Immunological Tolerance, Autoimmunity

Overview

Immunological tolerance:

Unresponsiveness of the immune system to an antigen that is induced by previous exposure to that antigen.

Antigens that induce tolerance are called **tolerogens**, or **tolerogenic antigens.** *(immunogens on contrary are antigens that induce immunity).*

Tolerance to self antigens, **self-tolerance**, is a fundamental property of the normal immune system.

If mechanisms of immunological tolerance fail, the immune system may attack self antigens (= **autoimmunity**). The disease this might cause are called **autoimmune diseases**.

How does the immune system maintain unresponsiveness to self antigens?

What are the factors that may contribute to the development of autoimmunity?

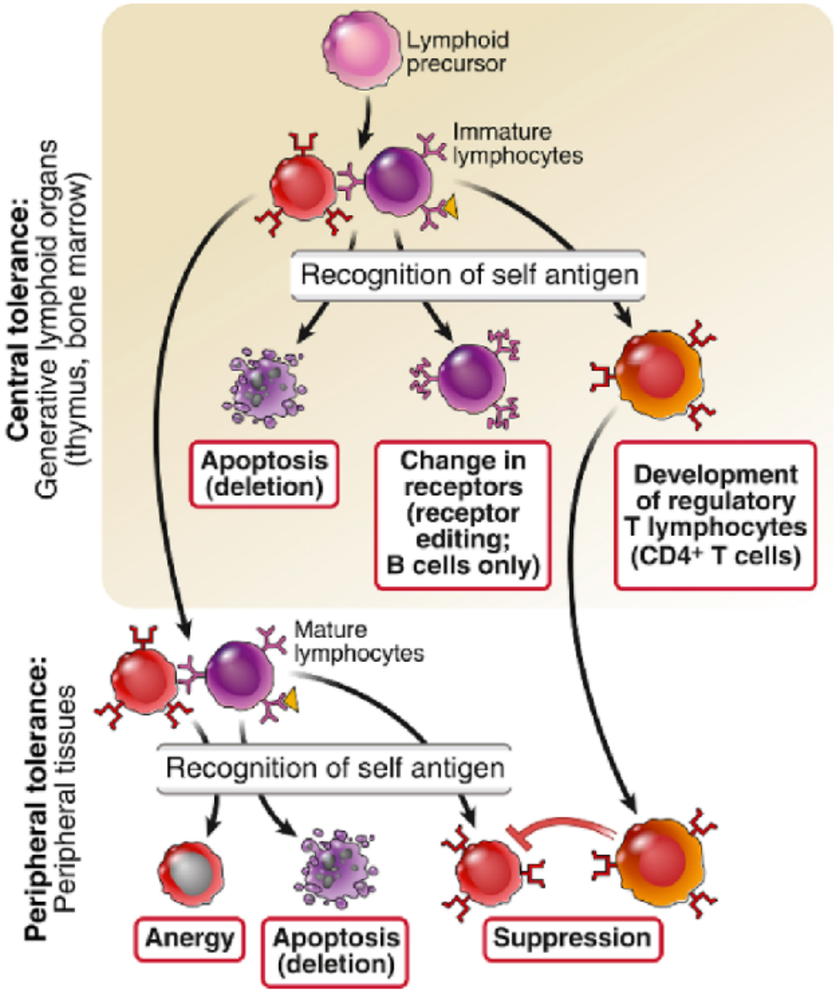
What differentiates autoimmunity from autoinflammation?

Overview - Immunological tolerance

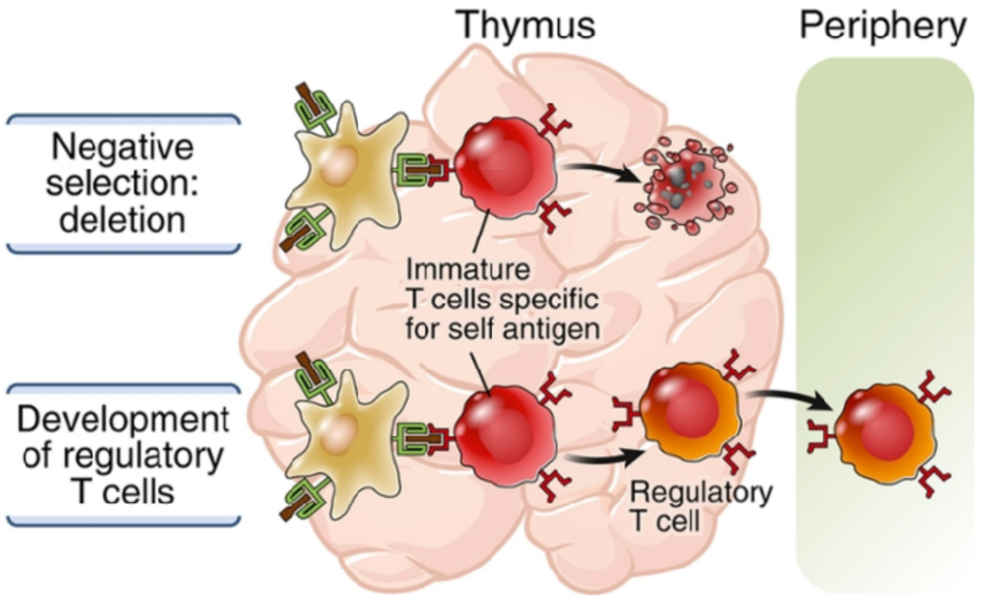
- The mechanisms of tolerance eliminate and inactivate lymphocytes that express high-affinity receptors for self-antigens.
- Tolerance is antigen specific and thus contrasts “immunosuppression”, which affects lymphocytes of many specificities. Whether an antigen is a tolerogen or immunogen depends on multiple factors, e.g. timing of antigen exposure or presence of co-stimulatory factors.

Overview - Immunological tolerance

Immunological tolerance to antigens may be induced during lymphocyte development in the generative lymphoid tissues (**central tolerance**) or upon self antigen encounter in peripheral lymphoid organs or peripheral tissues (**peripheral tolerance**).



Central T Lymphocyte Tolerance

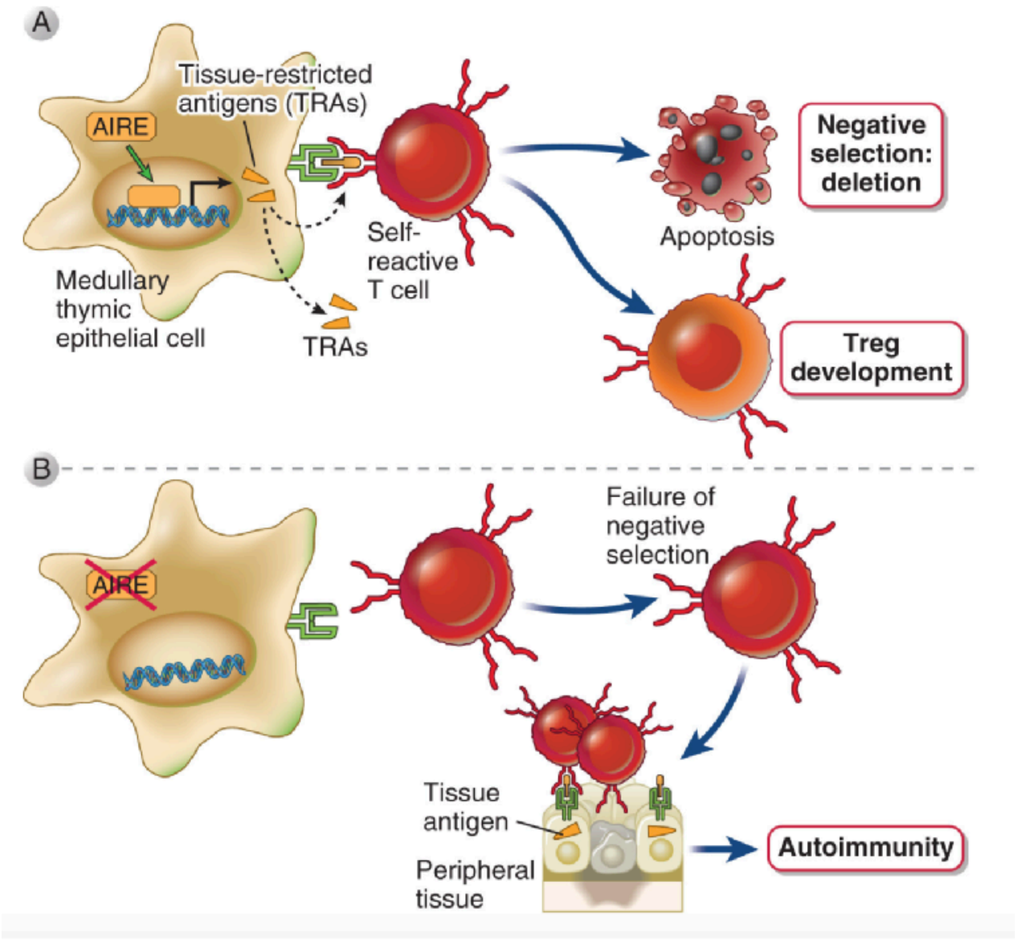


During their maturation in the thymus, many immature T cells that recognise antigens with high avidity **die**, and some of the surviving cells in the CD4+ lineage develop into **Tregs**. What determines the fate of self-reactive T cells is not known, but may involve the strength of AG binding, the APC presenting self-AGs or the presence of cytokines.

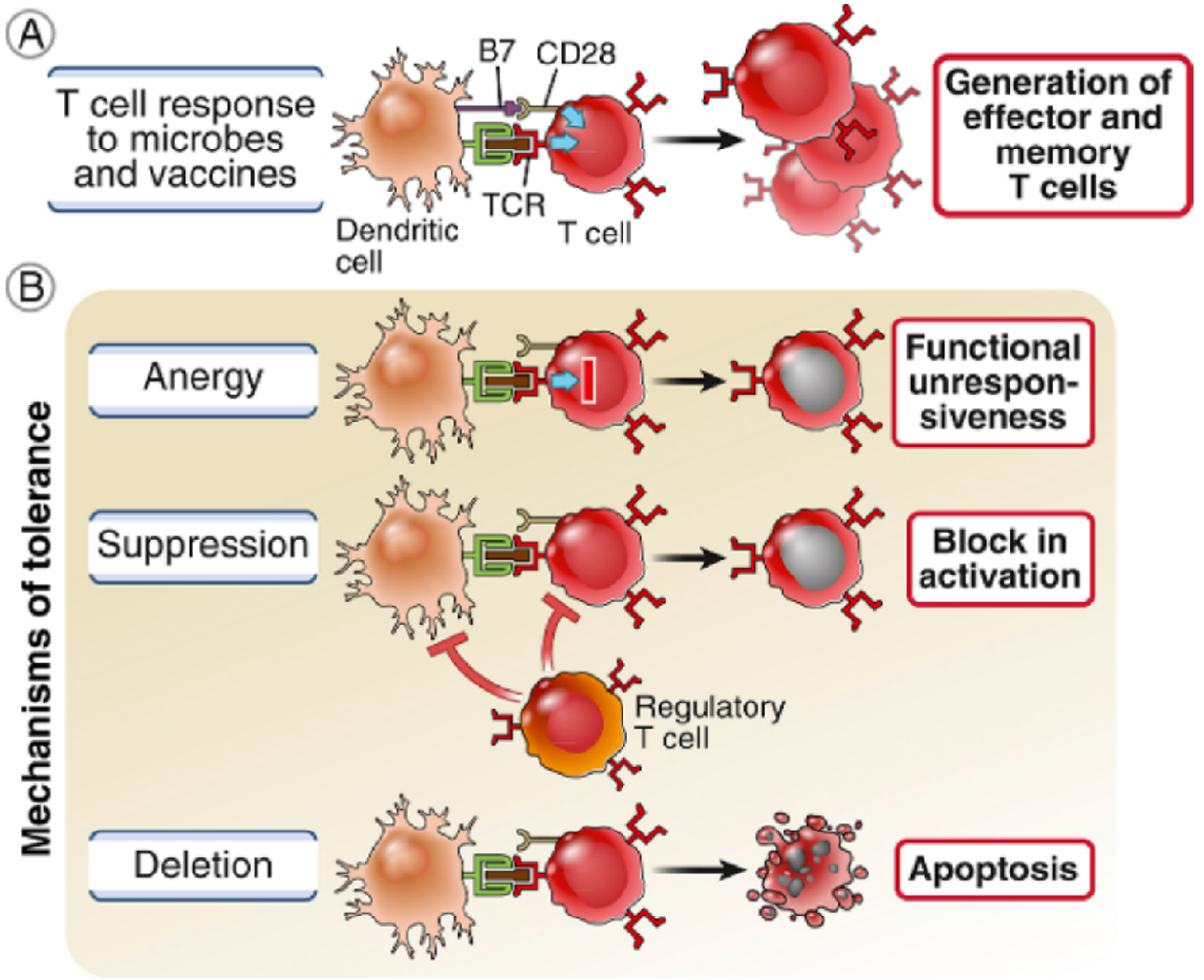
Control of TRA expression in the thymus

AGs present in the thymus may be either **ubiquitous AGs** or AGs may be delivered to the thymus by **blood**. In addition, medullary thyme epithelial cells express **AIRE** (*autoimmune regulator*) protein, which functions as a transcriptional regulator that promotes the expression of tissue-restricted antigens (TRAs), for example insulin.

Defects in the *AIRE* gene are associated with a severe autoimmune syndrome - **autoimmune polyendocrine syndrome type 1** (APS1).



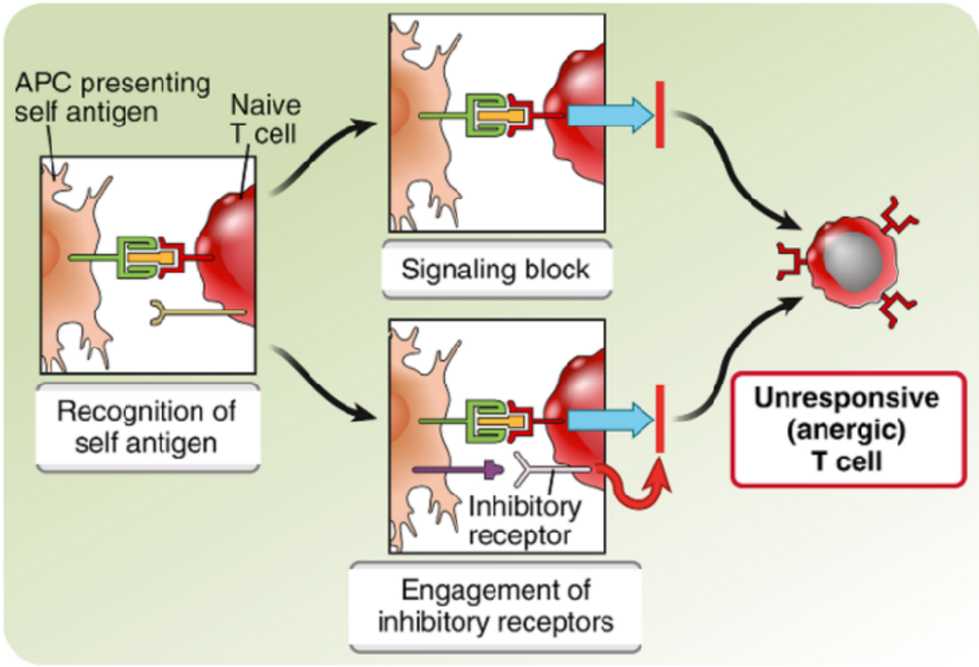
Peripheral T Lymphocyte Tolerance



Anergy

~ refers to long-lived *functional unresponsiveness* induced upon self antigen recognition

Signaling block: Ag recognition w/o costimulation, may lead to alterations in TCR signaling including reduction of TCR expression or recruitment of inhibitory molecules. Self-AG may also induce ubiquitin ligases that target TCR adaptor molecules for degradation (e.g., Cbl-l).

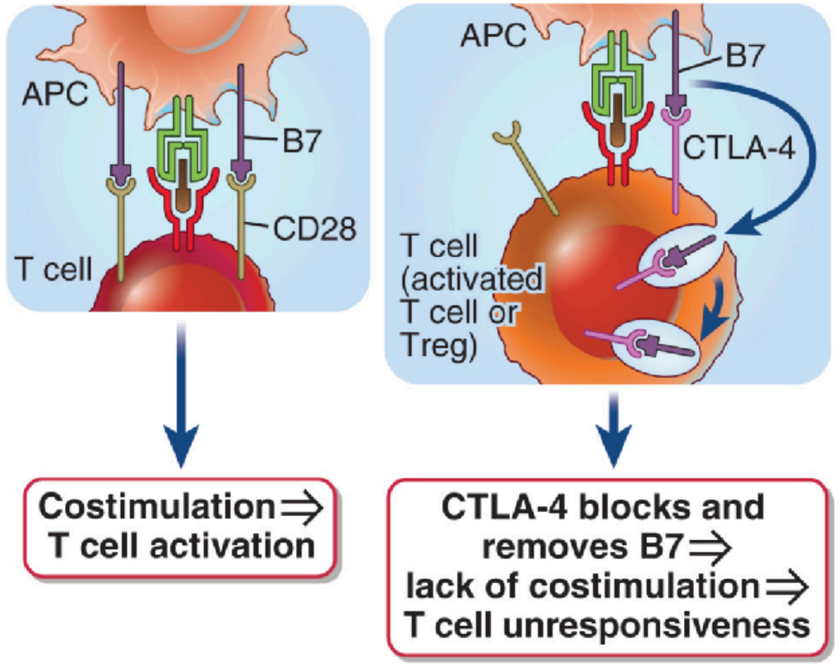


Inhibitory coreceptors: Ag recognition may engage CTLA-4, PD-1.

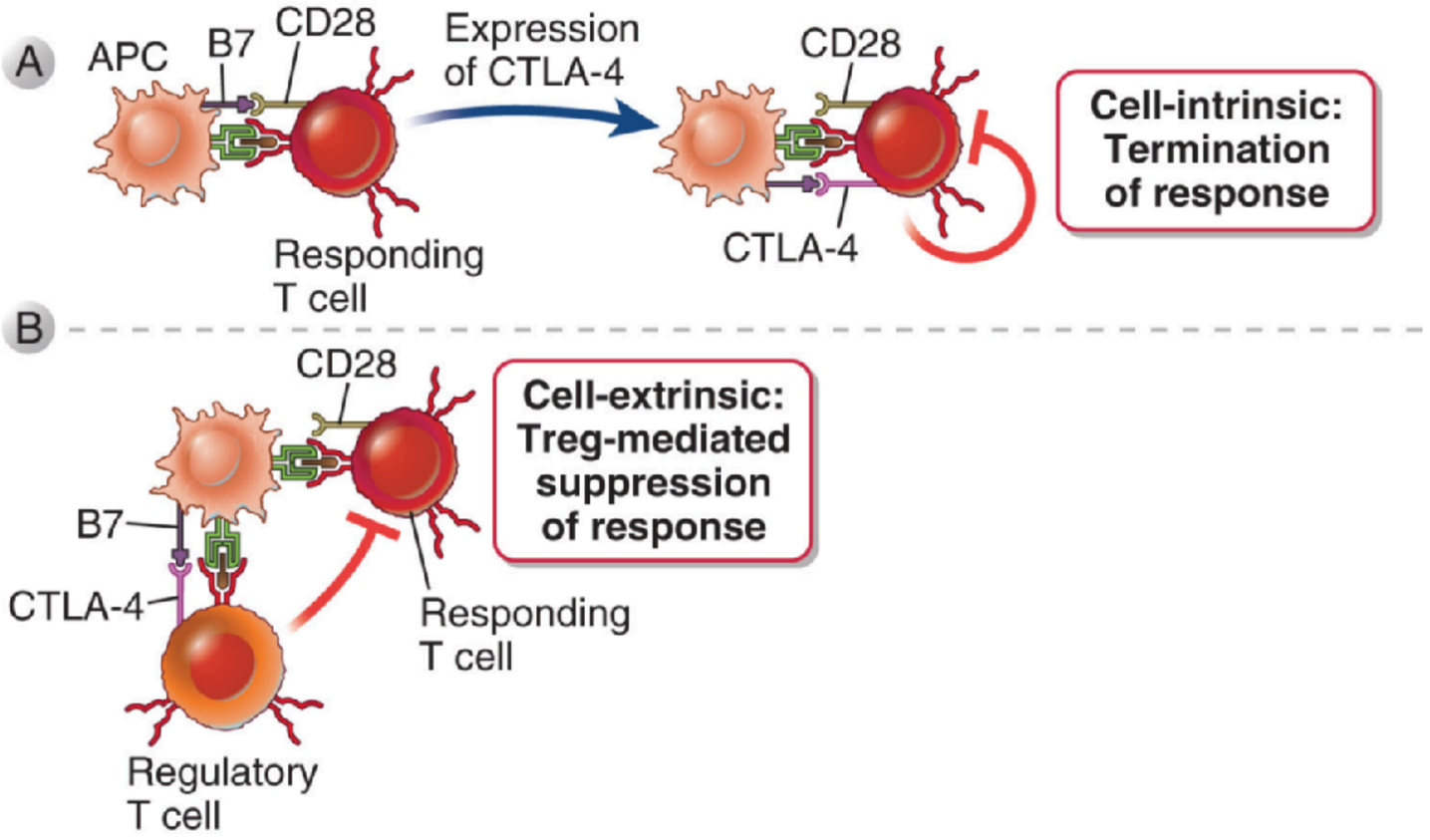
Regulation of T cells by inhibitory coreceptors

CTLA-4 = cytotoxic T lymphocyte antigen-4

- Member of CD28 receptor family and binds to B7 molecules with 10-20x higher affinity than CD28 >> out-competes CD28-B7 interactions
- CTLA-4 lacks a signaling domain, but instead is an endocytic receptors that removes B7 molecules on APCs
- Mice deficient for *Ctla4* gene develop severe autoimmune and inflammatory symptoms



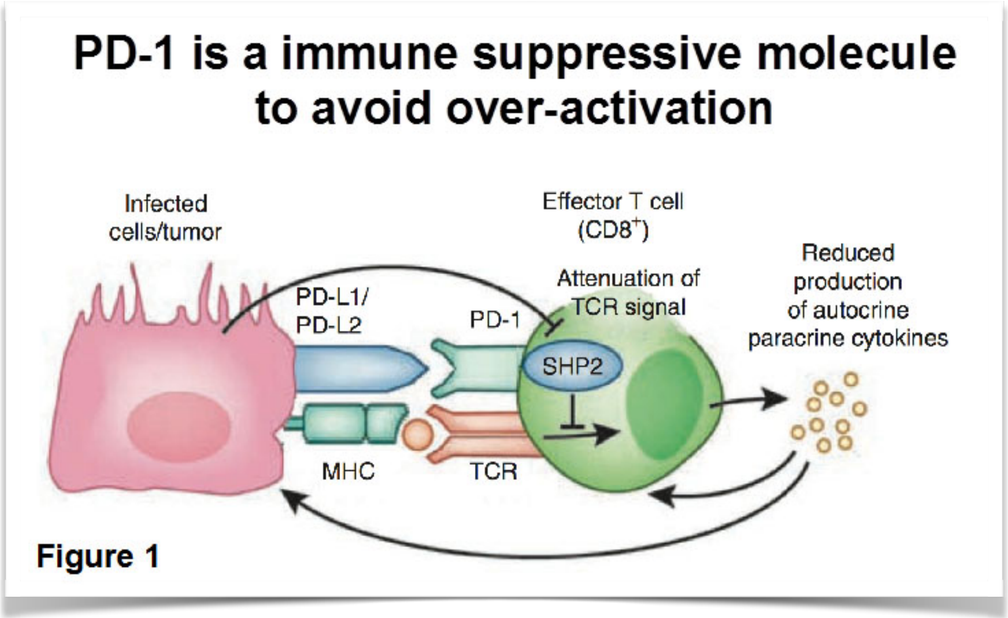
Regulation of T cells by inhibitory coreceptors



Regulation of T cells by inhibitory coreceptors

PD-1 = Programmed death-1

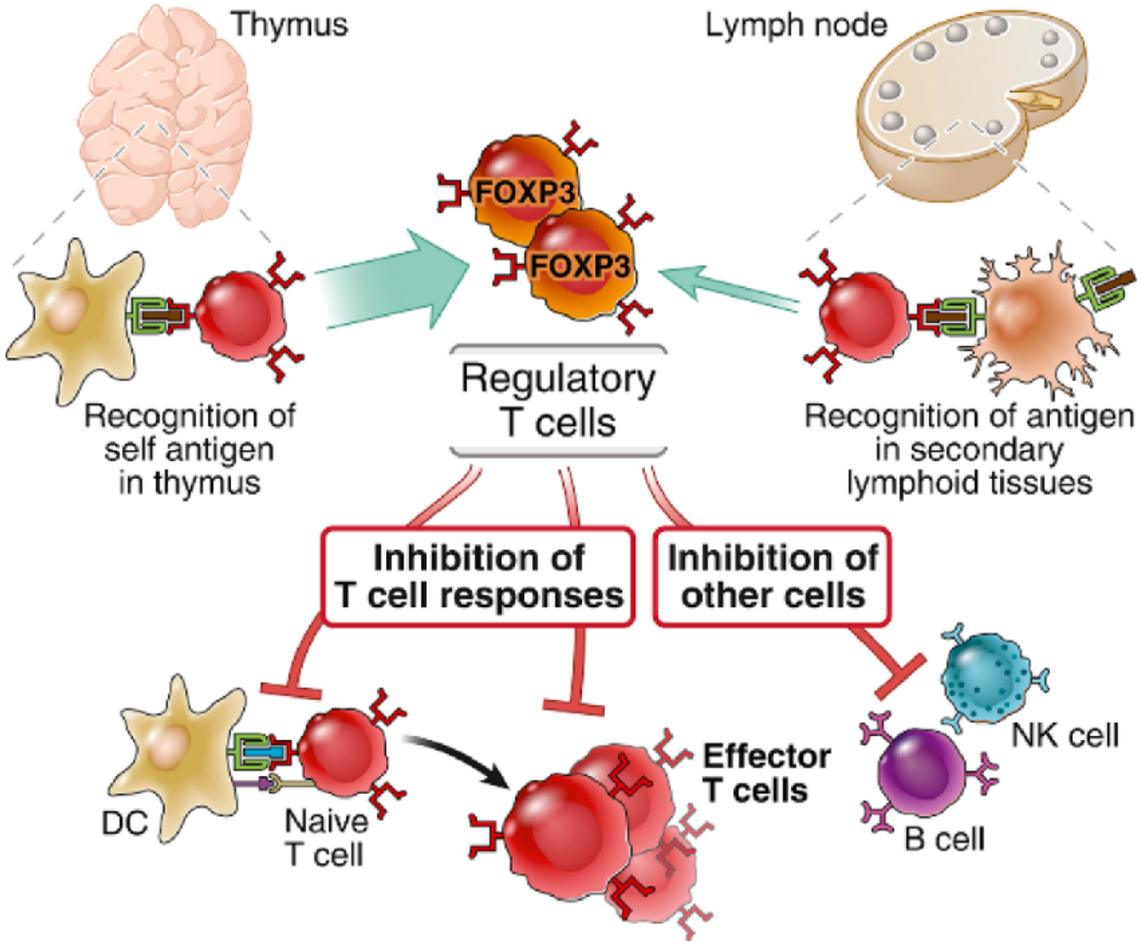
- Member of CD28 receptor family, expressed on activated T cells
- Ligands of PD-1 are expressed on APCs (PD-L1/2) and tissue cells (PD-L1)
- PD-1 inhibits TCR signalling leading to the inactivation of T cells



	CTLA-4	PD-1
Major site of action	Secondary lymphoid organs	Peripheral tissues
Stage of immune response that is inhibited	Induction (priming)	Effector phase
Cell type that is inhibited	$CD4^+$ and $CD8^+$	$CD8^+ > CD4^+$
Cellular expression	Tregs, activated T cells	Activated T cells
Main signals inhibited	Competitive inhibitor of CD28 costimulation (by binding to B7 with high affinity and removing B7 from APCs)	Inhibits kinase-dependent signals from CD28 and TCR (by recruiting and activating phosphatase following binding to its ligands PDL-1 or PDL-2)
Role in Treg-mediated suppression of immune responses	Yes	Probably no

APCs, Antigen-presenting cells; *TCR*, T cell receptor; *Tregs*, regulatory T cells.

Immune Suppression by Regulatory T cells



Immune Suppression by Regulatory T cells

Regulatory T cells (T_{reg} cells) develop in the thymus or in peripheral tissues upon self AG recognition and suppress the activation of lymphocytes specific for self AGs.

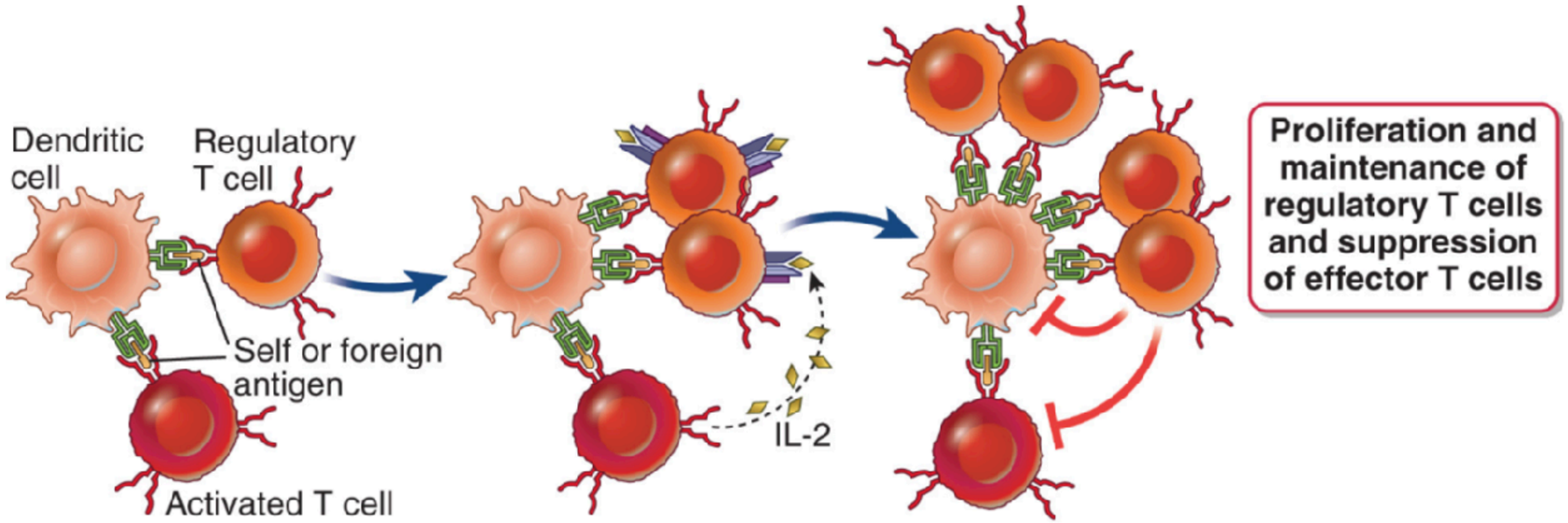
Phenotypic characteristics of T_{reg} cells:

$CD4^+$ and high expression of CD25 (alpha chain of IL-2 receptor) and the transcription factor FoxP3. They also express high levels of CTLA-4.

Generation and maintenance of T_{reg} cells:

- Treg cells arise in the thymus (natural Tregs) or in the periphery (induced Tregs). The induction of Tregs in both cases depends on the recognition of self-AGs. Induced Tregs may also be generated upon sensing foreign AGs or after an inflammatory reaction.
- The generation of Tregs requires TGF-beta and IL-2. Both cytokines promotes the expression of FoxP3.

IL-2 is required for the maintenance of Tregs



Immune Suppression by Regulatory T cells

Mechanism of action of Tregs:

- Production of immunosuppressive cytokines (see below)
- Reduced ability of APCs to stimulate T cells via CTLA-4
- Consumption of IL-2: this deprives other T cells from this growth factor and impedes their proliferation

Inhibitory cytokines produced by Tregs:

- IL-10
  - inhibits the activation of macrophages and dendritic cells (negative feedback mechanism)
  - inhibits the production of IFN-ɣ by T cells

The immunosuppressive function of TGF-β

Inhibitory cytokines produced by Tregs:

- TGF-β
  - inhibits the proliferation of T cells and the activation of macrophages
  - regulates the differentiation of induced Treg cells and Th17 cells
  - promotes tissue repair

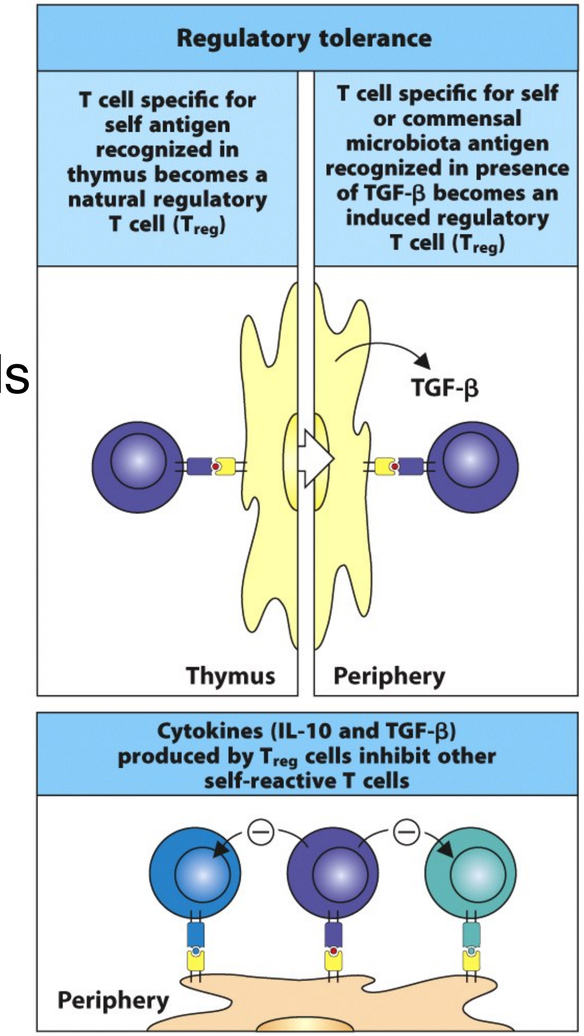


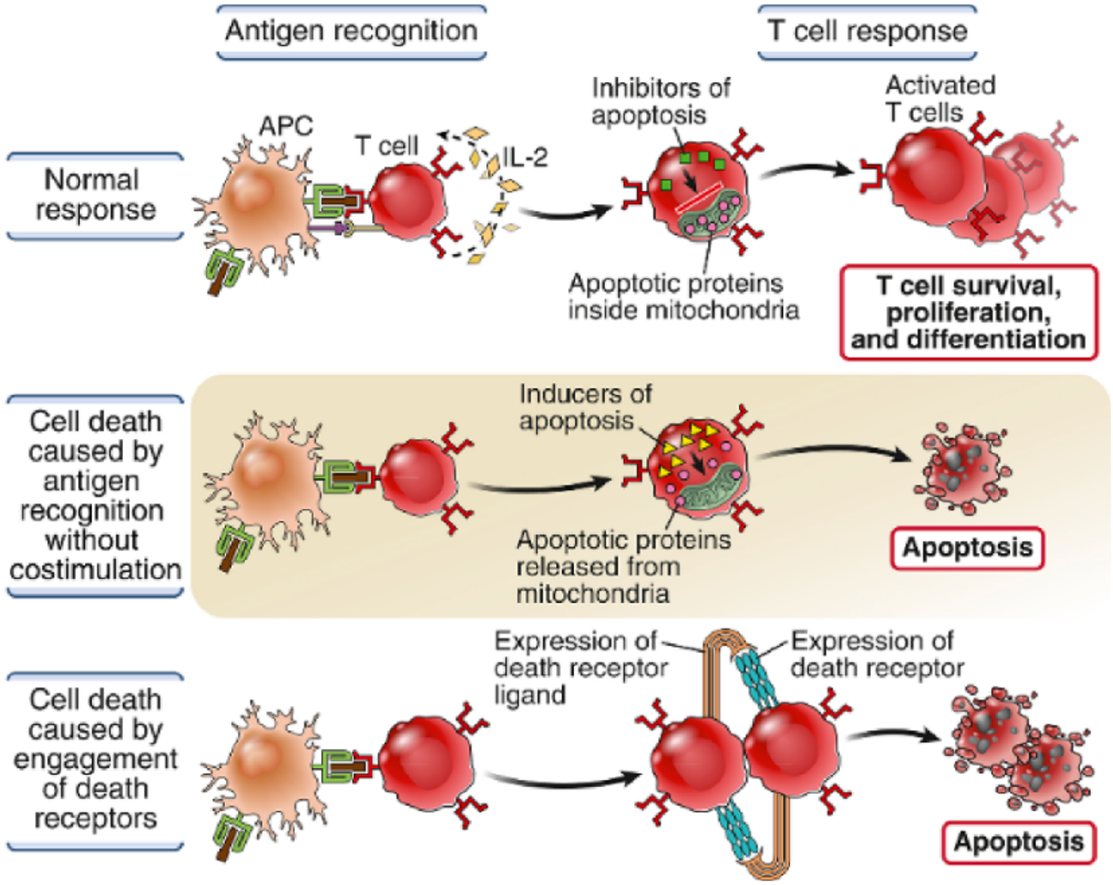
Figure 15.9 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

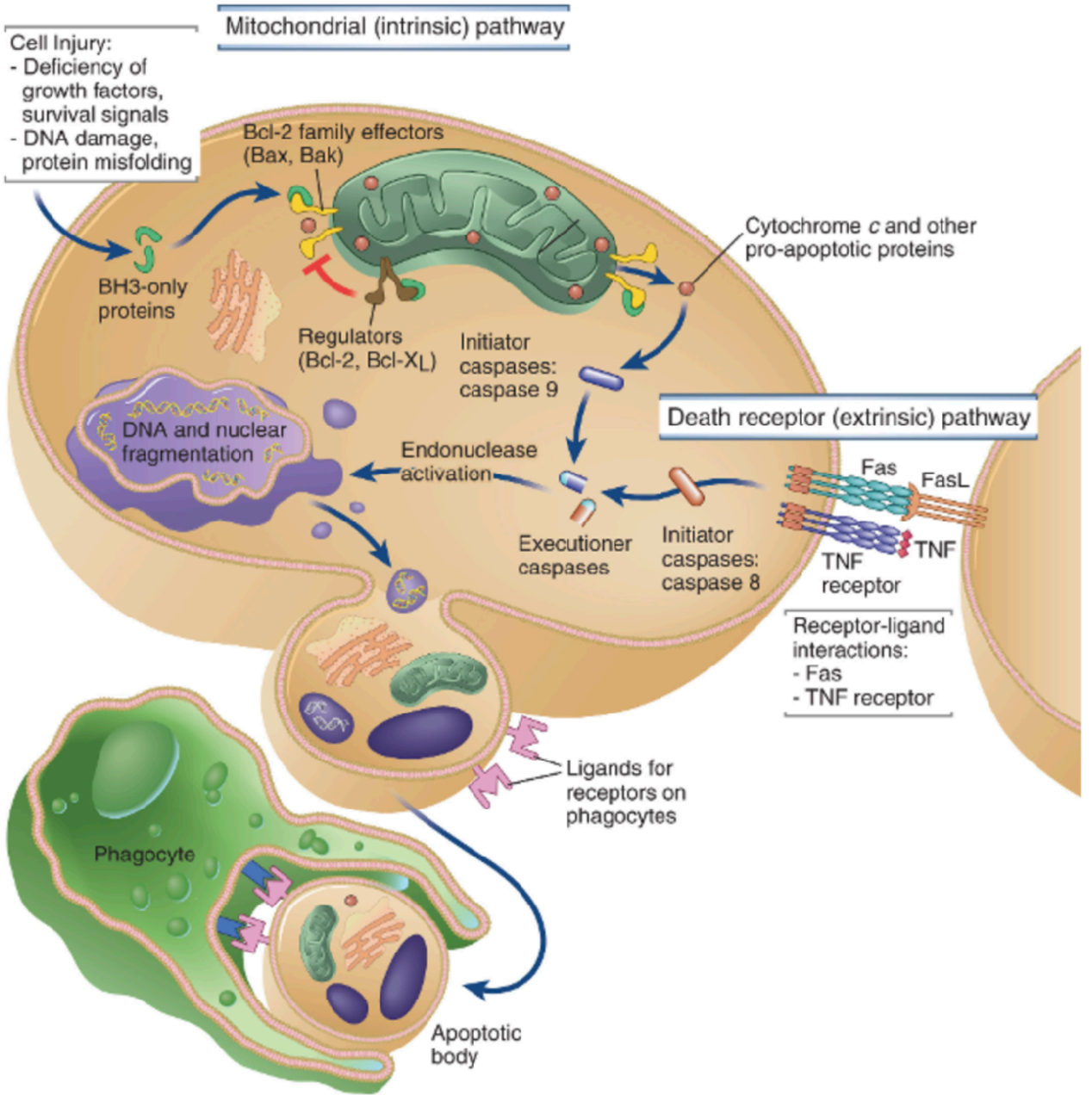
Deletion: Apoptosis of Mature lymphocytes

Self AG recognition may trigger **apoptosis**, that eliminate self-reactive T cells.

<u>Mechanisms of apoptosis:</u>

- Cell intrinsic expression of pro-apoptotic genes (BH3-only proteins)
- Induced expression of death receptors (Fas (CD95) and Fas ligand (FasL) interactions)




Mitochondrial (intrinsic) pathway
Cell Injury:
- Deficiency of growth factors, survival signals
- DNA damage, protein misfolding
Bcl-2 family effectors (Bax, Bak)
BH3-only proteins
Regulators (Bcl-2, Bcl-XL)
Cytochrome c and other pro-apoptotic proteins
Initiator caspases: caspase 9
DNA and nuclear fragmentation
Endonuclease activation
Executioner caspases
Death receptor (extrinsic) pathway
Fas
FasL
TNF
TNF receptor
Initiator caspases: caspase 8
Receptor-ligand interactions:
- Fas
- TNF receptor
Ligands for receptors on phagocytes
Phagocyte
Apoptotic body

Connecting apoptosis and autoimmunity

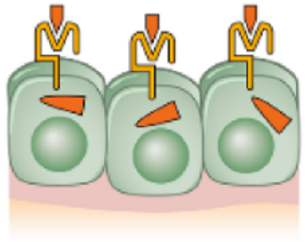
AG in the absence of co-stimulation:

- Normally T cells integrate TCR signaling with growth factor signaling, and co-stimulation, which triggers expression of Bcl-2 anti-apoptotic proteins
- When T cells recognise AG in the absence of co-stimulation, they activate Bim without the anti-apoptotic proteins

Repeated stimulation of T cells:

- FasL is expressed on the cell surface and interacts with Fas expressed on adjacent cells

Immunogenic AGs versus tolerogenic AGs

Feature of antigen	Tolerogenic self antigens	Immunogenic foreign antigens
	 Tissue	 Microbe
Location of antigens	Presence in generative organs (some self antigens) induces negative selection and other mechanisms of central tolerance	Presence in blood and peripheral tissues (most microbial antigens) permits concentration in peripheral lymphoid organs
Costimulation	Deficiency of costimulators may lead to T cell anergy or apoptosis, development of Treg, or sensitivity to suppression by Treg	Expression of costimulators, typically seen with microbes, promotes lymphocyte survival and activation
Duration of antigen exposure	Long-lived persistence (throughout life); prolonged TCR engagement may induce anergy and apoptosis	Short exposure to microbial antigen reflects effective immune response

Central B Lymphocyte Tolerance

Strong interaction of B cells with self AGs in the bone marrow can result in the following outcomes:

1) *Receptor editing:*

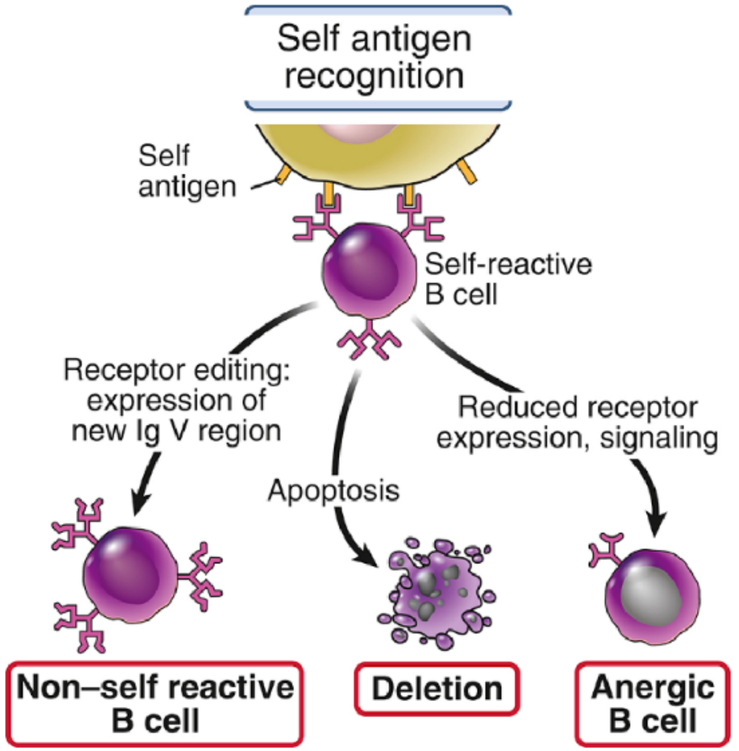
B cells might express an new Ig light chain

2) *Deletion:*

B cells are eliminated by apoptosis

3) *Anergy:*

B cells that recognize self AG with low avidity become anergic

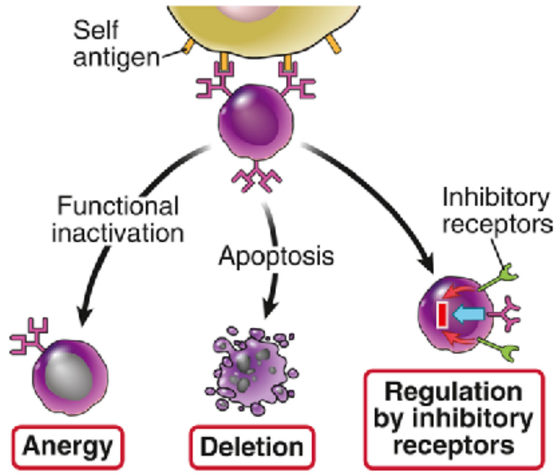


Peripheral B Lymphocyte Tolerance

Recognition of self AGs by B cells in the absence of T cell help, complement or innate immune activation are rendered tolerant.

Peripheral tolerance involves:

1) **Anergy and deletion:** Repetitive stimulation by self antigens may promote anergy, which hinders B cells to proliferate. Strong interaction with self antigens may also trigger B cell death.
2) **Signaling by inhibitory receptors** (e.g., CD22)



Autoimmunity

~ defined as an immune response against self (autologous) antigens involving autoantibodies or autoreactive T cells.

It is estimated that ~ 5% of the population is affected by autoimmune diseases.

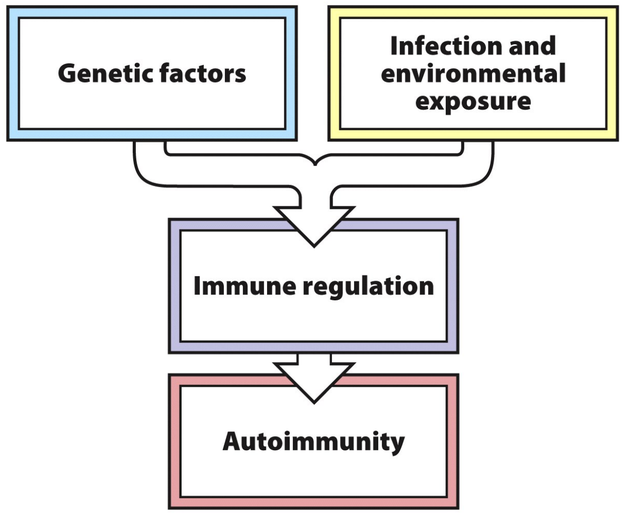


Figure 15.3 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

CAVE: Differentiation between autoimmunity and autoinflammation!

Chronicity of autoimmune disease

„Normal“ immune response:

Pathogen → **Immune response** → Tissue damage → Elimination of the „trigger“ → Tissue recovery

„Autoimmune“ response:

Self antigen → **Immune response** → Tissue damage → Release of further „triggers“ → Chronic state*

*Exception: in „organ-specific“ autoimmune disease, when tissue is completely destroyed (type I diabetes)

Autoimmunity - Classification

From a clinical perspective one can distinguish „organ-specific“ from „systemic“ autoimmune diseases

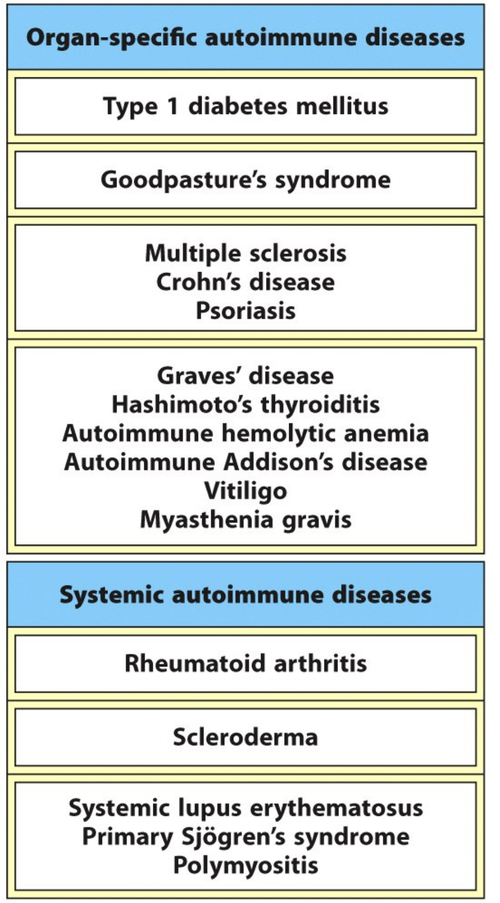
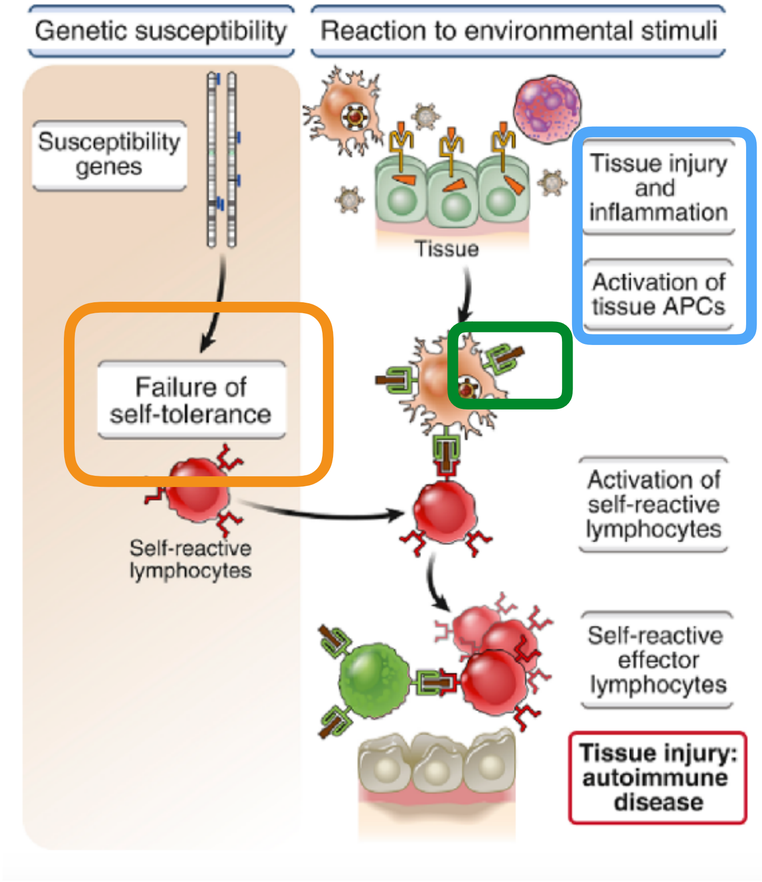


Figure 15.11 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Autoimmunity - Pathogenesis

- Defects in deletion of T or B cells or receptor editing
- Defective numbers or function of regulatory T cells
- Defective apoptosis
- Inadequate function of inhibitory receptors



- (Abnormal) inflammation, tissue injury

- Abnormal display of self Antigens (e.g. neoantigens)

Autoimmunity - Genetic factors

- Twin studies, autoimmunity runs within families, females versus males - for example T1D shows a concordance of 35-50% in monozygotic twins and only 5-6% in dizygotic twins
- Genome-wide association studies (GWAS) identified different polymorphisms (=common variations such as deletions, SNPs)
- Rarely, autoimmunity is caused by mutations in a single gene (Mendelian disorders).

Most autoimmune diseases are complex **polygenic traits**, in which multiple genic loci act together with environmental factors.

Autoimmunity - Association with MHC alleles

Many autoimmune diseases in humans and inbred animals are linked to particular MHC alleles.

Disease	MHC allele	Relative risk
Ankylosing spondylitis	HLA-B27	90
Rheumatoid arthritis	HLA-DRB1*01/*04/*10	4-12
Type 1 diabetes mellitus	HLA-DRB1*0301/0401	35
Pemphigus vulgaris	HLA-DR4	14

Autoimmunity - Association with MHC alleles

- Even though an HLA-disease association may be identified, the actual association may be with other alleles that are linked to the typed allele and inherited together (linkage disequilibrium).
- The disease-associated nucleotide polymorphism often encode amino acids in the peptide-binding clefts of the MHC molecules.
- Disease-associated HLA sequences are found in healthy individuals and most will never develop the disease.

Hypotheses for explaining the MHC allele associations:

- Differences of antigen-presenting capability of MHC molecules
- Differences in shaping TCR repertoire (e.g., poor binding of certain autoantigens in the thymus)
- Induction of negative selection of pathogenic T cells for alleles that are protective
- Promoting of Treg development for protective MHC alleles

Polymorphisms in non-MHC alleles

Gene	Function of Protein	Disease
Signaling and Transcription Factors		
PTPN22	TCR and BCR signaling and other?	RA, SLE, AITD, T1D
BLK	B cell activation	SLE
IRF5	Type I IFN production	SLE
TRAF1	Regulates TNFR signaling, NF-κB pathway	RA
STAT4	IFN-γ response	RA, SLE
Innate Immunity		
NOD2	Cytosolic receptor for bacterial peptidoglycans	CD
Complement C1q, C2, C4	Clearance of immune complexes and apoptotic bodies; role in B cell tolerance?	SLE
Cytokines, Cytokine Receptors, Cytokine Signaling		
IL-2/IL-21	T cell activation, Treg maintenance (IL-2)	T1D, RA, Celiac disease
IL-23R	Th17 differentiation	PSA, PSO, CD, AS
IL-2Rα (CD25)	T cell activation, Treg maintenance	MS, T1D, GD
IL-7Rα	Survival of naïve and memory T cells	MS
IL-12B (p40)	Th1 differentiation	PSO, CD
IL-10	Inhibition of Th1 responses	IBD, SLE, T1D
Lymphocyte Regulation		
CTLA-4	T cell inhibition, Treg function	T1D, RA
FcγRIIB	Feedback inhibition of B cells	SLE
Autophagy Related		
ATG16L1	Autophagy	CD
Autoantigens		
Insulin	Islet β cell antigen	T1D
TSH receptor	Thyroid antigen	AITD
Antigen Processing or Modifying Enzymes		
ARTS1	Peptide trimming for class I MHC pathway	AS
PAD14	Citrullination of self peptides	RA

Single-gene mutations causing autoimmunity

TABLE 15.5 Examples of Single-Gene Mutations That Cause Autoimmune Diseases

Gene	Phenotype of Mutant or Knockout Mouse	Mechanism of Failure of Tolerance	Human Disease
AIRE	Destruction of endocrine organs by antibodies, lymphocytes	Failure of central tolerance	APS
C4	SLE	Defective clearance of immune complexes; failure of B cell tolerance	SLE
CTLA4	Lymphoproliferation; T cell infiltrates in multiple organs; lethal by 3–4 weeks	Defective function of Tregs; failure of T cell anergy	Systemic inflammatory disease
Fas/FasL	Anti-DNA and other autoantibodies; immune complex nephritis; arthritis; lymphoproliferation	Defective deletion of self-reactive B cells and $CD4^+$ T cells	ALPS
FoxP3	Multiorgan lymphocytic infiltrates, wasting	Deficiency of functional Tregs	IPEX
IL10, IL10R	Inflammatory bowel disease	Defective control of mucosal immune responses	Colitis (IL10R mutations)
IL2, IL2Rα/β	Inflammatory bowel disease; anti-erythrocyte and anti-DNA autoantibodies	Defective development, survival, or function of Tregs	None known
SHP1	Multiple autoantibodies	Failure of negative regulation of B cells	None known

The roles of these mutations in causing autoimmunity have been established by inherited

Environmental factors can trigger autoimmune disease

- Disease distribution differs in between certain geographic regions (e.g., MS higher incidence in northern than in southern European countries)
- Genetically identical mice develop autoimmunity at different rates and severity
- Drugs (Procainamide) or toxins can trigger autoimmunity (SLE, hemolytic anemia)

  Mechanism:

  Drugs react with self antigens —>
  haptenated self antigens lead to inflammation —>
  tissue damage —>
  response to original self antigen
- Exposure to sunlight (Ultraviolet light) can trigger SLE symptoms

The role of infection in autoimmune diseases

Infections may promote the development of autoimmune diseases in several different ways:

1) **An infection may break T cell tolerance**

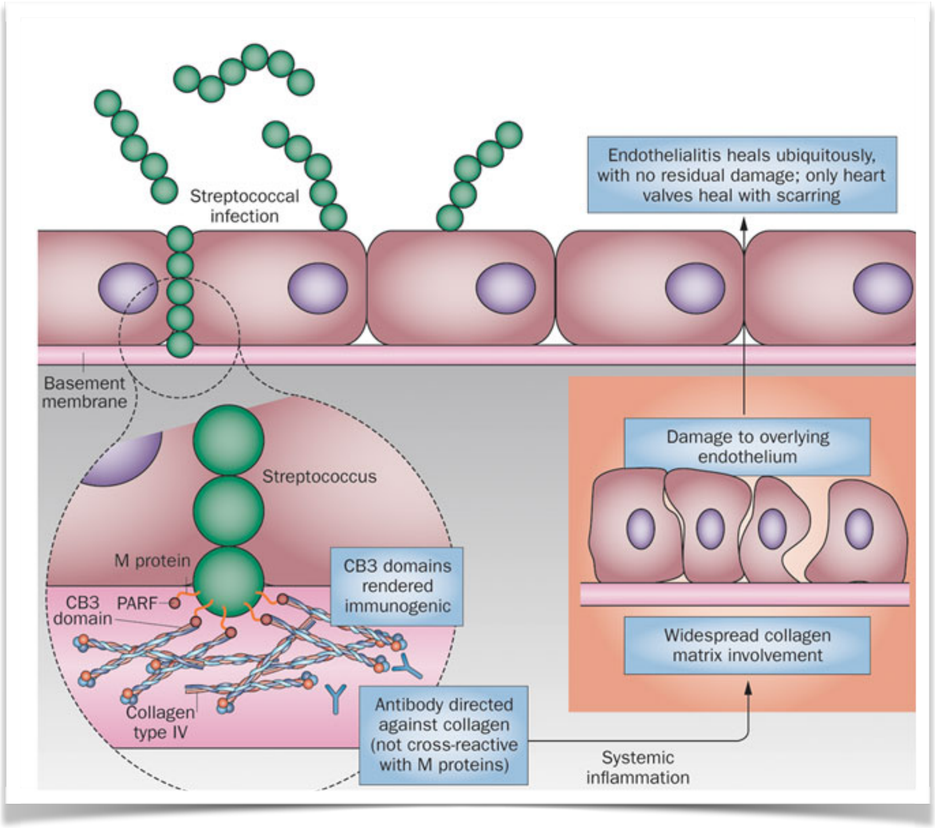
   Infections may induce local innate immune responses >> expression of costimulators and cytokines by APCs >>
   Breakdown of tolerance
   = bystander activation

The role of infection in autoimmune diseases

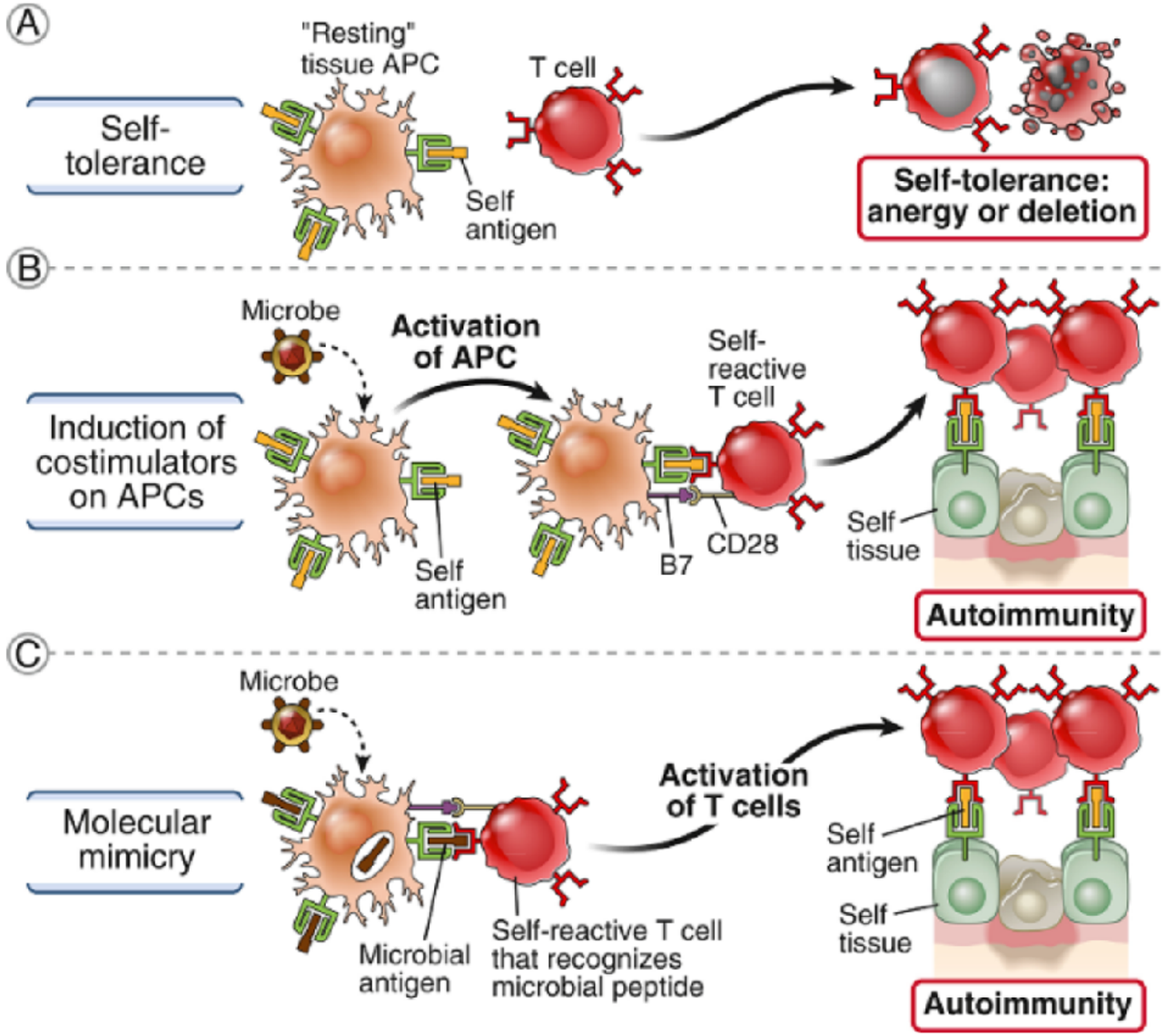
2) Infectious microbes may produce antigens, which are similar to self antigens. This can lead to the cross-reaction of immune response directed against self antigens (**molecular mimicry**).

Rheumatic fever

- Infection with *Streptococcus pyogenes*
- Molecular mimicry with antigens of S.p. leads to destruction of heart valves
- Can also involve joints, skin, brain
- Typically develops 2/3 weeks after infection
- Often transient, but may become chronic



The role of infection in autoimmune diseases



The role of infection in autoimmune diseases

3) The innate immune response may alter the chemical structure of self antigens.

Rheumatoid arthritis

Infection-triggered conversion of arginine residues to citrulline residues

4) Infection-triggered release of self antigens in „privileged tissues“ (eye, testis)

Post-traumatic uveitis/orchitis

Sequester antigens in “immunological” privileged sites may not have induced self-tolerance. Trauma can release such “hidden” antigens and cause the activation of lymphocytes.