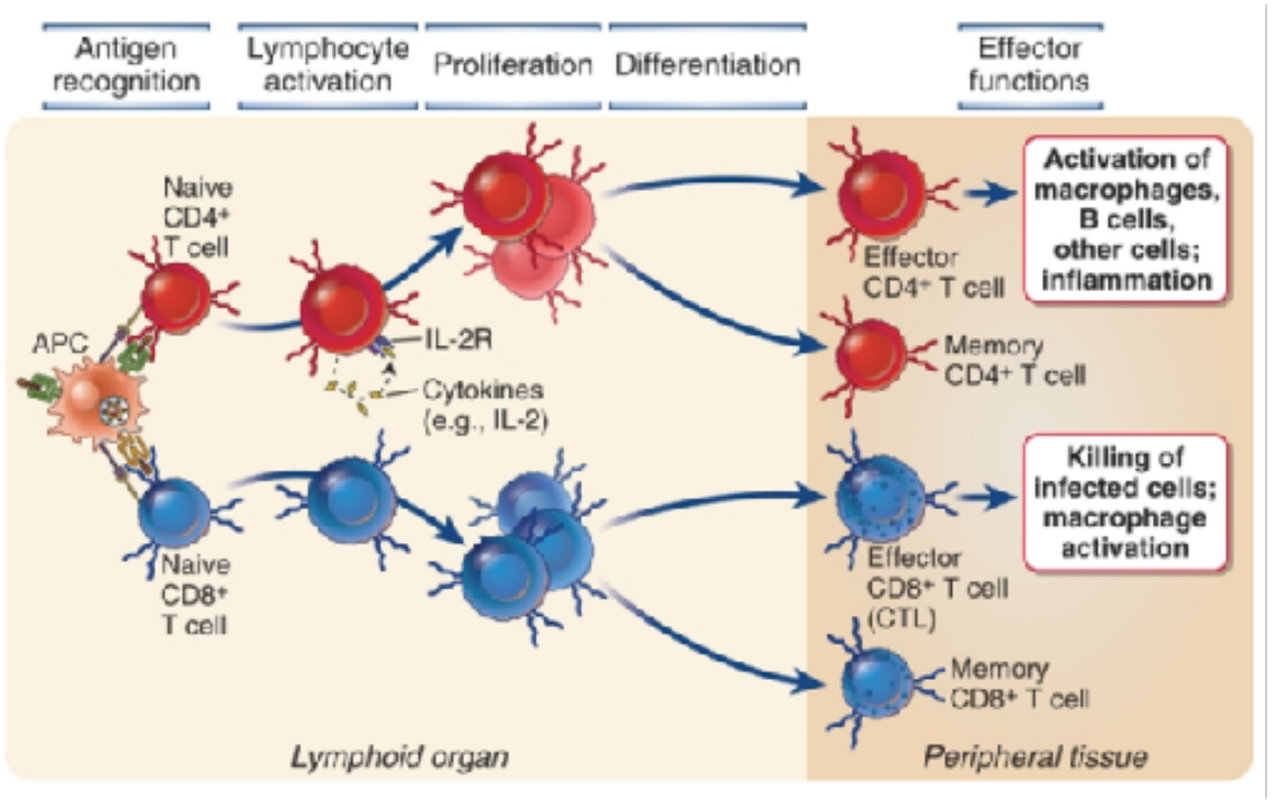
- **Negative feedback mechanisms** inhibit further activation and provide limits to the response (e.g. molecules expressed on activated T cells, cytokine secretions)

Activation of effector T cells by antigen

Effector T cells: respond to antigens and carry out their functions in *any tissue*, migrate to any site of infection/inflammation where they *encounter again the antigen* and respond in ways to eliminate the source of the antigen

- **T cell contraction**: important decline as the majority of antigen-activated effector T cells die by *apoptosis* after antigen elimination, returning to a state of equilibrium

Memory T cells: *long-lived* with enhances ability to react against antigen, present in recirculating lymphocyte pool and abundant in *mucosal* tissue, skin and lymphoid organs, respond *rapidly to subsequent encounter* with the antigen



Activation of T cells requires:

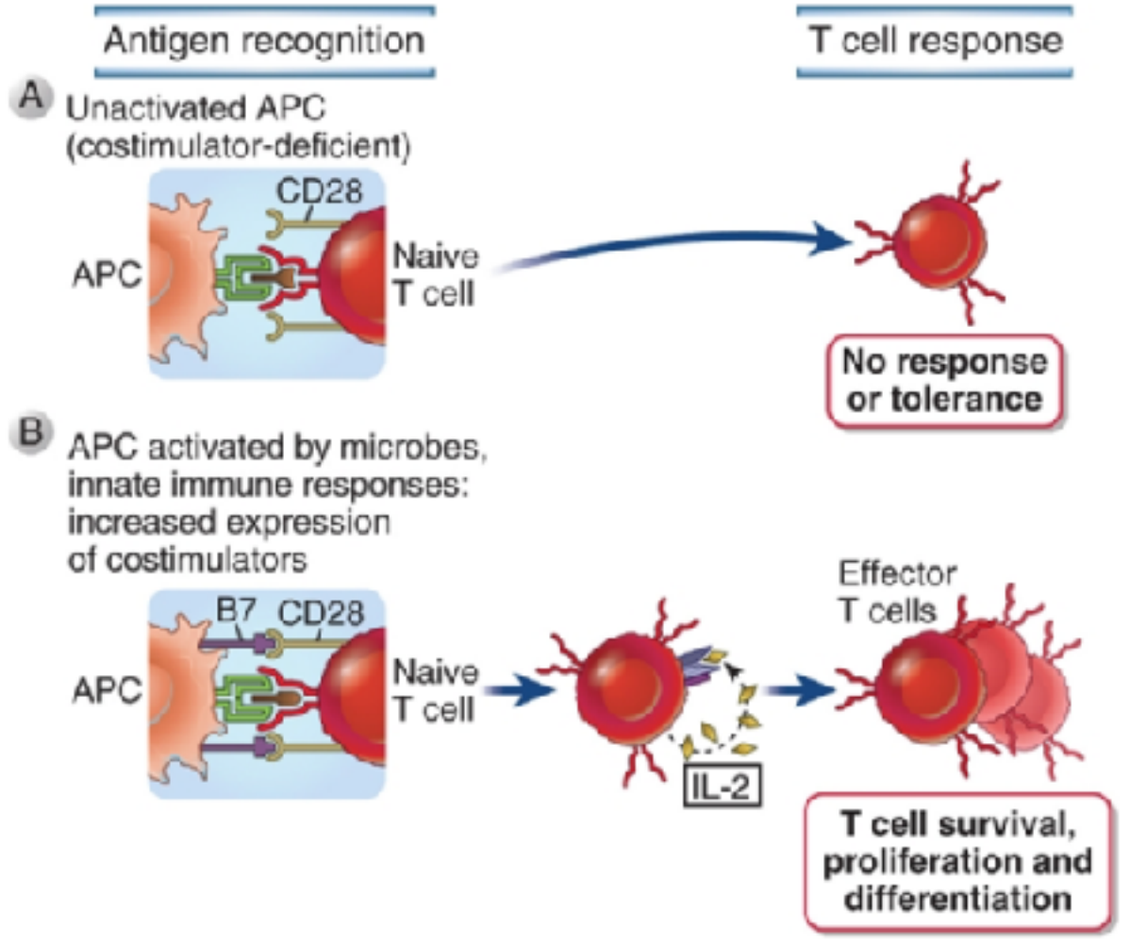
1. Antigen recognition
2. Costimulation
3. Cytokines

Signals for T Lymphocyte activation

1. **Antigen recognition (= First signal)**
   - Ensures that the response is *antigen-specific*
   - APCs are appropriately located to *interact with naive T cells* and present both peptides derived from endocytosed protein antigens mainly in association with class II MHC to $CD4^+$ T cells, and peptides derived from cytosolic and nuclear proteins displayed by class I MHC to $CD8^+$ T cells.

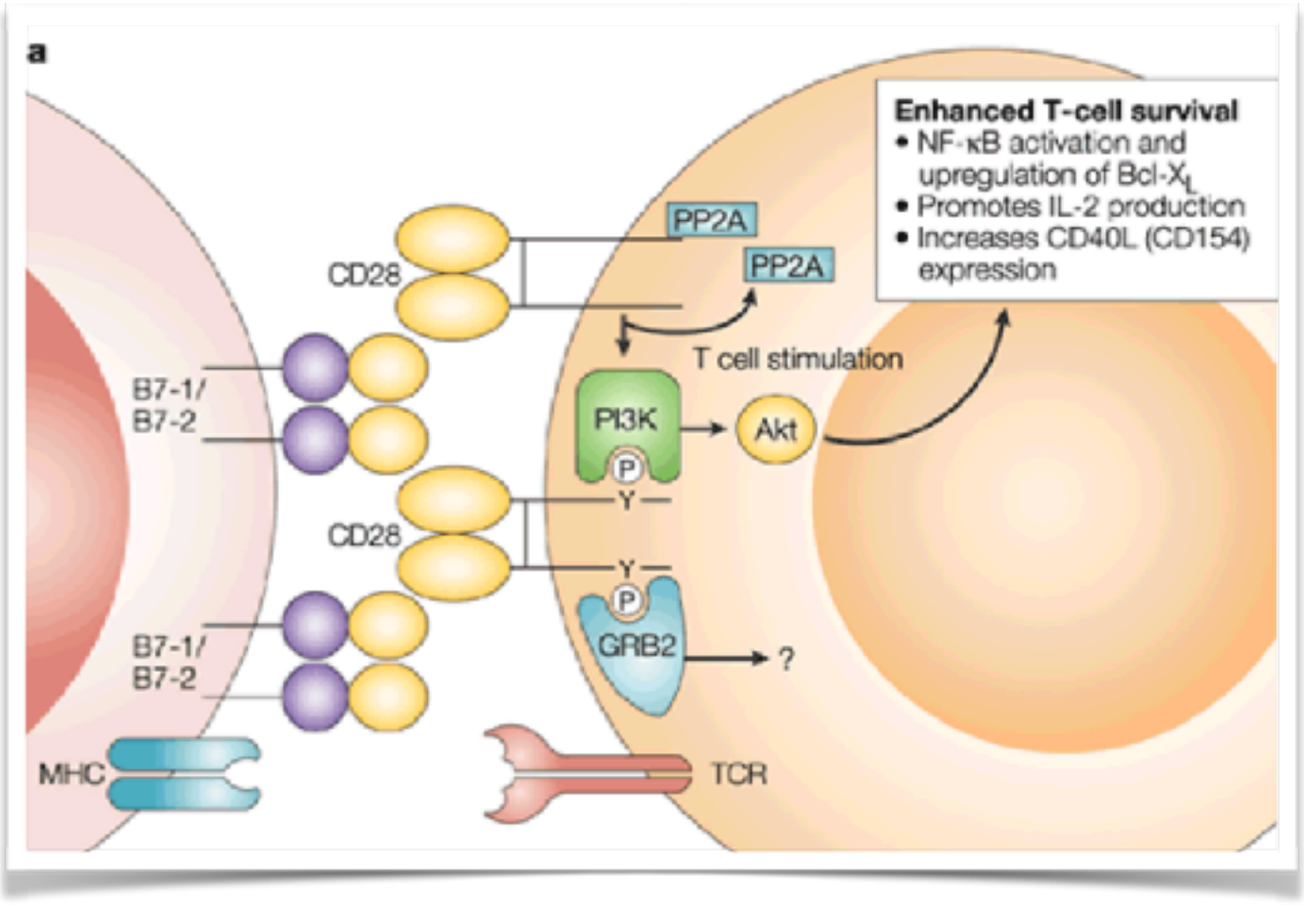
Signals for T Lymphocyte activation

2. **Costimulation (= Second signal)**
   - Signals provided by *molecules on APCs* (e.g. T cell surface CD28 binding to B7-1 and B7-2 on the surface of activated APCs)
   - Expression (low level resting) is *increased by microbial products and cytokines* such as *IFN-γ* during innate immune responses
   - Positive feedback loop from activated $CD4^+$ T cells enhance costimulator expression on APCs to amplify T cell responses
   - *DCs* express the highest levels (most potent stimulators of naive T cells)



The B7-CD28 family of costimulators

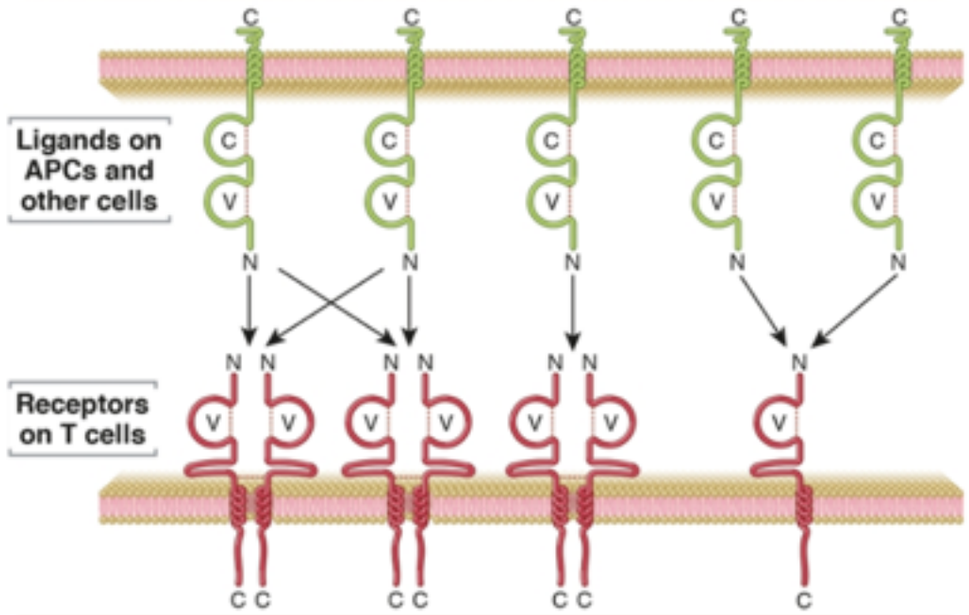
- B7-1/2 (CD80/86) are integral *membrane proteins*
- Expression levels are *regulated by PRR* signaling pathways and *cytokine* stimulation
- CD28 on T cells binds to B7-1/2 on APCs
- Activation of CD28 triggers *cytokine* expression, promotes cell *survival*, *proliferation*, metabolic activity, and T cell *differentiation*



Additional costimulators and coinhibitors

ICOS is another important costimulatory receptor, which binds to ICOS ligand expressed on DCs, B cells and plays a role in T cell-dependent antibody responses.

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)**



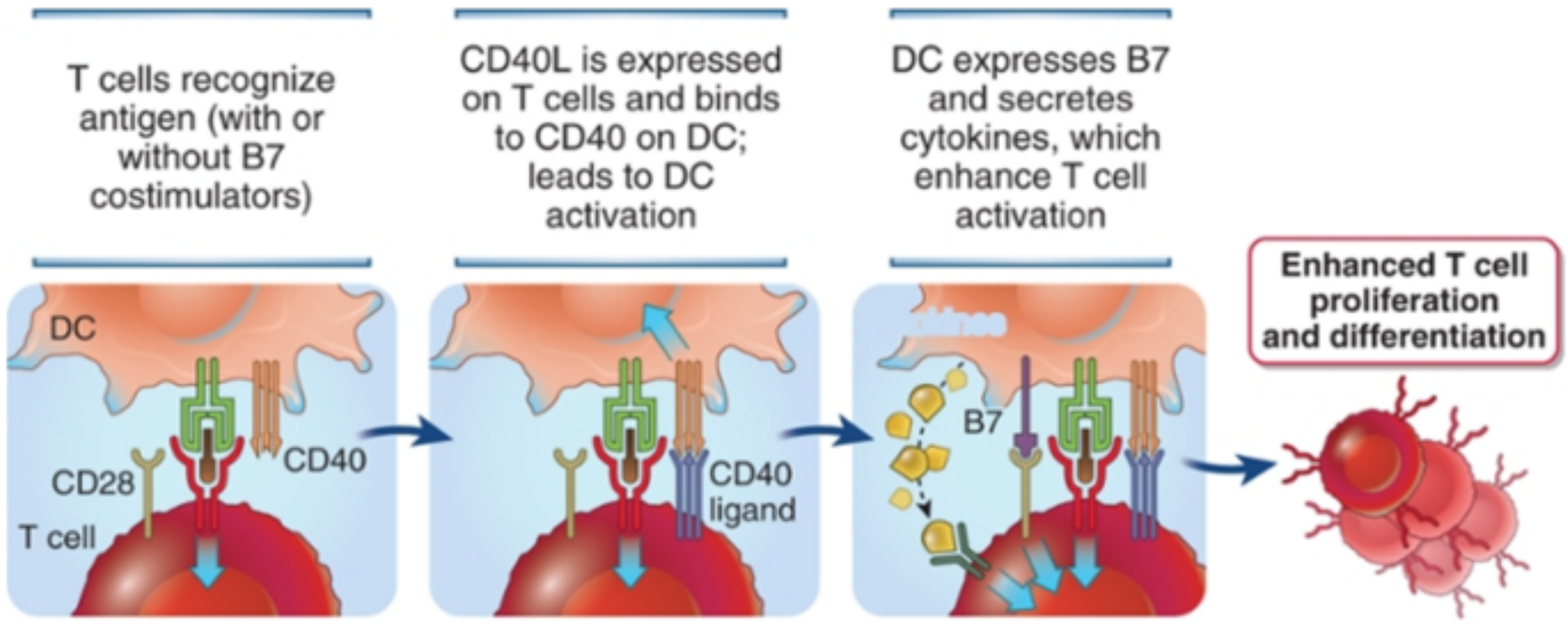
Name	CD28	CTLA-4	ICOS	PD-1
Expression on T cells	Naive T cells	Regulatory T cells; activated T cells	Activated T cells; T follicular helper (Tfh) cells	Activated T cells
Major function	Activation of naive T cells; induction of immune responses	Inhibition of T cell activation	Generation of T follicular helper cells	Inhibition of T cell activation (mainly of effector T cells)

The outcome of T cell activation is influenced by a *balance* between engagement of activating and inhibitory receptors.

CD40-CD40L interaction

CD40 ligand is a TNF superfamily membrane protein expressed on *activated T cells* that interacts with CD40 on *APCs* to make them more potent by inducing *B7* expression and *cytokine* secretions (IL-2) promoting *T cell differentiation*.

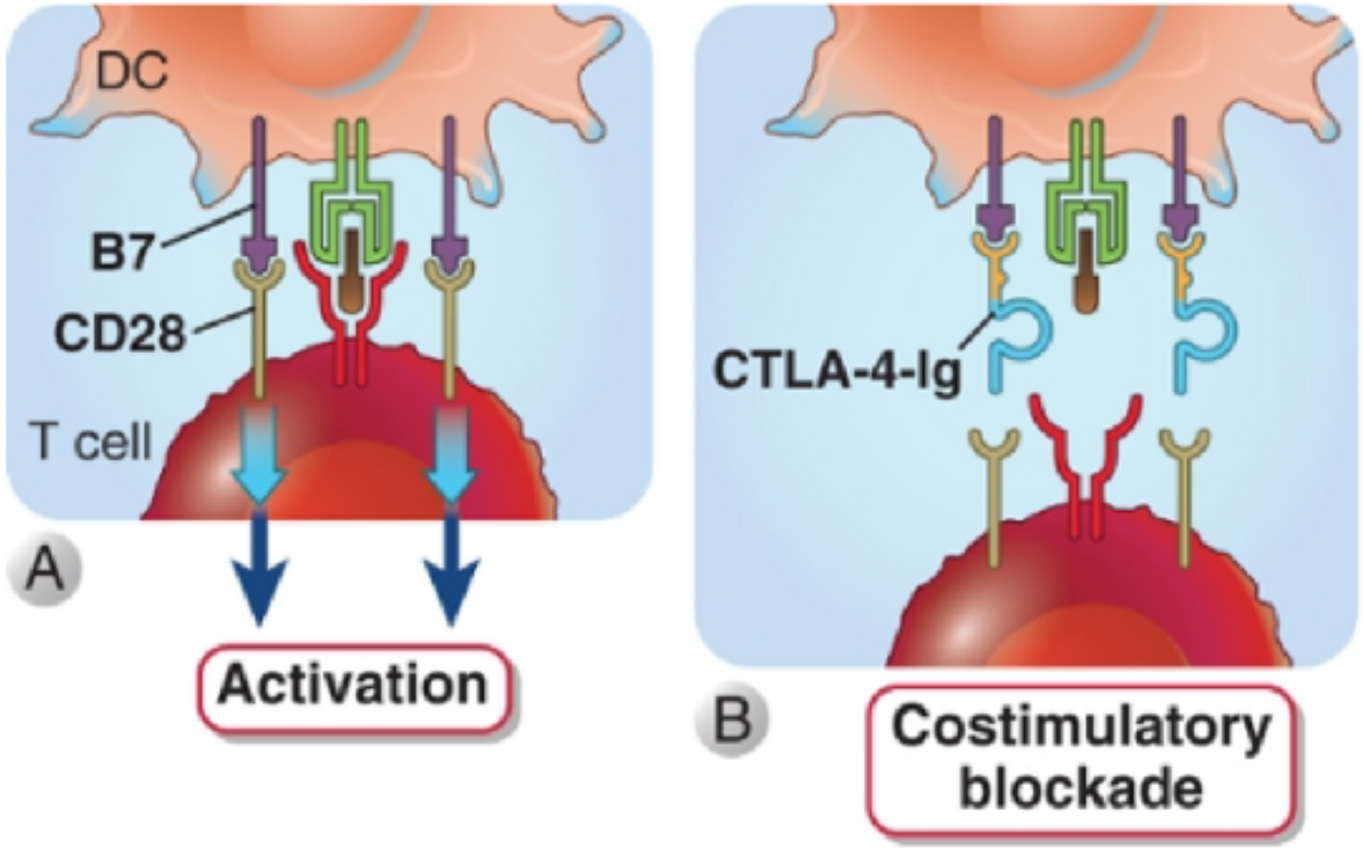
➔ pathway to indirectly amplify T cell responses by inducing costimulators on APCs



Therapeutic costimulatory blockade

Antibodies blocking *CTLA-4 and PD-1* inhibitory receptor are approved for *immunotherapy of tumors* (reduce inhibition, thus enhance T cell activation and enable cancer-bearing individuals to mount more *effective antitumor immune responses*

➔ but as they play a role maintaining self-tolerance, these immunotherapies can also induce autoimmune reactions

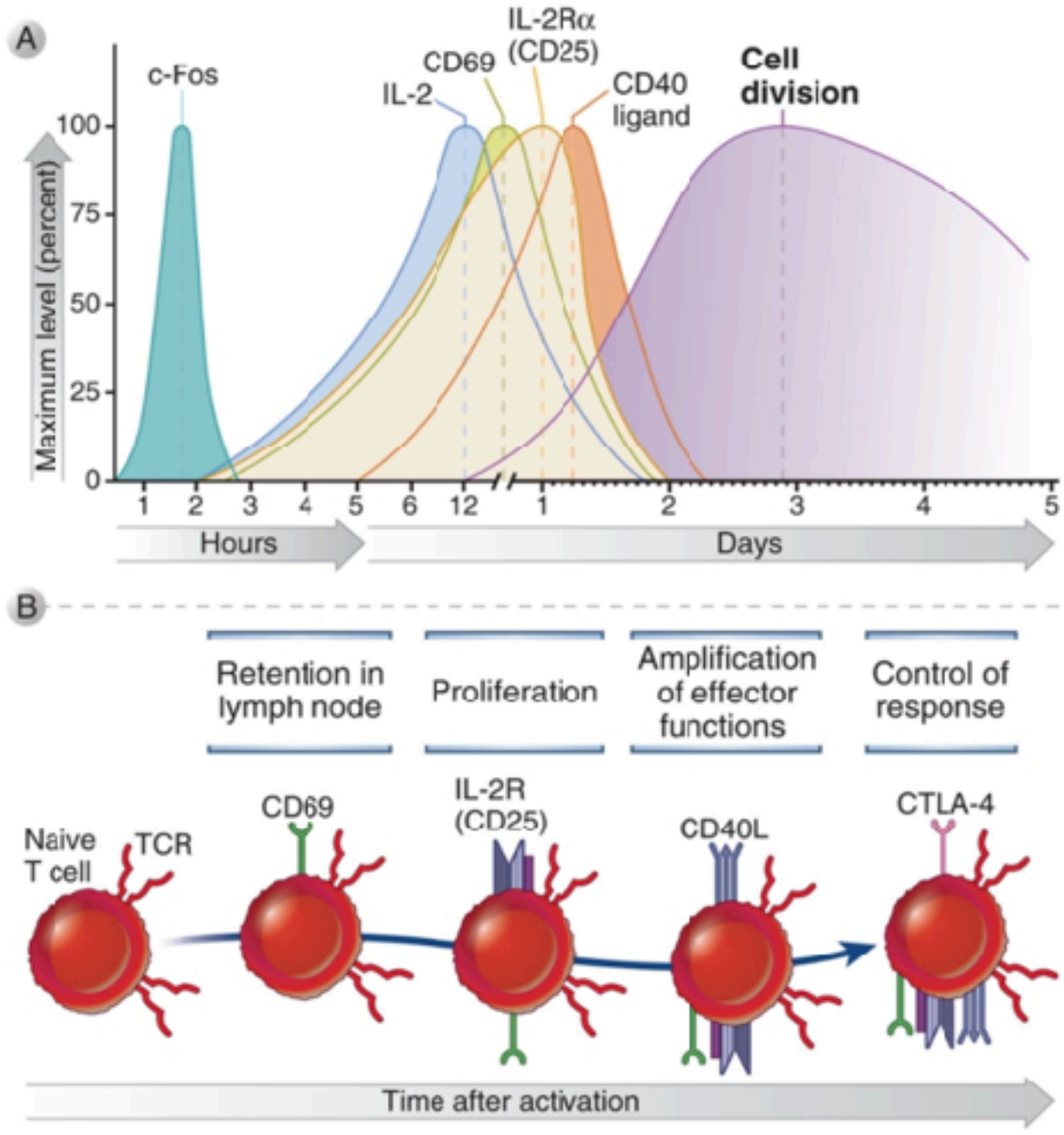


Functional consequences of T cell activation

1. Cell surface and cytokine expression
2. Proliferation
3. Differentiation

Changes in surface molecules during T cell activation

- CD69: important to be *retained in lymphoid organs* (low in differentiated effector T cells)
- CD25 (IL-2Ra): receptor for growth factor *IL-2*
- CD40 ligand (CD40L): within 24-48h after recognition, enables activated T cells mediated *effector function* via help from activates APCs
- CTLA-4: 24-48 after recognition
- Adhesion molecules and chemokine receptor: favour migration to *peripheral sites* of infection/injury and reduce lymphoid organs homing molecules

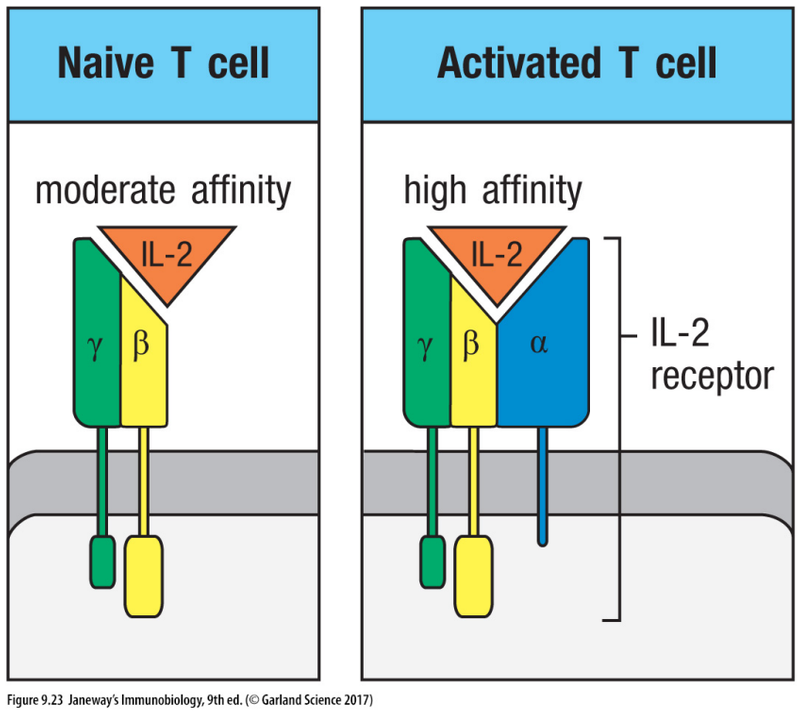


Cytokines in adaptive immune responses

- **CD4⁺ helper T cells**: make the *largest amount and variety* of cytokines
- **APCs cytokines:** especially important for naive T cells differentiation
  ➔ Cytokines mostly acts on the cells that produce them (*autocrine* action) or on nearby cells (*paracrine* action)

IL-2 and IL-2 Receptor

- IL-2 is important for T cell growth, survival and differentiation
- IL-2 is mainly produced by *CD4⁺ T cells* early after AG recognition; *rapid and transient* and declines by 24h
- High local concentration at *immune synapse* between T cell and APC
- Receptor transiently expressed on activated T cells, *always expressed on Tregs.*



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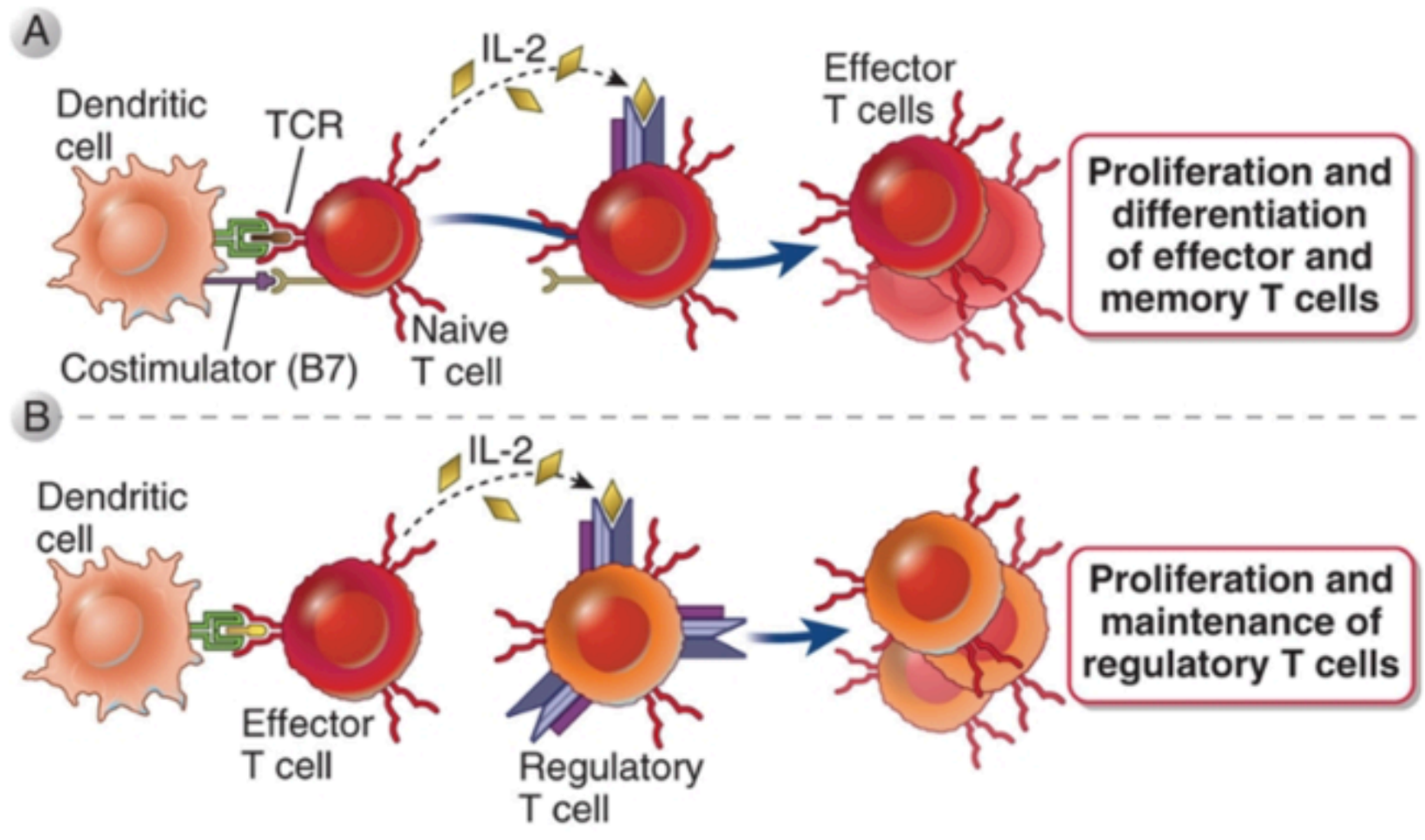
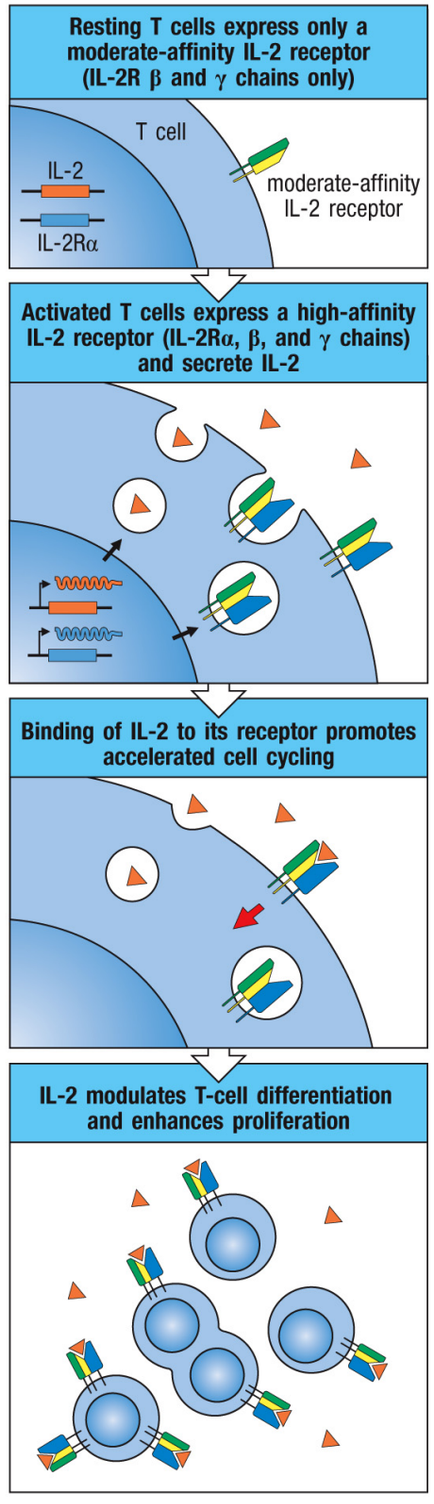
IL-2 plays a role in promoting and controlling T cell responses

- *Survival, proliferation, differentiation* of *antigen-activated T cells* (induces anti-apoptotic Bcl-2 protein)
- Required for *survival and function of Tregs* (suppress immune responses against self and other antigens, these cells depend on IL-2 made for other cells to survive)





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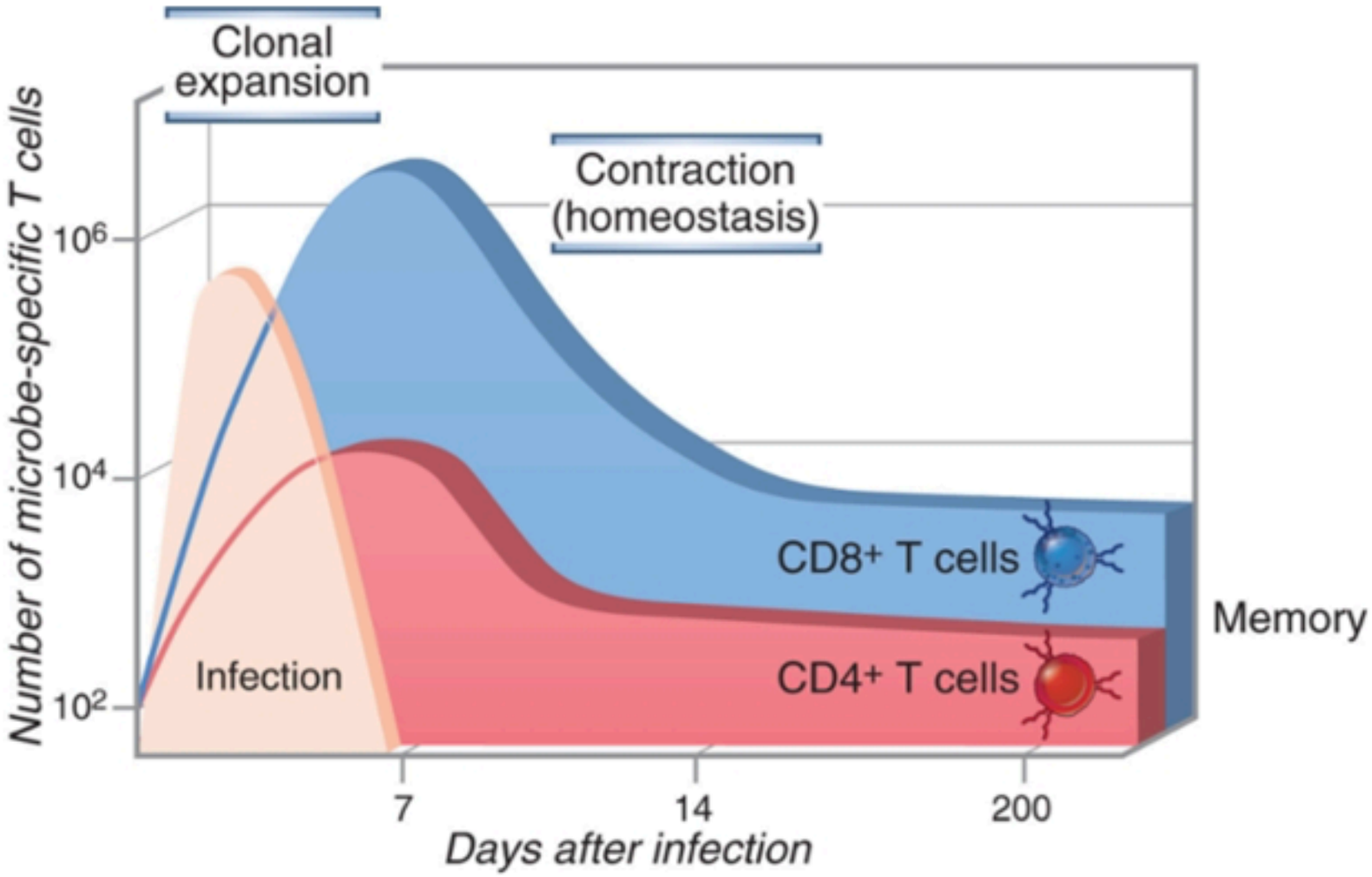
Clonal expansion of T cells

- **Combination of signals** lead to *T cell proliferation* and *expansion of antigen-specific clones* to convert a small pool of naive lymphocytes into a large number of cells that can eliminate the antigen
- **Expansion** can be as much as *50'000 fold increase* of antigen specific *$CD8^+$ T cells* and *1000 fold* for *$CD4^+$ T cells*

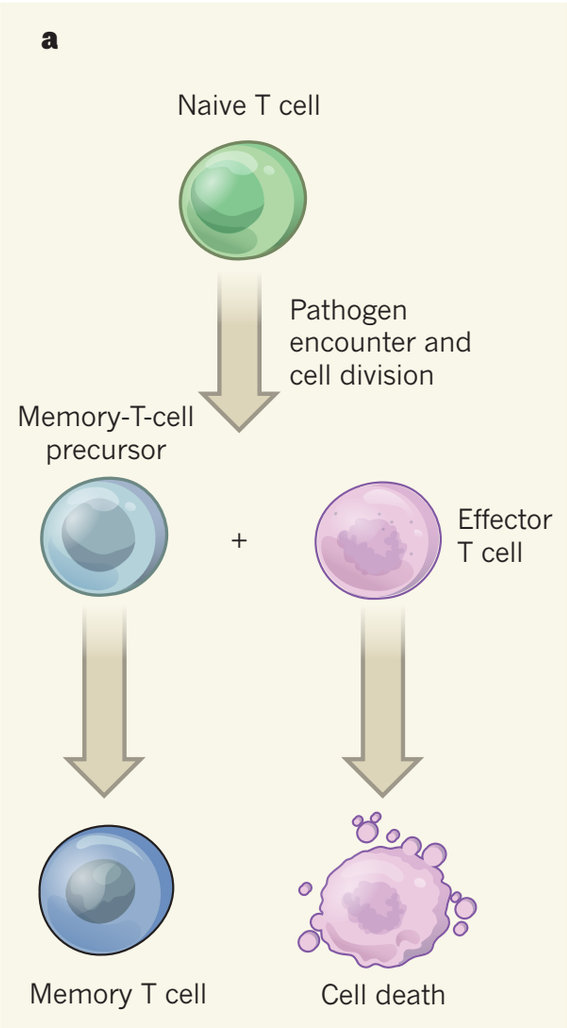


Development of memory T cells

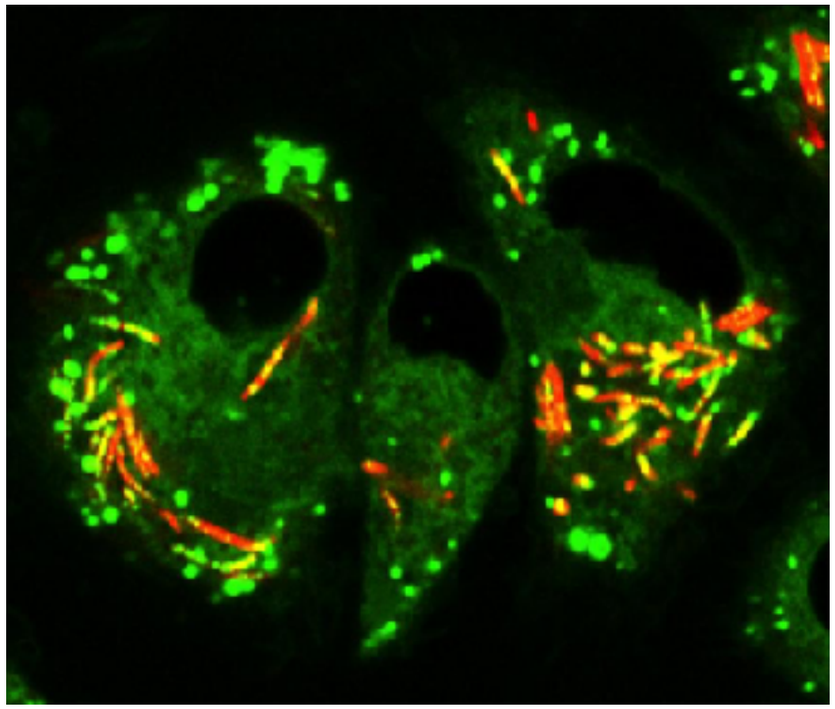
Central memory T cells versus **Effector memory T cells**

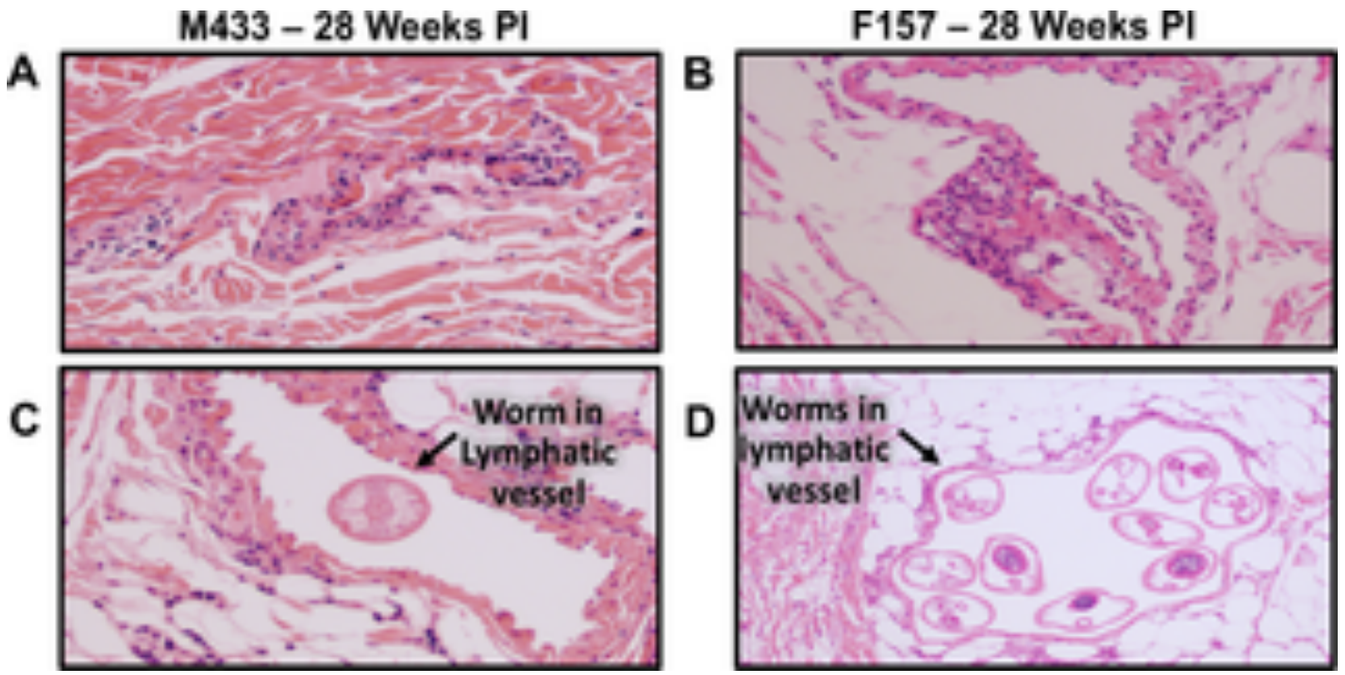
Some memory T cells migrate in nonlymphoid tissues and survive for long periods = **tissue resident memory cells** that provide rapid responses to recurrent entry of microbes into tissues

- **Survival**: *quiescent state* after antigen elimination, increased levels of *anti-apoptotic proteins* and their maintenance requires *cytokines* (IL-7, IL-15)
- **Response**: in comparison to naive cells specific for the same antgeins, mount *larger and more rapid* response, present in *greater number* and are *less dependent on costimualtion* for activation, they can migrate to *peripheral tissues* and respond to antigens at these sites.



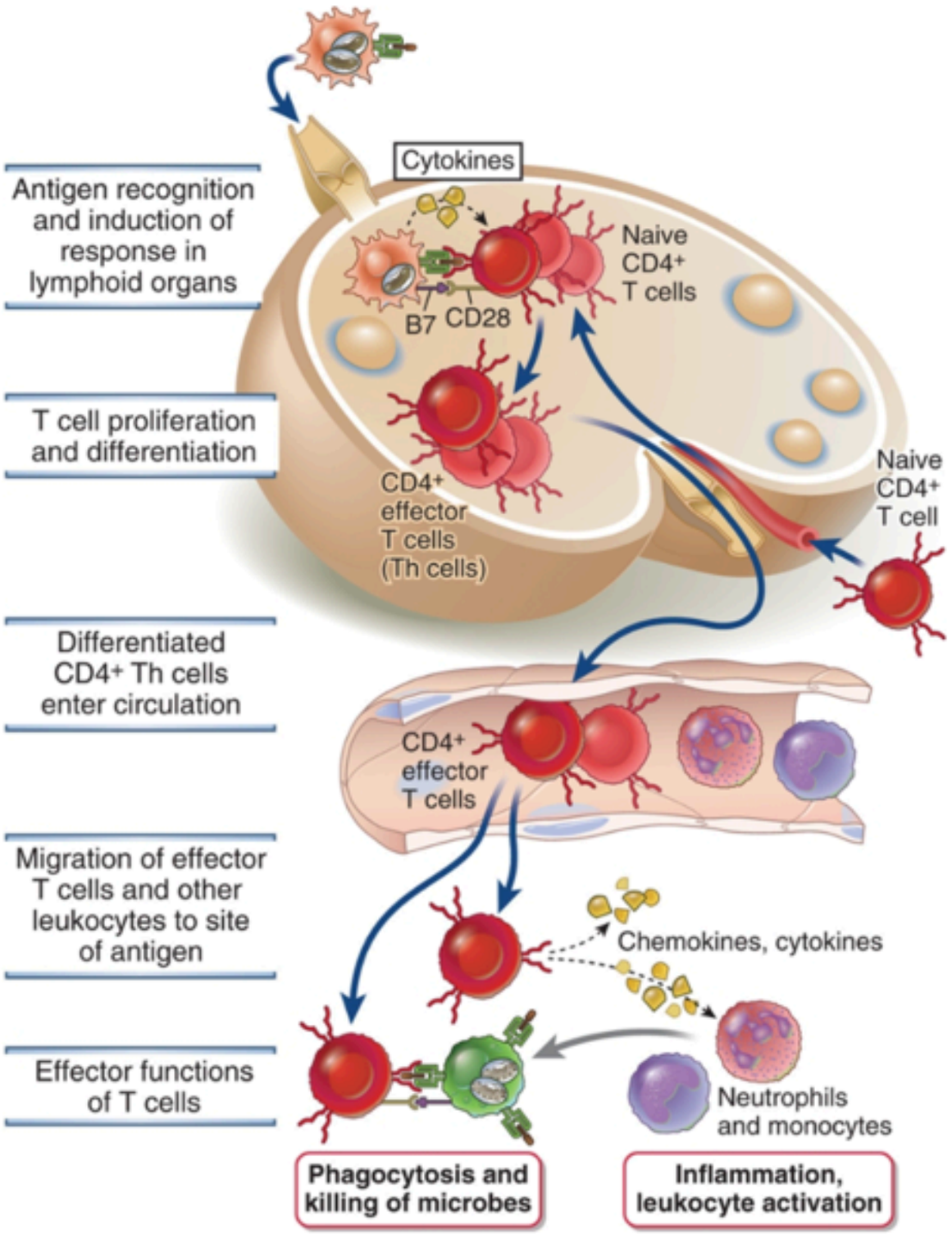
Differentiation and Functions of CD4^{+} Effector T cells





How can the same CD4 T cells mediate such different responses?

Steps in CD4+ T cell-mediated immune responses

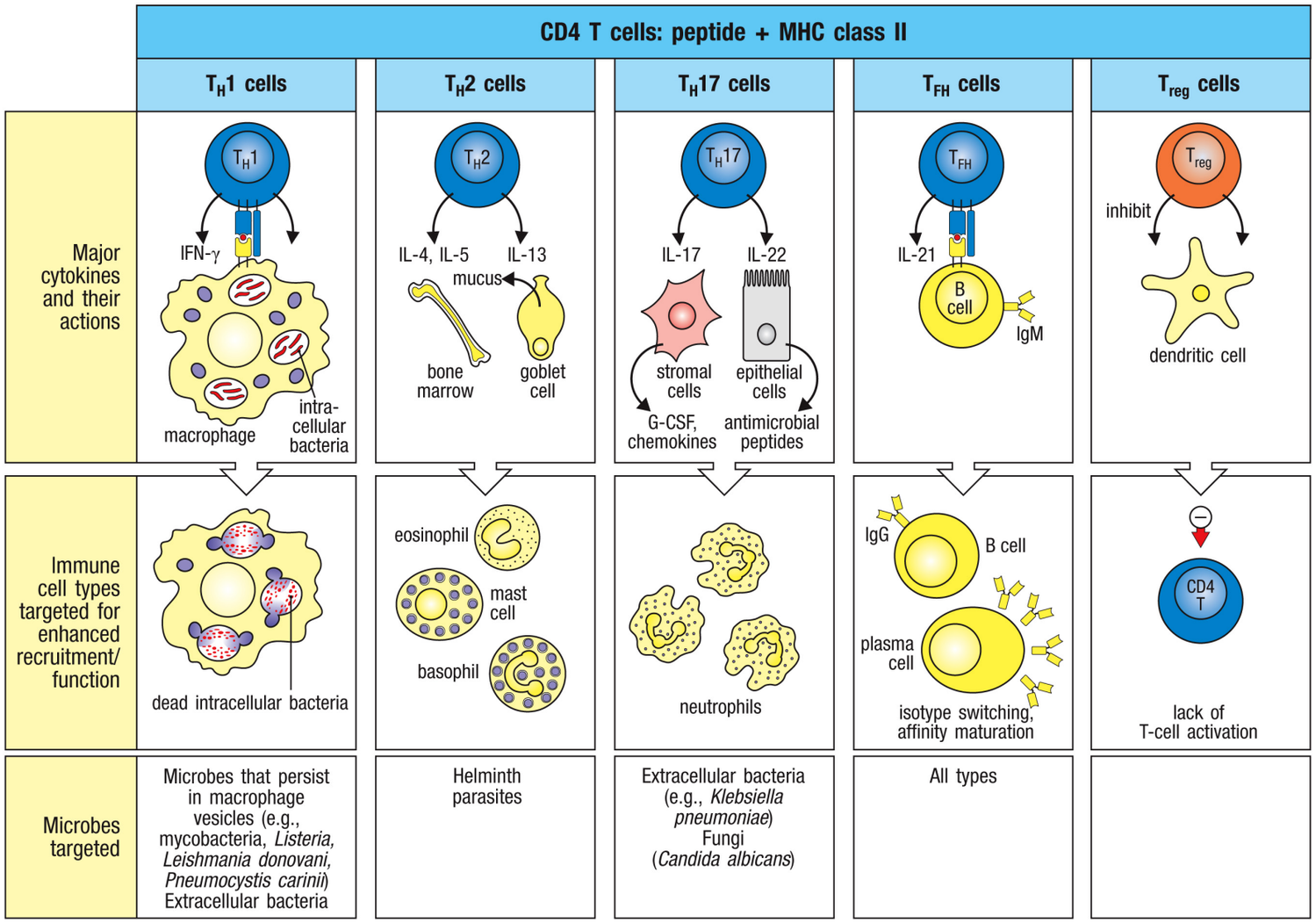


- **Migration to the site of infection** is dependent on *endothelial adhesion molecules and chemokine* expression. Adhesive and chemotactic interactions *retain antigen-specific T* cells at the extravascular site.

- **B cell help** (AB production and isotype switch) is mediated by a fraction of CD4+ T cells activated in secondary lymphoid organs that migrate into *lymphoid follicles*

- Link specific recognition with the *recruitment* and *activation of other leukocytes* that destroy the microbe

Major subsets of CD4+ helper T cells



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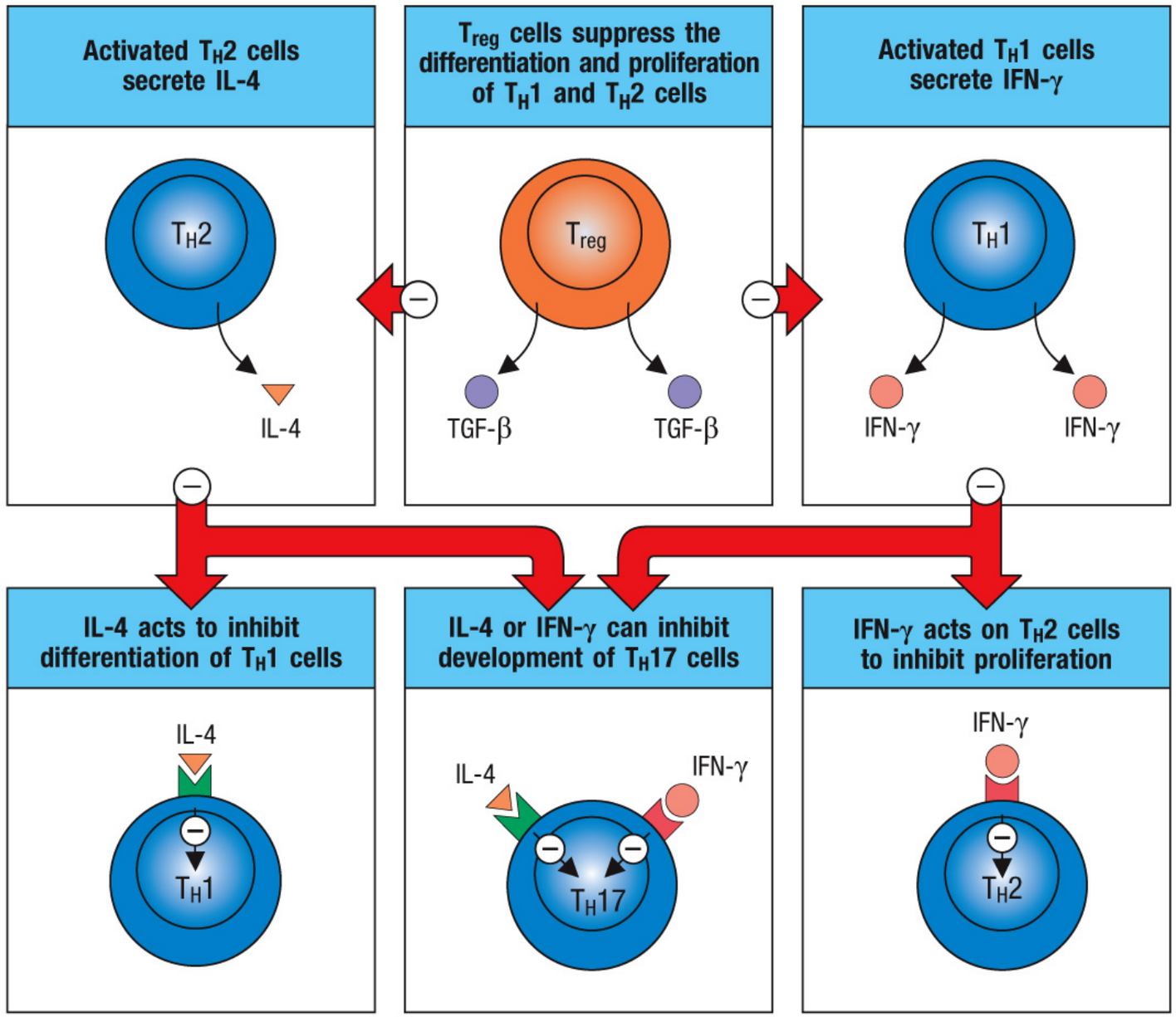
- **T-cell dependent inflammation** serves as an *antimicrobial* mechanisms but also may *damage normal tissues* (delayed-type hypersensitivity DTH)
- **Functions** are largely mediated by distinct *cytokines*

General features about CD4 T cell differentiation



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Major subsets of $CD4^+$ helper T cells

Elicit phenotypically diverse immunologic reactions:

- Bacteria surviving in phagocytes: activated *macrophages*
- Helminth parasites: production of *IgE antibody* and *eosinophils* activation
- Many chronic autoimmune disease: tissue damage caused by *inflammation* with accumulation of neutrophils and macrophages
- Allergic disorders: lesions containing abundant *eosinophils* and other leukocytes

Differential TF expression (sustained by epigenetic modifications at cytokine genes)

- Production of different *cytokines + chemokine R* by APCs (primarily DCs and macrophages) and other immune cells (NK, mast cells)
- Determine *effector functions* and may suppress the development of the other subsets ➔ *polarization*
- Distinct pattern of *homing*
- *Specialization*: ability to respond in a way optimal for combating specific microbes

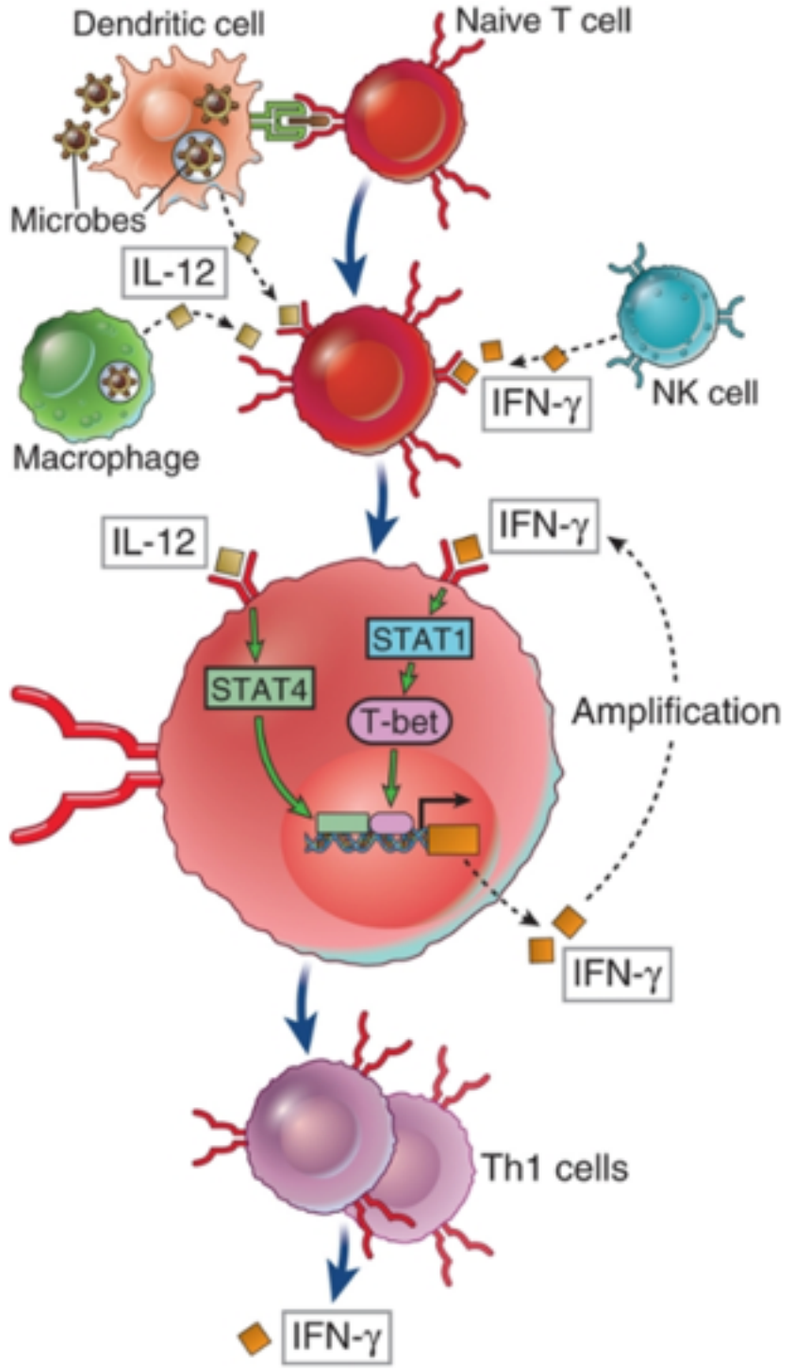
Th1 Subset

- **Stimuli:** microbes that *activate DCs, macrophages and NK* cells (e.g. ingested microbes surviving within phagocytes)

- **Differentiation** driven mainly by IL-12, IL-18 and IFN-γ

- **TF activation**: T-bet, STAT1 and STAT4

- **Functions**:
  - IFN-γ mediated *macrophage activation* (kill and destroy microbes)
  - Cytokine secretions (e.g. TNF-a) to *recruit leukocytes* and enhance *inflammation*
  - *IL-10* mediated negative feedback loop (suppress Th1)



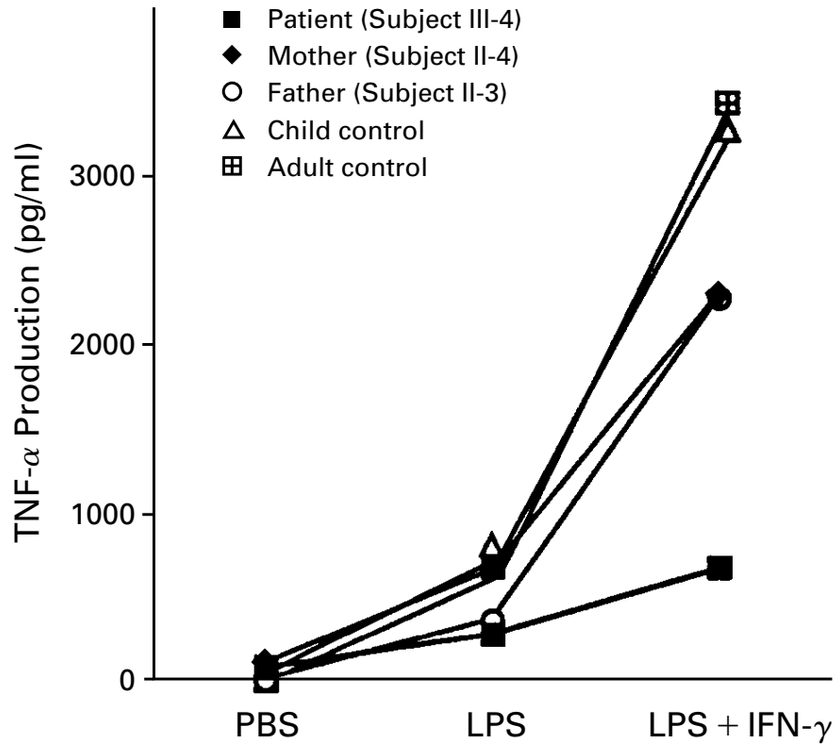
A MUTATION IN THE INTERFERON-γ–RECEPTOR GENE AND SUSCEPTIBILITY TO MYCOBACTERIAL INFECTION

MELANIE J. NEWPORT, M.D., PH.D., CLARE M. HUXLEY, PH.D., SARA HUSTON, B.SC., CATHERINE M. HAWRYLOWICZ, PH.D., BEN A. OOSTRA, PH.D., ROBERT WILLIAMSON, PH.D., AND MICHAEL LEVIN, F.R.C.P., PH.D.

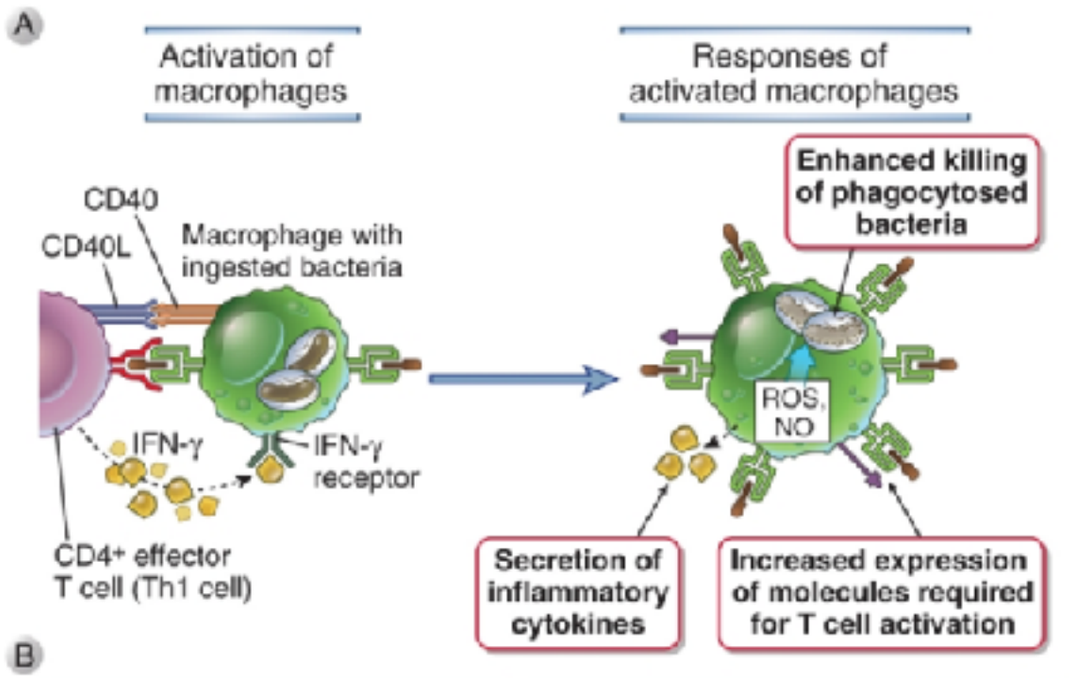
Patients

The characteristics of the patients have been described elsewhere.[11] Briefly, four children from the same small town in Malta presented with disseminated atypical mycobacterial infection in the absence of a recognized immunodeficiency. They all had fever, weight loss, hepatosplenomegaly, bone lesions, and an intense acute-phase response. Two of the affected children are brothers

We have previously described a group of related children from a village in Malta who appear to have a familial immunologic defect predisposing them to infection with a range of mycobacteria.[11] Despite intensive treatment three of the four affected patients have died, and the survivor has persistent infection. Immunologic studies have shown that the affected children have defective production of tumor necrosis factor α (TNF-α) in response to endotoxin and a failure to up-regulate this cytokine in response to interferon-γ.[11]



Th1-mediated classical macrophage activation



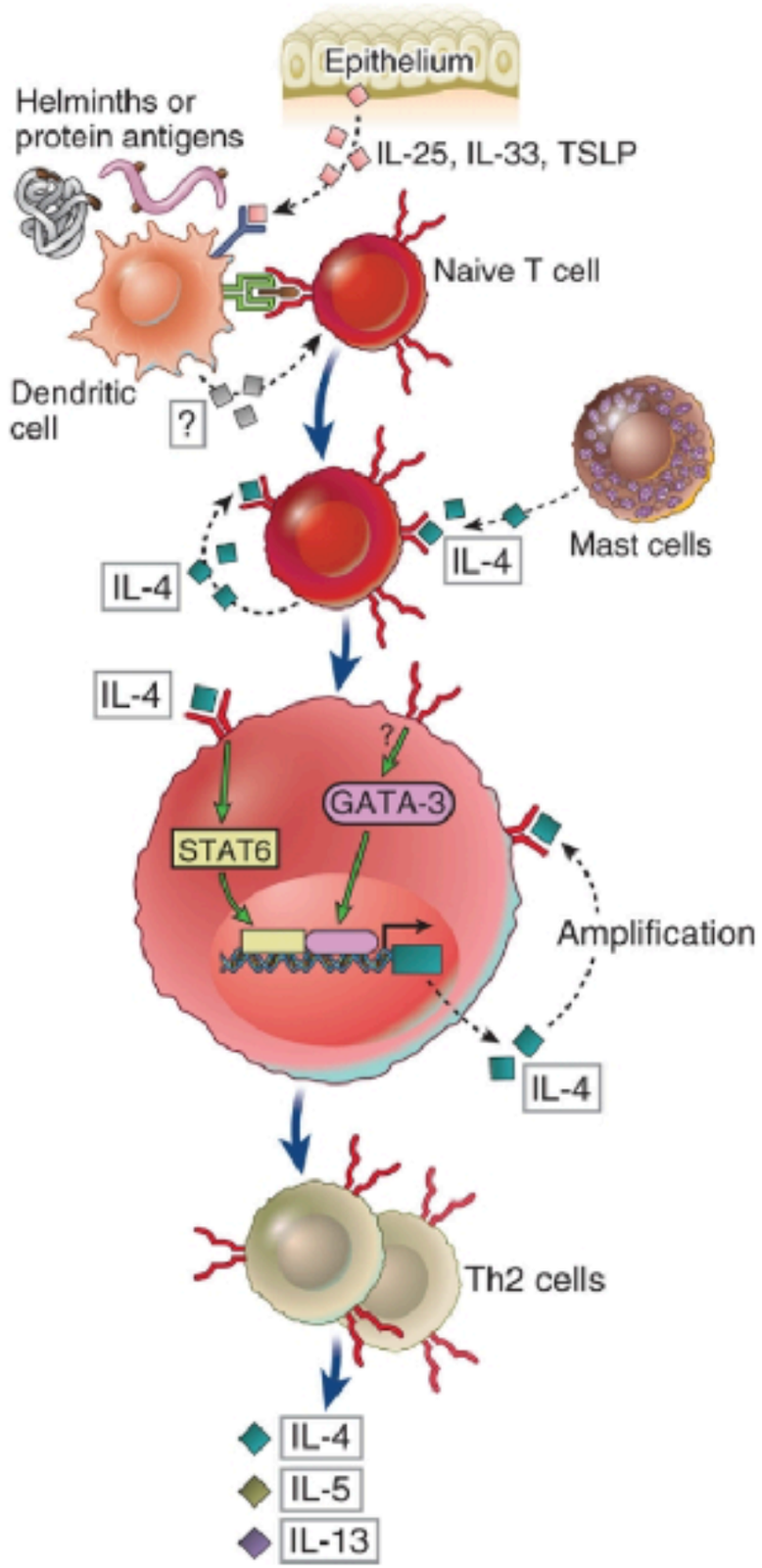
B

Macrophage response	Role in cell-mediated immunity
Production of nitric oxide, increased lysosomal enzymes, reactive oxygen species	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)

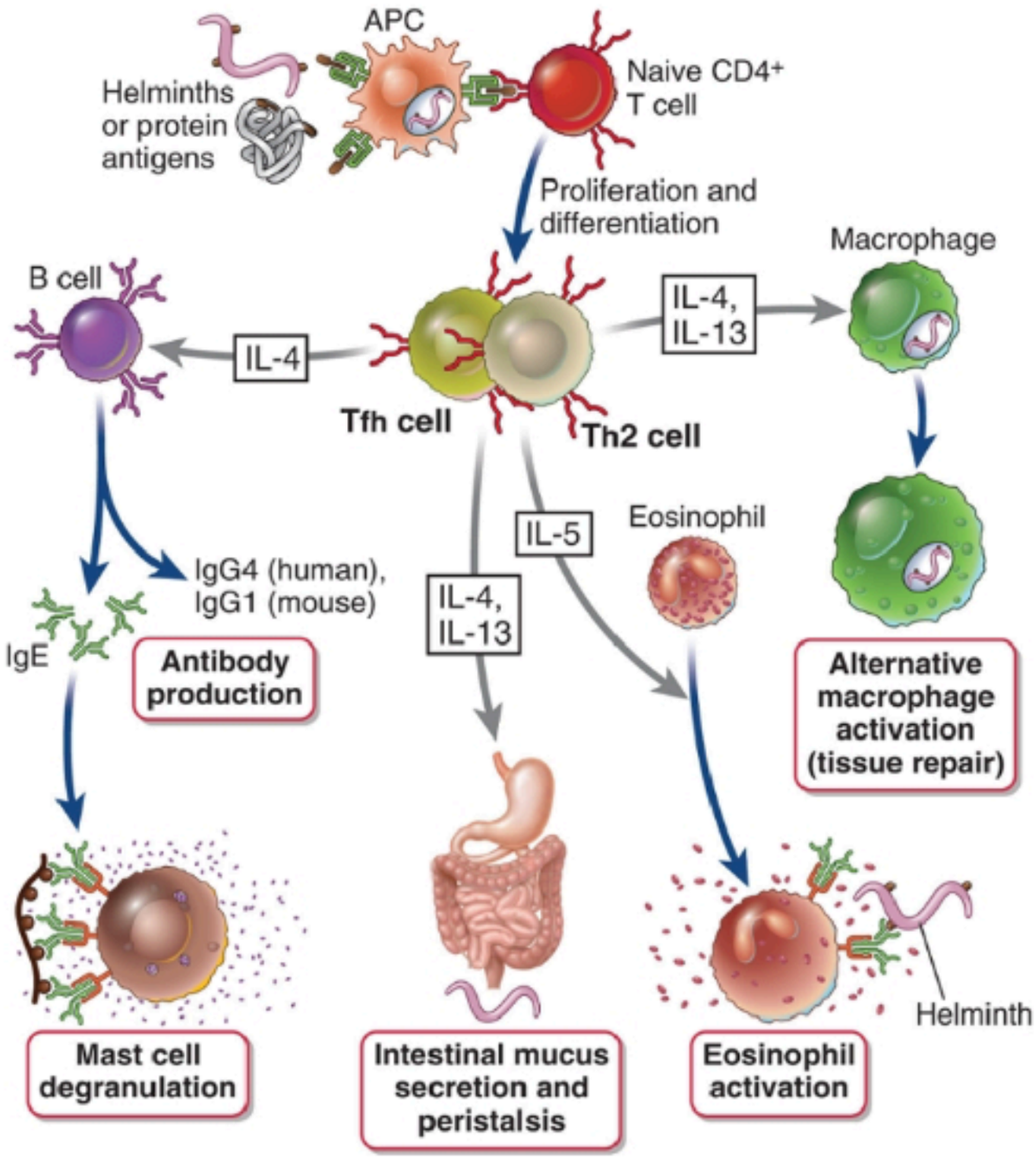
- **Contact-mediated signals** (CD40L-CD40 interaction and IFN-γ)
- **Activated macrophages** kill phagocytosed microbes mainly by the actions of *NO*, *lysosomal enzymes and ROS* (can also cause damage to normal adjacent tissue)
- **Several other host defence reactions:** *inflammation* stimulation, increased *antigen processing* capability and *costimulation*, cytokine secretion to stimulate *T cell differentiation* into effectors
- **Microbial products** released are capable of *injuring normal tissue* (usually limited in extent and duration)

Th2 Subset

- **Stimuli**: *helminthic* infections, microbes in *mucosal tissues and allergens*
- **Differentiation** driven mainly by IL-25, IL-33, IL-4
- **TF activation**: STAT-6, GATA-3
- **Functions**:
  - Stimulate reactions to eradicate infections by microbes *too large* to be phagocytosed
  - Promote *eosinophils degranulation* to destroy helminths
  - Increase *barrier immunity* to block the entry and favour the expulsion of microbes from mucosal organs
  - *Termination* of the inflammation and tissue *repair* initiation



Functions of Th2



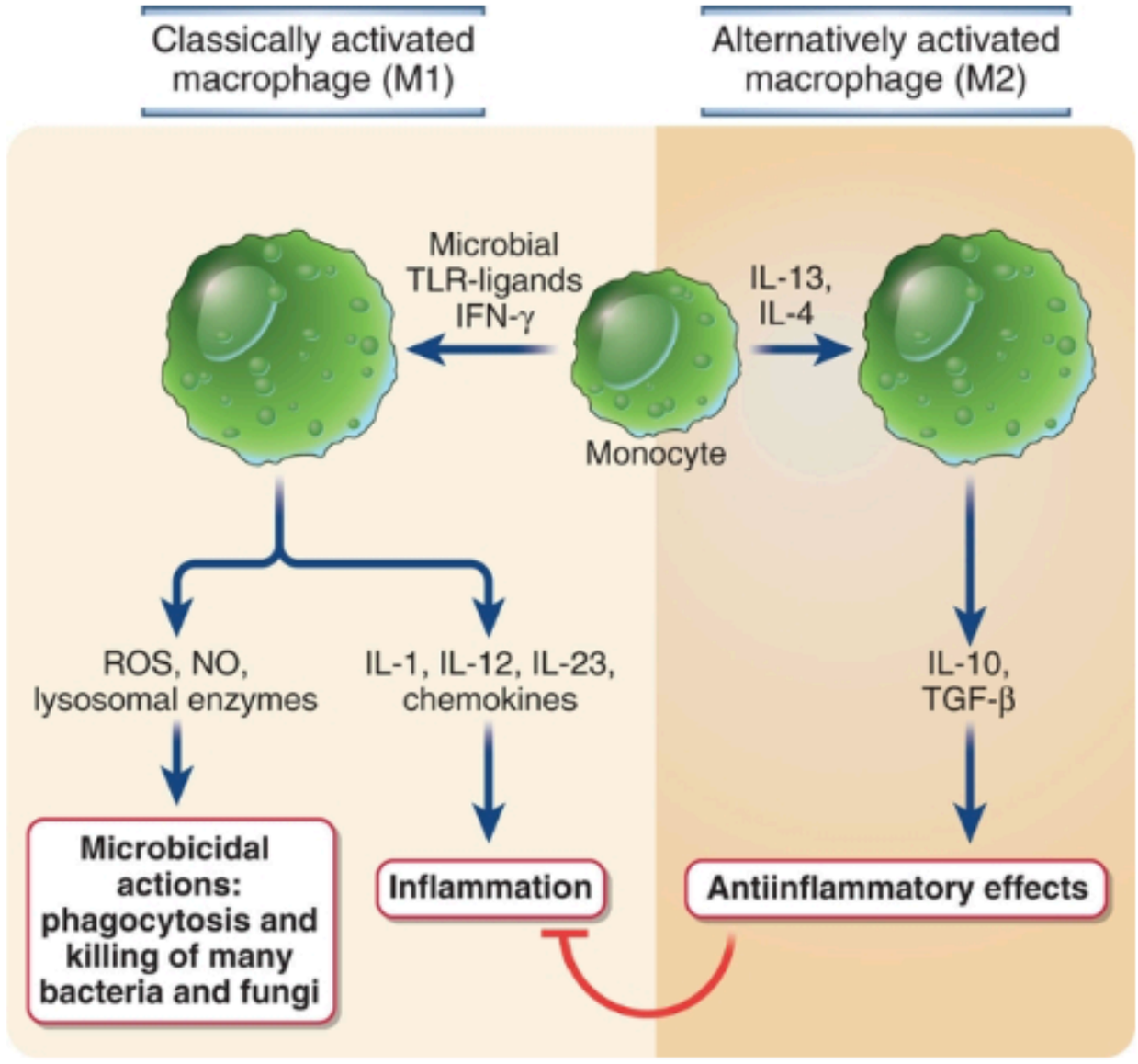
- IL-5: activation and maturation of *eosinophils*

- IL-4: both inducer (by mast cells and Th2 cells) and effector of *Th2* cells (alternative macrophage activation, peristalsis stimulation in GI, eosinophils recruitment)

- IL-13: similar action to IL-4, alternative macrophage activation, *mucus* production stimulation by airways epithelial cells and important in *allergic response*

Alternative macrophage ‘M2’ activation

- Induced by IL-4 and IL-13
- Produce cytokines that *terminate inflammation* and initiate *tissue repair*
- Induce *scarring and fibrosis* by secreting growth factors stimulating fibroblast proliferation, collagen synthesis and angiogenesis



Numerous other subpopulations have been described and M1 and M2 macrophages are likely not fixed subsets

Th17 Subset

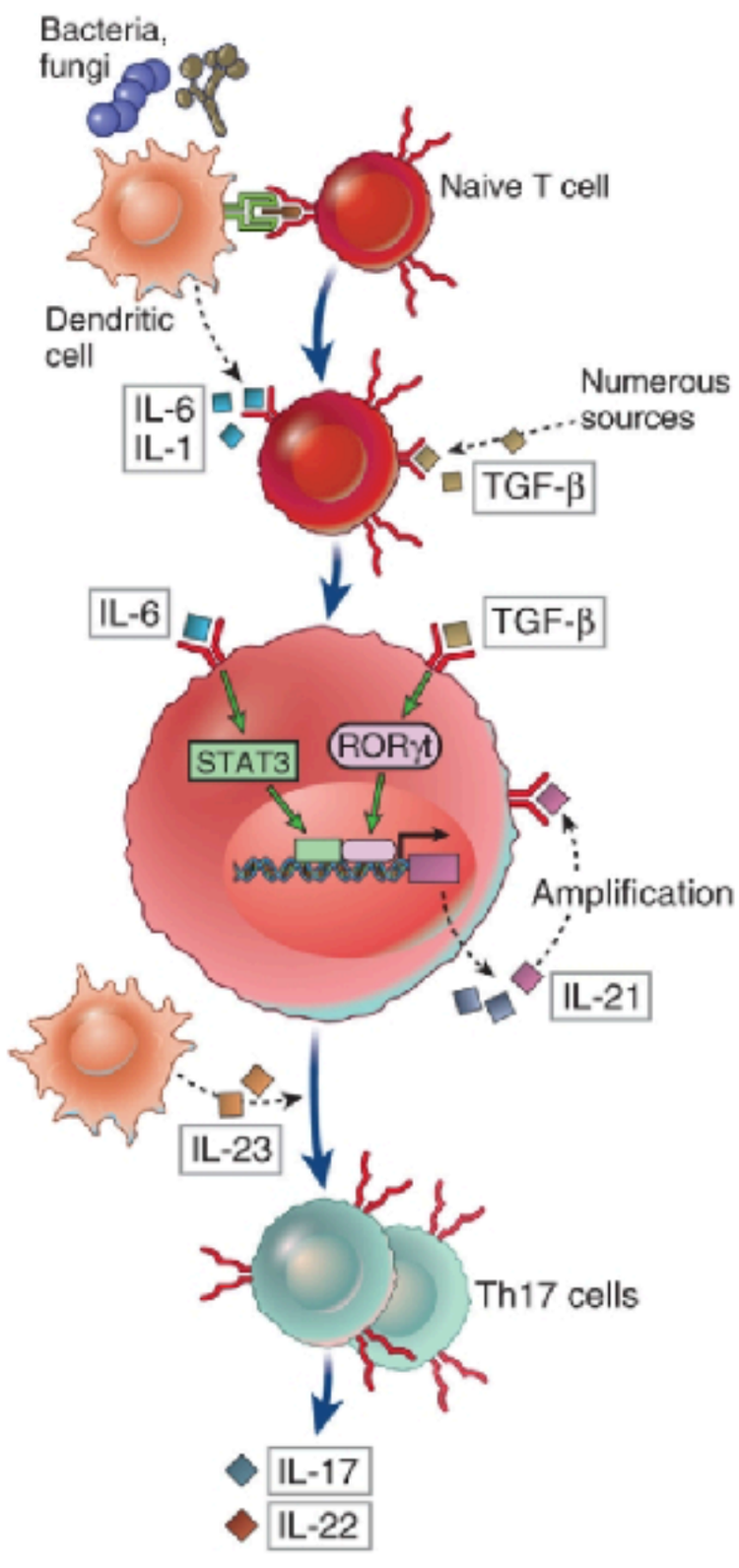
- **Stimuli**: *bacteria, fungi* and microbes killed by phagocytes

- **Differentiation:** driven mainly by IL-6, IL-1, IL-23 *pro-inflammatory cytokines* produced in response to bacteria/fungi, abundant in *mucosal tissues*, therefore dependent on local *microbial* population (e.g. commensals in the intestine)

- **TF activation**: RORγt, STAT3

- **Functions**:

- Leukocyte recruitment (mainly *neutrophils*)
- Destruction of *extracellular* bacteria and fungi
- Pathogenesis of many *inflammatory diseases* (e.g. psoriasis, IBD, rheumatoid arthritis, multiple sclerosis)
- Maintain epithelial *barrier integrity,* stimulate local production of *antimicrobial peptides*

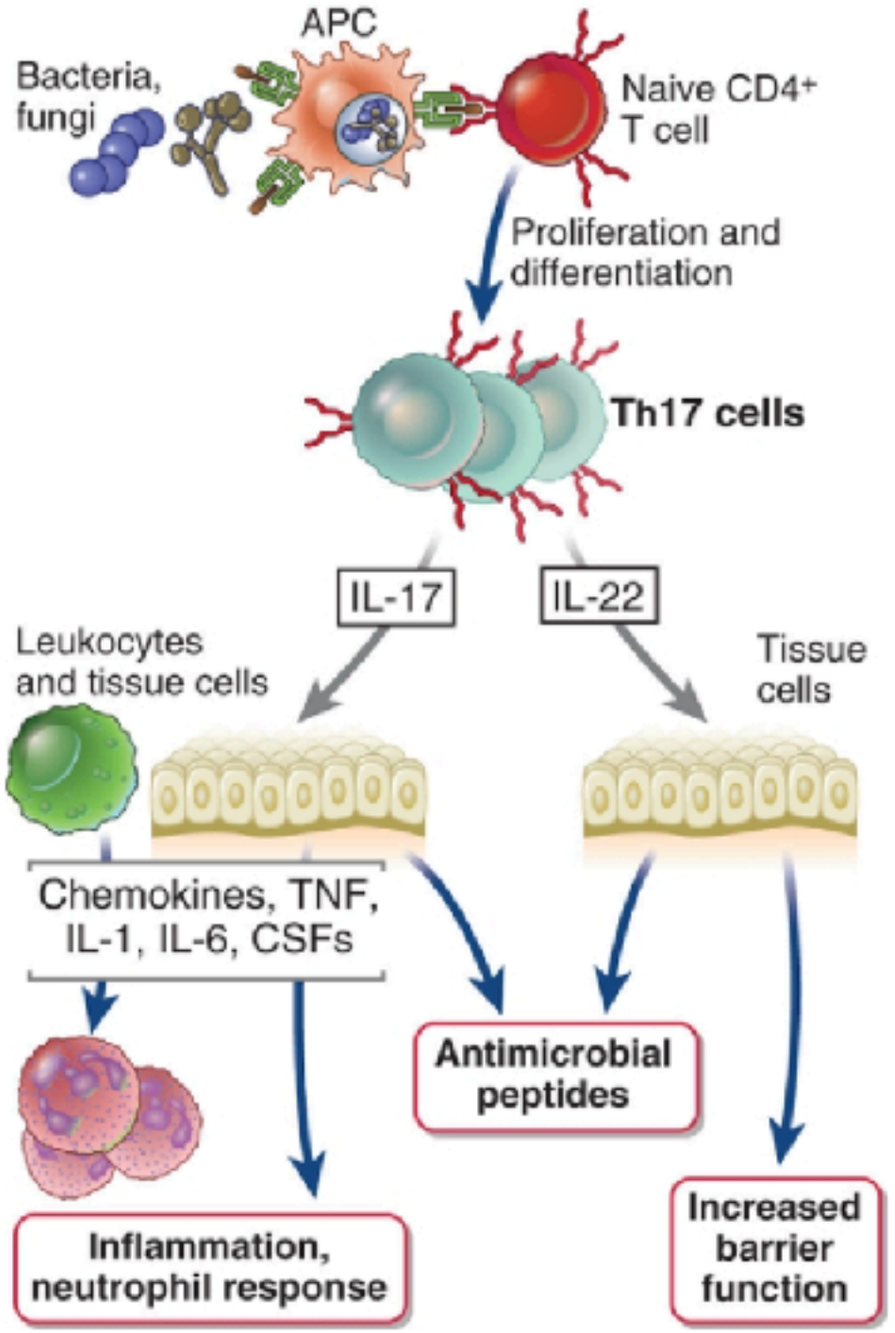


Functions of Th17 cells

- IL-17: induce *neutrophil-rich inflammation* (stimulating their generation via G-CSF and recruitment via chemokine/cytokine secretions) and stimulate the production of *antimicrobial substances* (e.g. defensins)

- IL-22: maintains epithelial *integrity* by stimulating repair reactions and inducing *antimicrobial peptide* production, contributes to *inflammation* by stimulating epithelial production of chemokines

- IL-21: promotes *Th17 differentiation* and provides autocrine signals *amplifying Th17 response*



Functions of other T cell subsets

γδ T cells, natural killer T (NKT) cells and mucosa-associated invariant T (MAIT) cells:

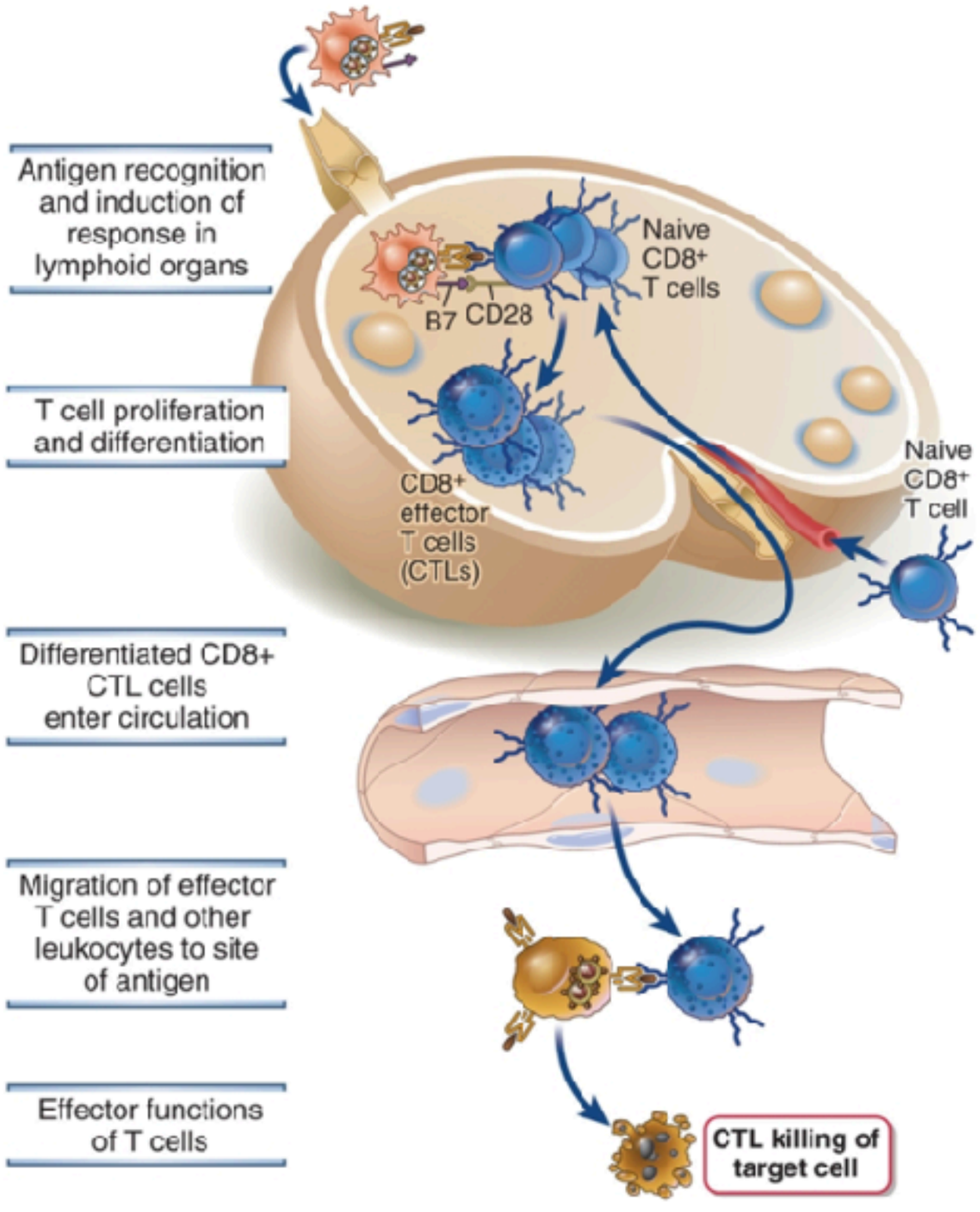
- Recognise *limited number* but *wide variety* of types of antigens (many are not peptides)
- Antigens are *not displayed by class I and class II MHC* molecules on APCs
- Antigen receptors have *limited diversity*
- Abundant in *epithelial* tissues (e.g. gastrointestinal tract)

Functions:

- *Early defence* against microbes in the epithelia before adaptive immune responses develop
- *Surveillance* against stressed cells (DNA damage, infection)
- Production of *cytokines* that influence later adaptive immune responses

Differentiation and Functions of $CD8^+$ Effector T cells

Induction and effector phases of CD8⁺ T cell responses



Naive CD8⁺ cells recognise antigens but need to *proliferate and differentiate* to generate a large pool of CTL to destroy the source of the antigen.

- **TF**: T-bet and eomesodermin

- **Activation** requires antigen recognition and second signals, often depends on the *cross-presentation* pathway and require *help from CD4⁺ T cells*

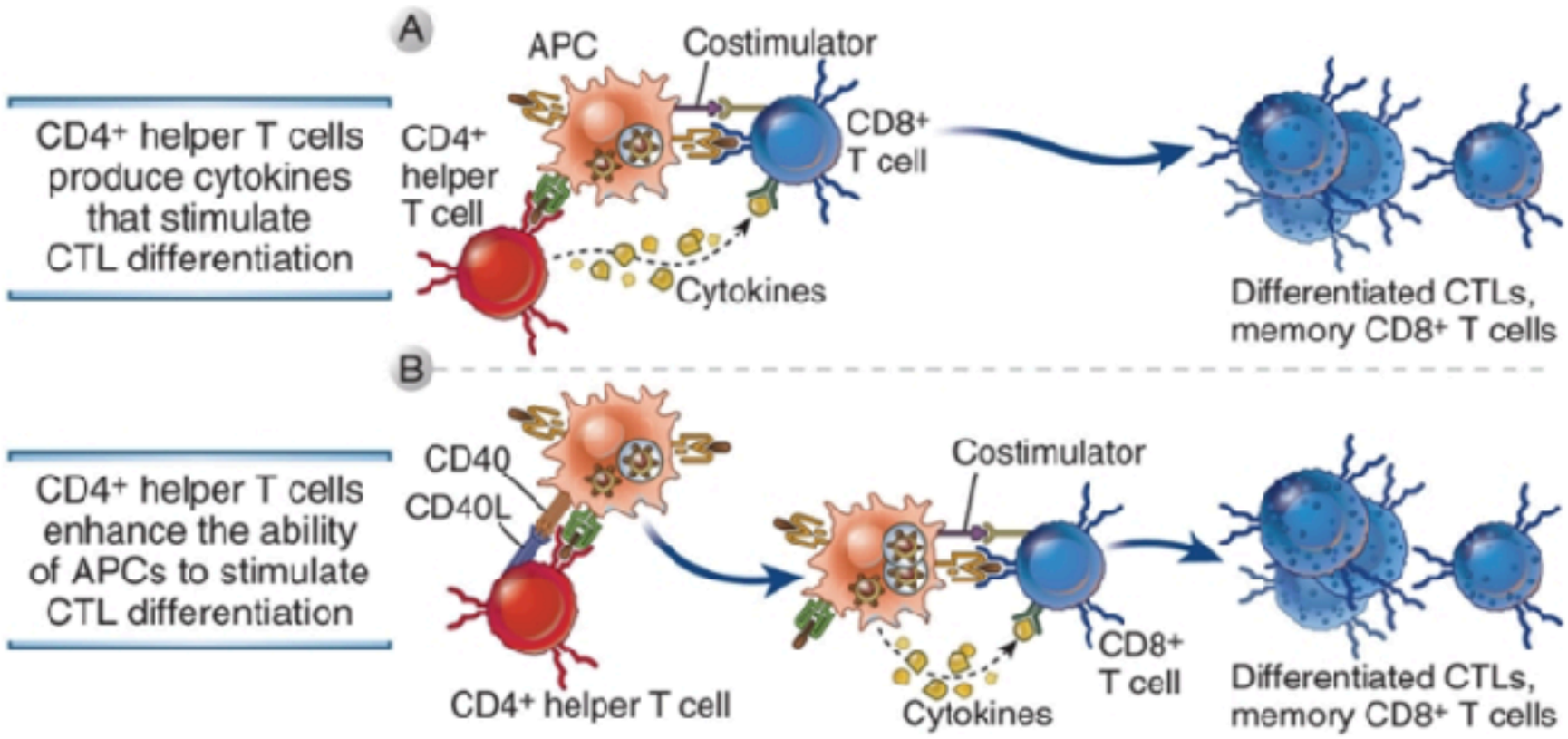
- **Functions**
  - CTLs are equipped with *granules* containing proteins that kill target cells (perforin, granzymes)
  - CTLs secrete *cytokines* to activate phagocytes (IFN-γ)

Nature of antigen and APCs for activation of CD8⁺ cells

Naive cells are best activated by antigens presented by *DCs but* viruses and tumor can affect many cell types *other than DCs*.
➔ Cross-presenting DC subsets are crucial

T helper cells are also required (with varying importance, especially viral infection and tumors that elicit weak innate immune reactions) as they provide:

- *Cytokines* that stimulating CD8⁺ T cell differentiation
- Indirect *licensing of APCs* to make them more efficient at stimulating CD8⁺ T cells (e.g. via costimulators)



Cytokines that contribute to the $CD8^+$ T cells differentiation

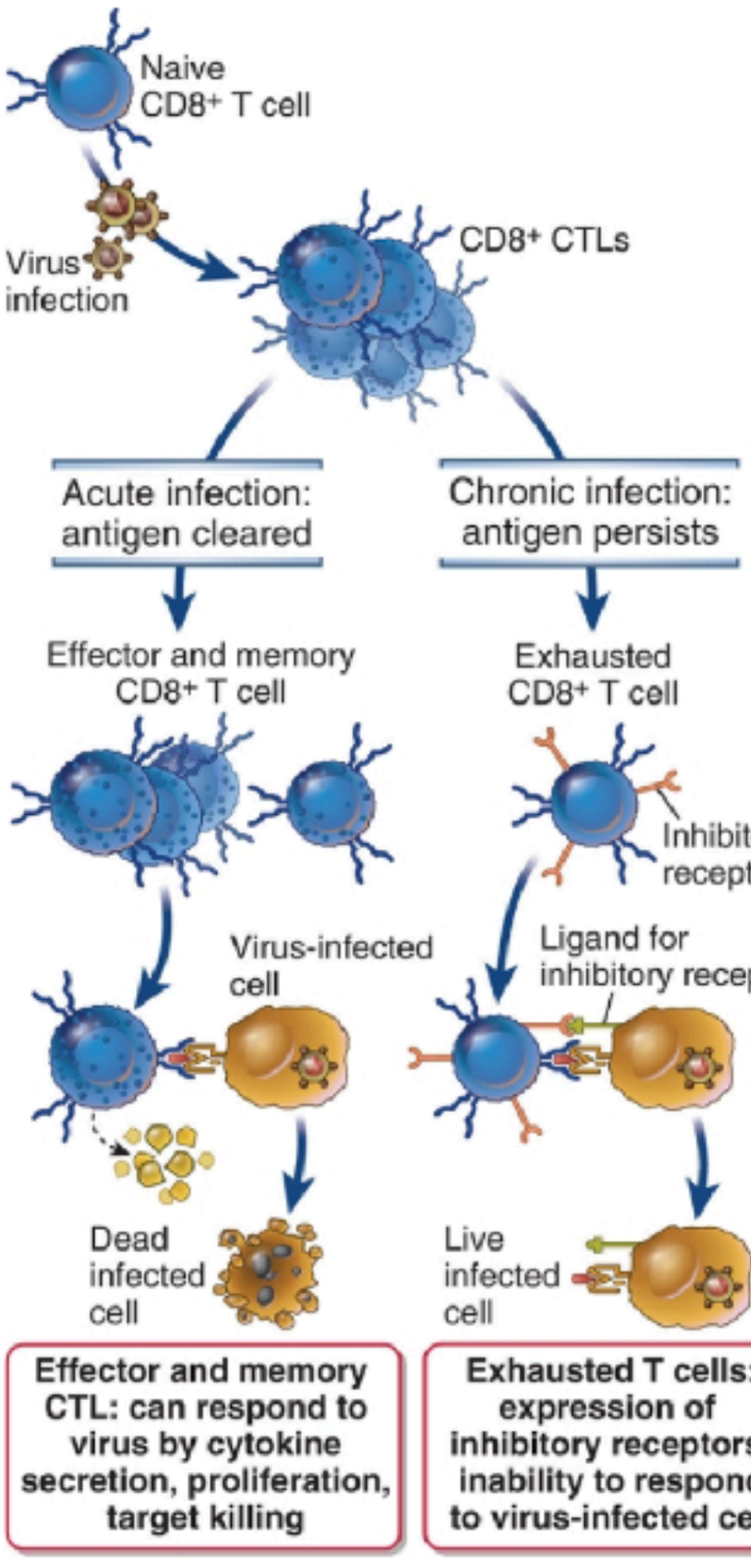
- IL-2: produced by **$CD8^+$ T cells** themselves and **helper T cells**, promotes *proliferation and differentiation*

- IL-12 and type I IFN: produced by **DCs** to stimulate *differentiation* into effector cells

- IL-15: produced by various cell types, important for *survival of memory* $CD8^+$ T cells

- IL-21: produced by activated **$CD4^+$ T** cells and induces *$CD8^+$ effector and memory* cells

T cell exhaustion



- **Development**
- Response to *persistent antigen* exposure
- Effector responses are gradually *extinguished*

- **Characteristics**
- Express TF associated with effector and memory cells (T-bet, eomesodermin)
- Remain *functionally inactive* (decreased proliferation, reduced IFN-γ production, poor cytotoxic activity)
- Express increased levels of *inhibitory receptors* (e.g. PD-1, CTLA-4, Tim-3, Lag-3)

- **Functions**
- May contribute to the *chronicity* of some viral infections (e.g. HIV and HCV) and ability of tumor cells to *evade* immune response
- May have evolved to *attenuate tissue-damaging* consequences of chronic infection

How can killing be specific to target cells?

Recognition of Antigens by CD8 T cells

- Binding and reaction to target cell is mediated by the TCR, the CD8 co-receptor, and adhesion molecules
  - Recognition via TCR + CD8
  - Adhesion via the “immune synapse”

Upon binding to peptide:MHC complex, TCR and co-receptor cluster at the site of cell-to-cell contact:

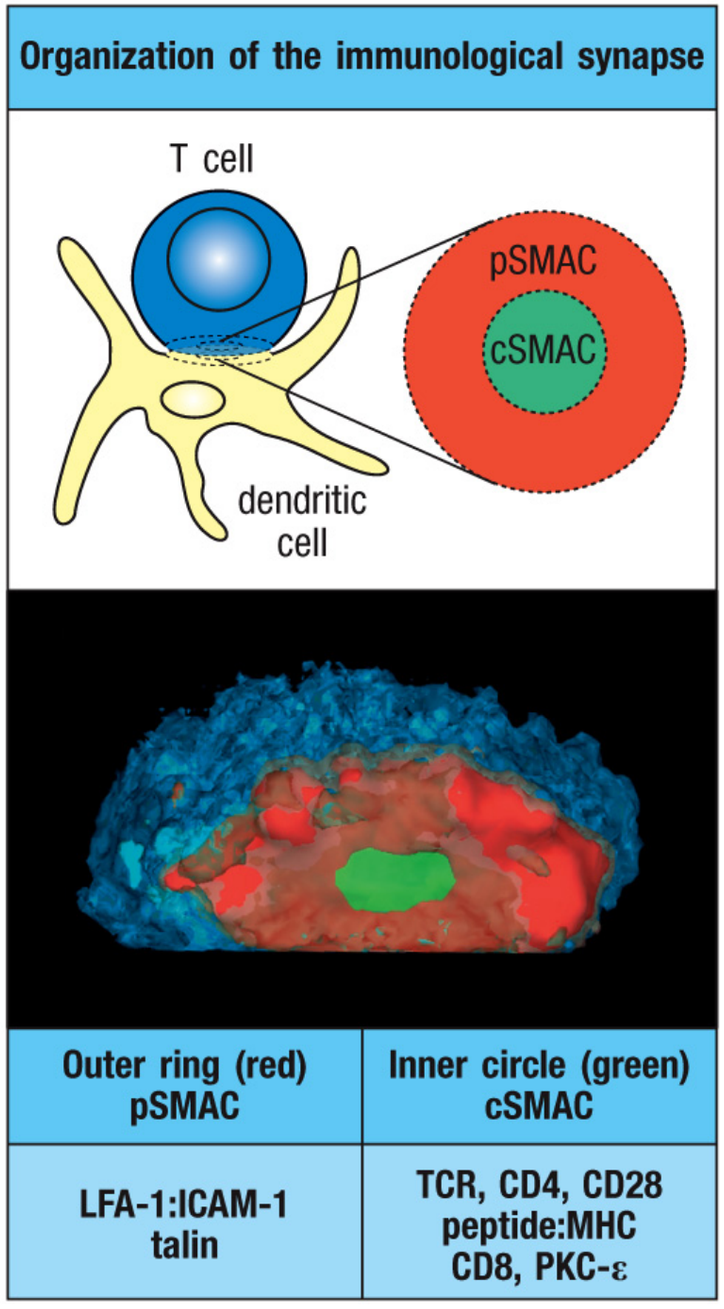
supramolecular activation complex (SMAC) ≈ "*the immunological synapse*"

+ LFA-1/talin cluster ➔ **tight seal**!

Two zones of SMAC:

a) *Central* zone (cSMAC): contains signaling molecules

b) *Outer* zone (pSMAC): contains LFA-1/talin



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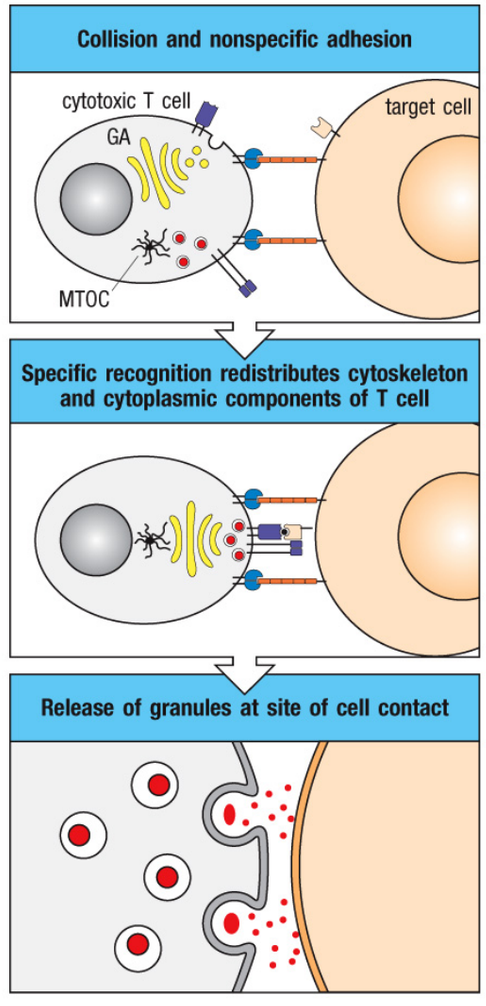
Recognition of Antigens by CD8 T cells

TCR clustering triggers *reorientation* of the **cytoskeleton** + *polarization* of effector cell

➔ release of *effector molecules* at the cell-to-cell contact site!

TCR signaling leads to:

- SMAC + tight contact with target cell
- Polarization of effector cell to guide secretion of cytokines
- Trigger synthesis and release of effector molecules



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The two pathways of apoptosis induced by cytotoxic T cells

Apoptosis

Regulated process activated upon the *presence of specific signals* or by the *absence of survival signals*

Hallmarks of apoptosis →
- Membrane **blebbing**
- Changes in the **distribution of lipids**
- **Fragmentation** of chromosomal DNA

Two general pathways of apoptosis

- **Extrinsic** pathway
- **Intrinsic** / **mitochondrial** pathway

Activation of *caspases* = aspartic acid-specific cysteine proteases

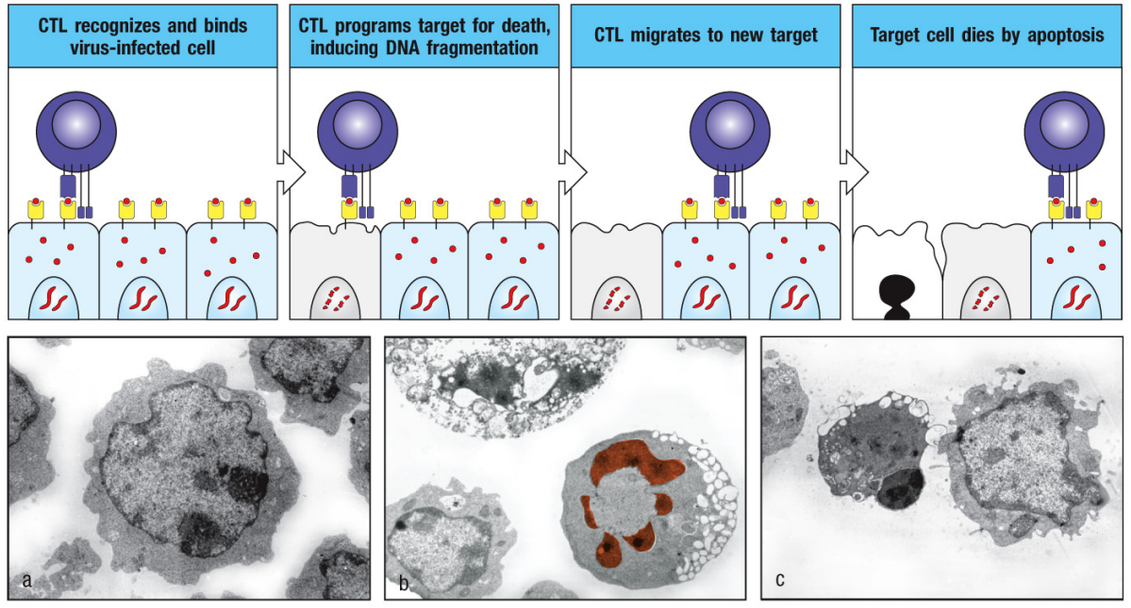
The two pathways of apoptosis induced by cytotoxic T cells

Caspases produced as inactive pro-enzymes

1. *Initiator* caspases: cleave / activate other caspases
   ↳ e.g. : Casp8/10 (extrinsic pathway) or Casp9 (intrinsic pathway)
2. *Executor* caspases: cleave proteins (nuclear membrane) or activate enzymes
   ↳ e.g. : Casp3, 6, 7 (nucleases)

Cytotoxic T cells kill through

- Extrinsic pathway of apoptosis: FASLigand, TNFα, LTα
- Intrinsic pathway of apoptosis: granules which are



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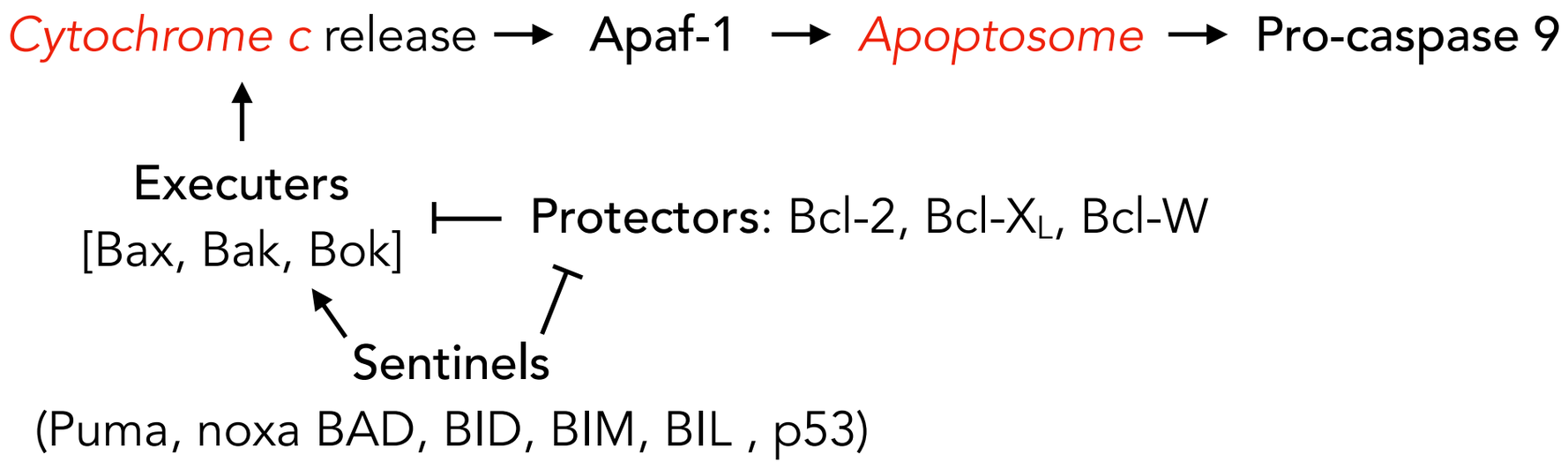
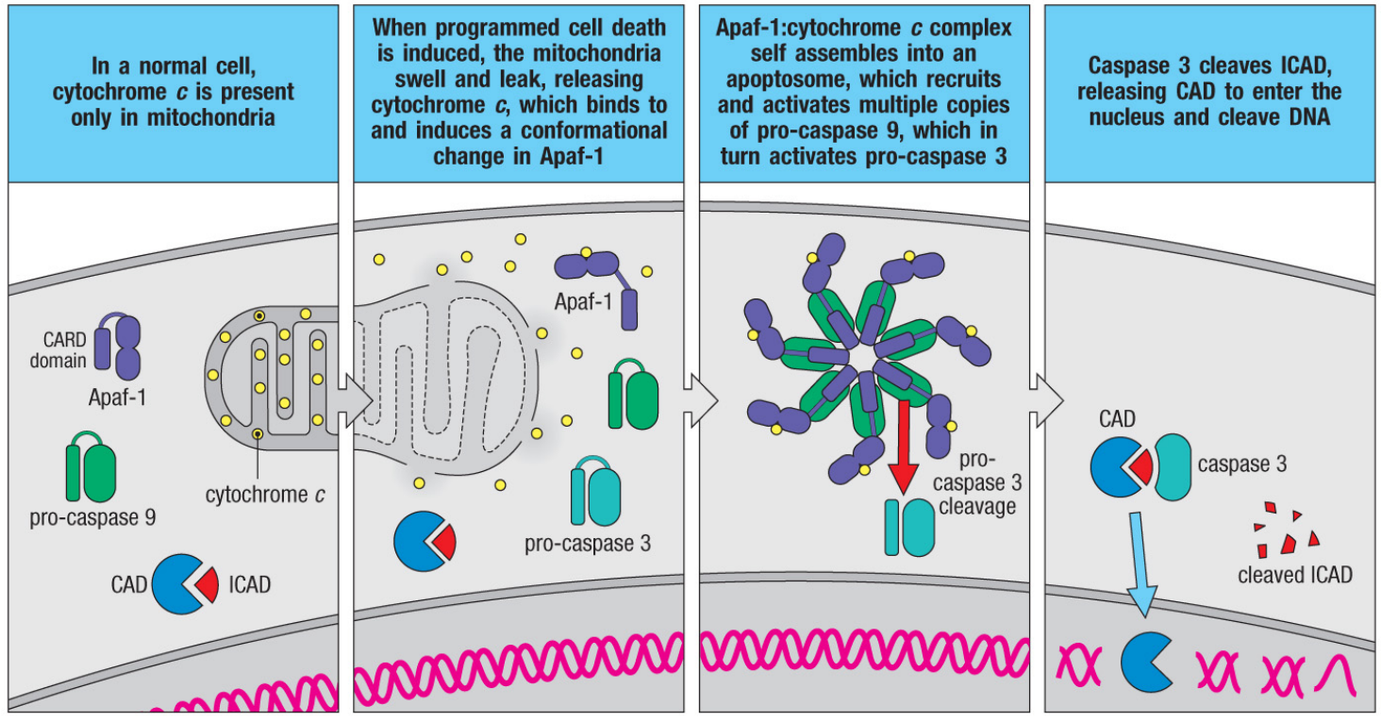
The intrinsic pathway





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Apoptosis-triggering cytotoxic effector proteins

AG recognition ➔ *Ca^{2+}*-dependent release of **cytotoxic granules** containing *effector molecules*:

~ modified lysosomes

1. Perforin: makes pores in target cell + induces apoptosis
2. Granzymes (5 in humans): activate apoptosis in target cell
3. Granulysin (only in human): antimicrobial activity

Protein in granules of cytotoxic T cells	Actions on target cells
Perforin	Aids in delivering contents of granules into the cytoplasm of target cell
Granzymes	Serine proteases, which activate apoptosis once in the cytoplasm of the target cell
Granulysin	Has antimicrobial actions and can induce apoptosis

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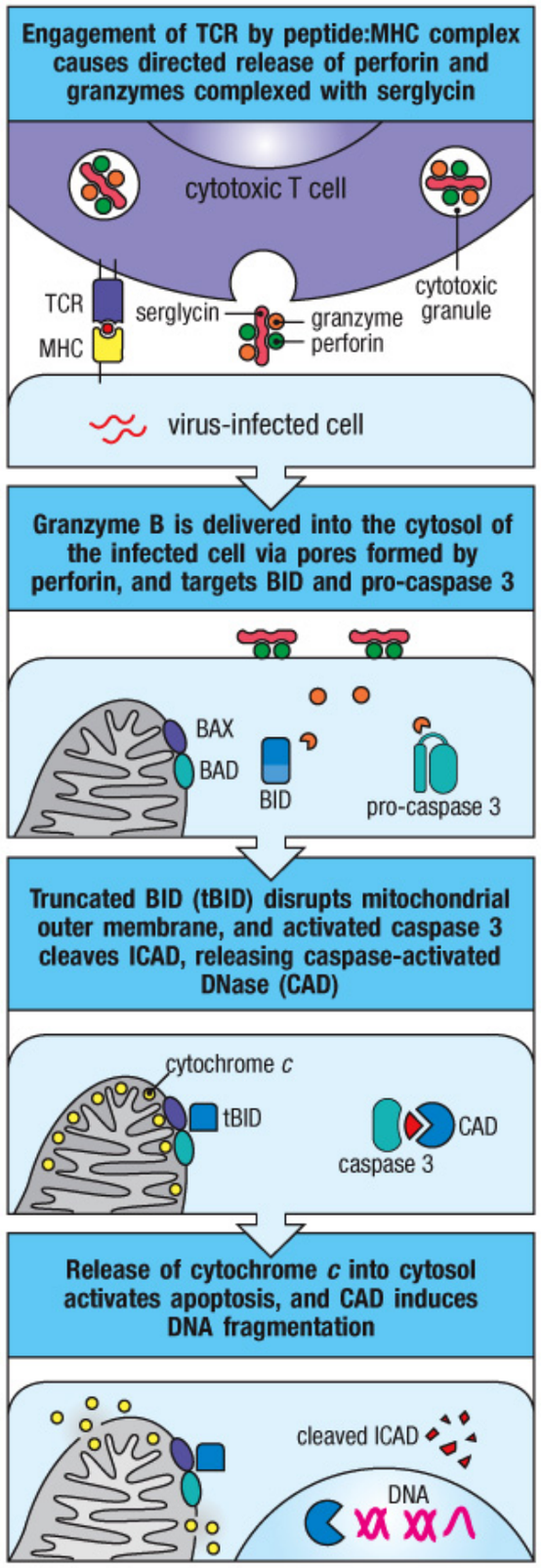
Apoptosis-triggering cytotoxic effector proteins



Granzymes induce apoptosis by

➔ *Mitochondrial* damage (Granzyme A)

➔ Cleavage of *Casp3* (Granzyme B) ------▸ activation of CAD

------▸ degradation of DNA

➔ Cleavage of *BID* → cytochrome c → Casp9 (Granzyme B)

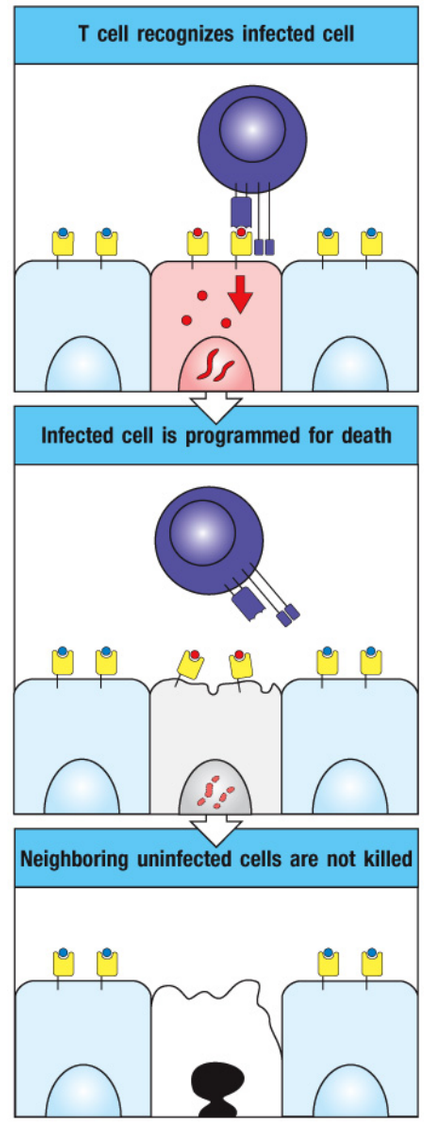
Degradation of apoptotic cell

Phosphatidylserine expressed on apoptotic cell: ingestion by **MΦ**

Killing of AG-specific cell by cytotoxic T cells

Cytotoxic T cells: *highly selective* in killing ➔ bystander cells and $CD8^+$ are protected!

- One cell at a time killing (reorientation of secretion apparatus)
- Preformed granules, but synthesis of contents only induced upon AG activation!



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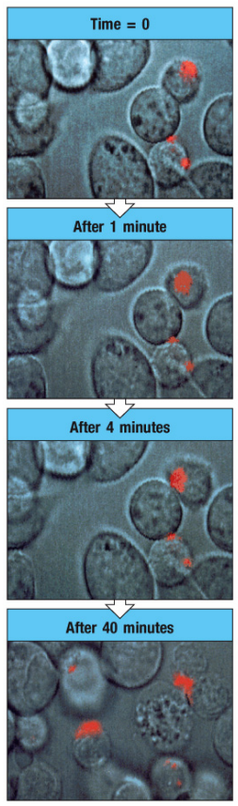

In red, granules of cytotoxic T cells

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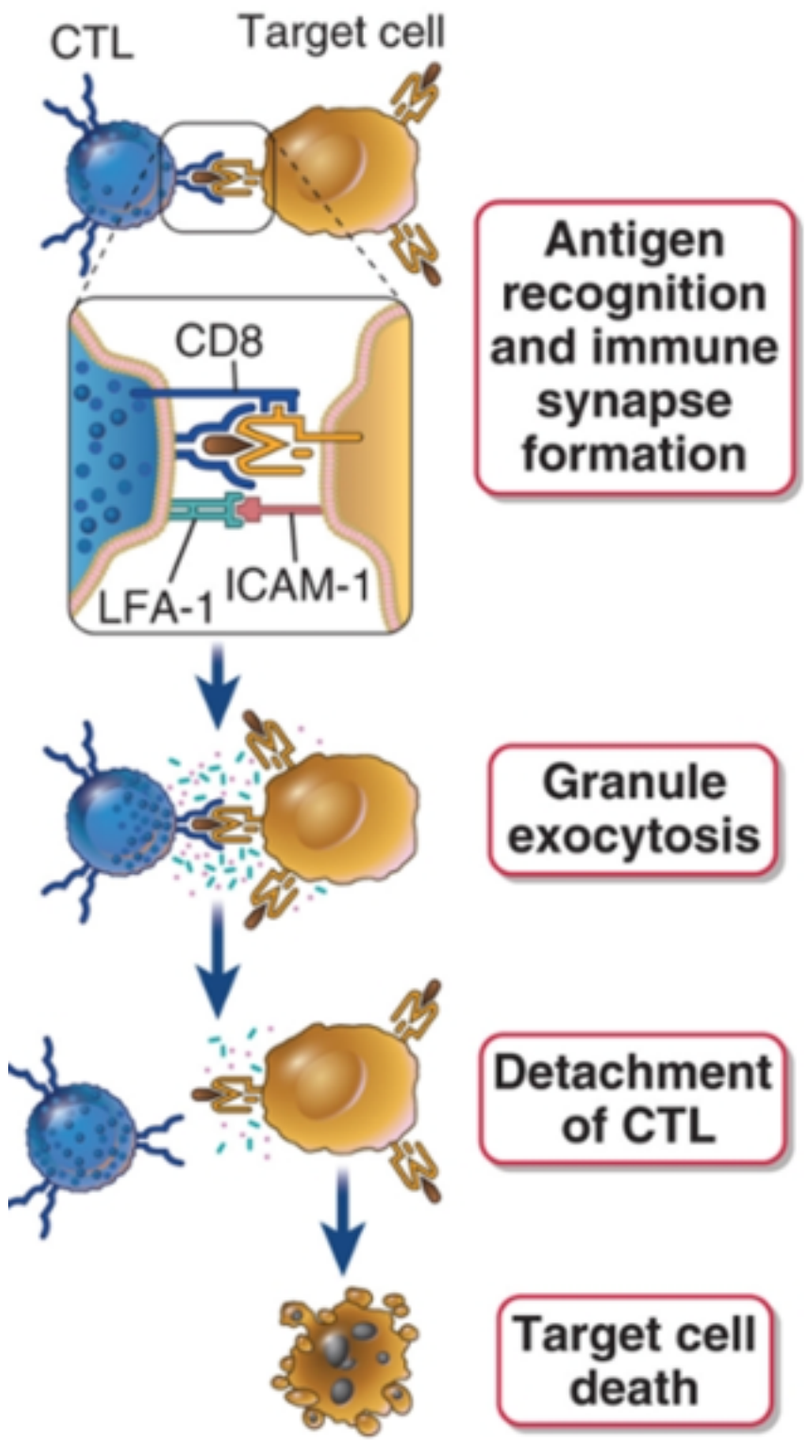
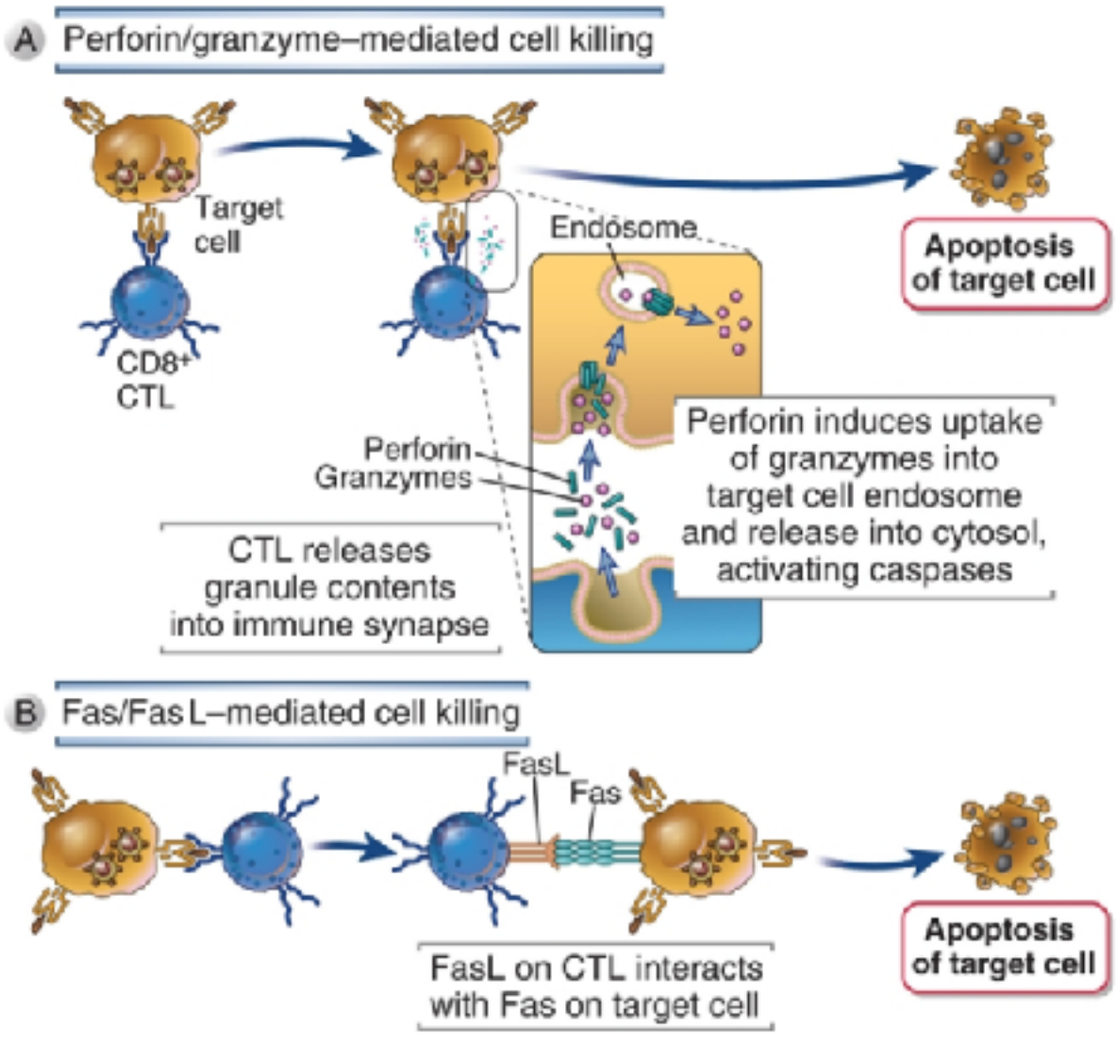
Effector functions of $CD8^+$ cytotoxic T cells



- CTLs *kill targets* expressing class I MHC displaying a peptide + coreceptor + stabilising adhesions
- Killing is mediated by delivery of cytotoxic proteins stored in cytoplasm granules to trigger apoptosis in the target cell
- **Lethal hit:** killing is highly *antigen specific* (no harm to adjacent uninfected cells) as the immune synapse between the CTL and the target cell directs the secreted molecules
- Cytokines and costimulation required for differentiation are *not necessary* for triggering the effector function of CTLs
- *Additional receptors* contribute to regulation and activation of CTLs (e.g. KIRs, NKG2D receptor)

Mechanisms of CTL-mediated killing of target cells



1. Exocytosis of granules into the space within synaptic ring:

Within *few min* after antigen recognition, cytoplasmic vesicles are transported along microtubules and are *concentrated in the region of the synapse* to fuse with the plasma membrane

- Granzyme: serine protease that cleaves and *activates caspases* to induce apoptosis
- Perforin: membrane perturbing molecule that facilitates the *delivery* of granzyme into the cytosol of target cell

2. FasL binds to death receptor Fas and this interaction activated caspases and apoptosis of Fas-expressing targets

Role of $CD8^+$ CTLs in host defence

- Massive *expansion* of $CD8^+$ T cells following infections provide a large pool of CTLs

- *Eradication of the reservoir* of infection (requires elimination of the infected cell)
  - Viruses living in cells that lack the phagosome/lysosome machinery
  - Some microbes escape from vesicles and live in the cytosol

- Secretion of IFN-γ to *activate macrophages*

- May contribute to the *immunopathology* associated with many common viral infections (e.f. influenza, hepatitis B and C viruses).

- Important mediators of *tumour immunity* but also *tissue destruction* in some autoimmune diseases and to the rejection of tissue grafts

The role of adjuvant

Adjuvant: essential role in inducing *primary T cell response to protein* antigens (e.g. vaccines), many are products of microbes, mimic microbial molecules to elicit *innate immune response* stimulating co-stimulators expression on APC and thereby T cell activation.

Inactivated APCs in normal tissues can present self antigens to self-reactive T cells, but these APCs express *low levels of co-stimulators* and therefore do not activate T cells, instead these may be rendered *unresponsive*.

Previously activated effector and memory T cells depend less on costimulation than naive cells: they can respond to antigens presented by various APCs in non lymphoid tissues that may express low level of co-stimulators (e.g. CTL can kill other cells that do not express costimulators)