Johns Hopkins Engineering

Immunoengineering

Allergy and Autoimmunity

When Tolerance Fails

JOHNS HOPKINS
WHITING SCHOOL
of ENGINEERING

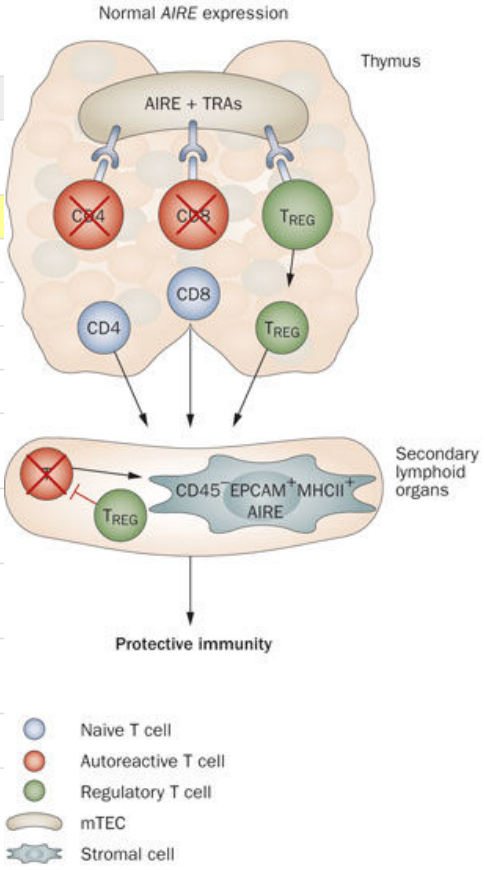
When Tolerance Fails – Autoimmune disorder mechanisms

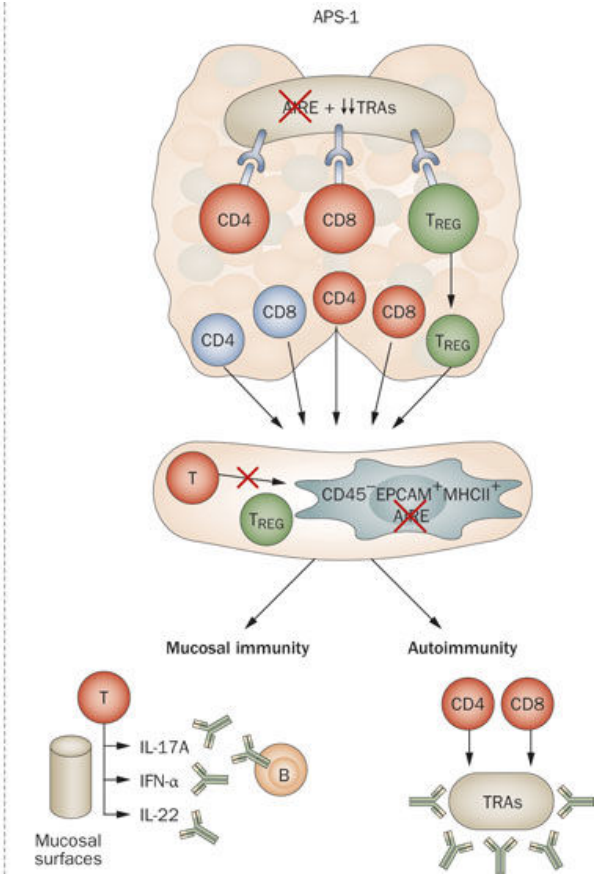
- Central Tolerance
- Antigen Segregation
- Peripheral Tolerance
- Regulatory T cells
- Functional Deviation
- Activation-induced Cell Death

Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy - APECED

Autoantigen	Disease association
Aromatic L-amino-acid decarboxylase	Hepatitis
Glutamate decarboxylase	Insulitis
Islet antigen 2	Insulitis
NALP5	Hypoparathyroidism
Tryptophan hydroxylase	Alopecia, enteritis
Cytochrome P450 enzymes	
Cholesterol side-chain cleavage enzyme	Hypogonadism, adrenalitis
Steroid 17α-hydroxylase	Adrenalitis
Steroid 21-hydroxylase	Adrenalitis, hypogonadism
Cytochrome P450 1A2	Hepatitis

Abbreviation: APS-1, type 1 autoimmune polyglandular syndrome.





Akirav, Eitan M., Nancy H. Ruddle, and Kevan C. Herold. "The role of AIRE in human autoimmune disease." *Nature Reviews Endocrinology* 7.1 (2011): 25-33.

Trauma can induce autoimmune response

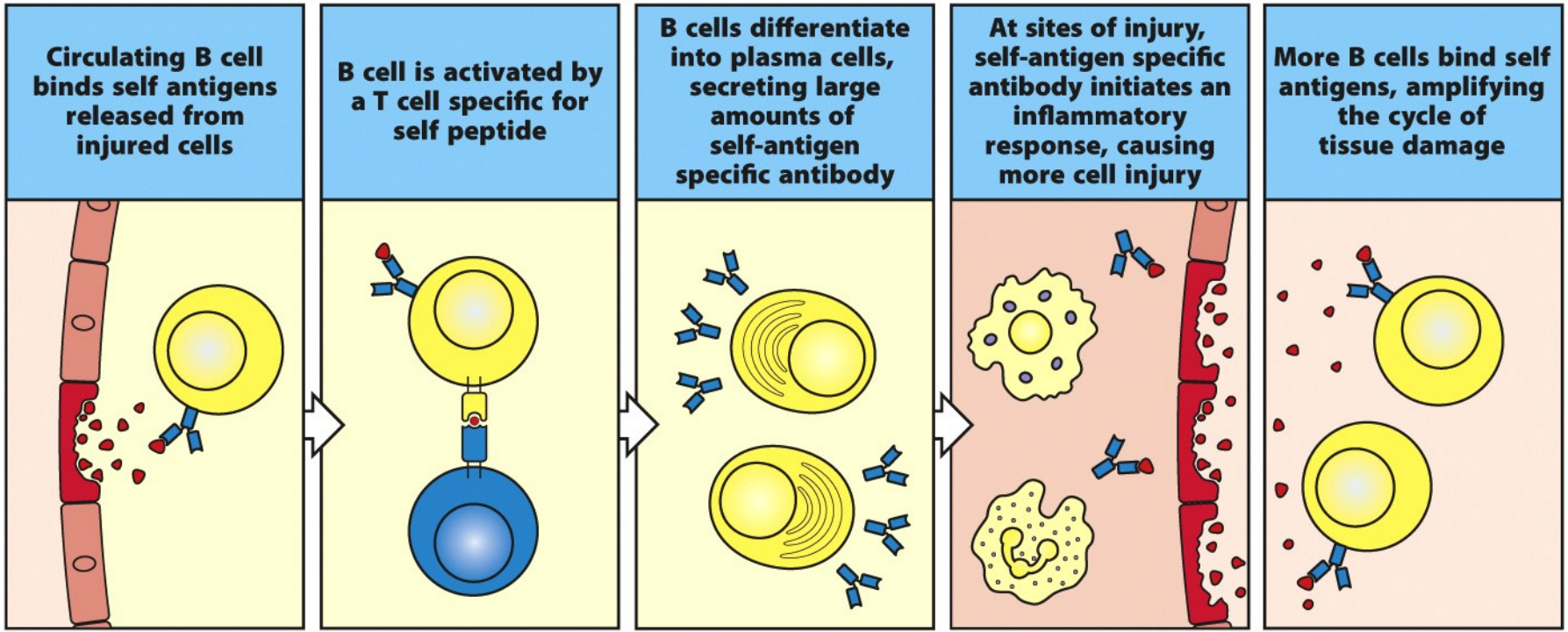
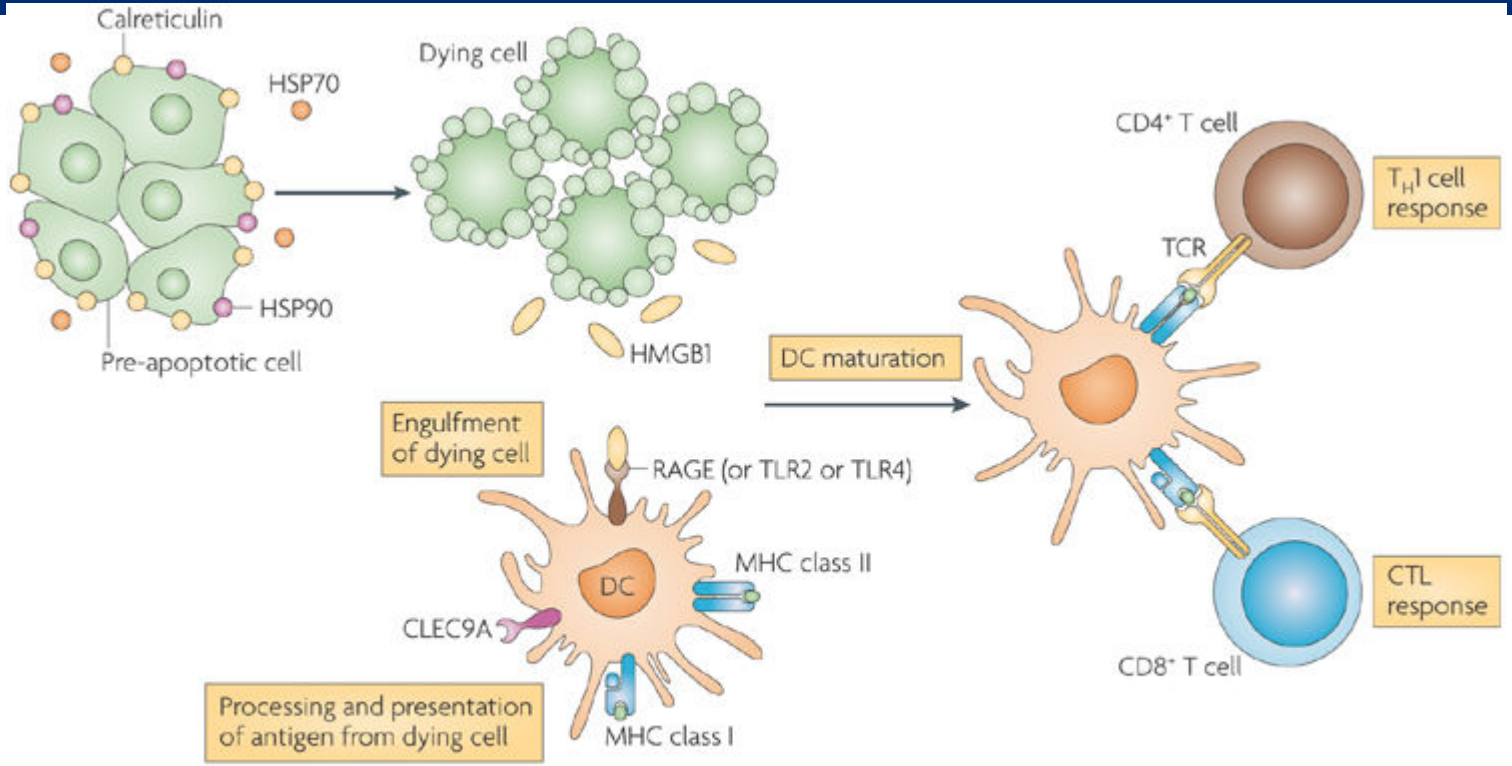


Figure 15.17 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

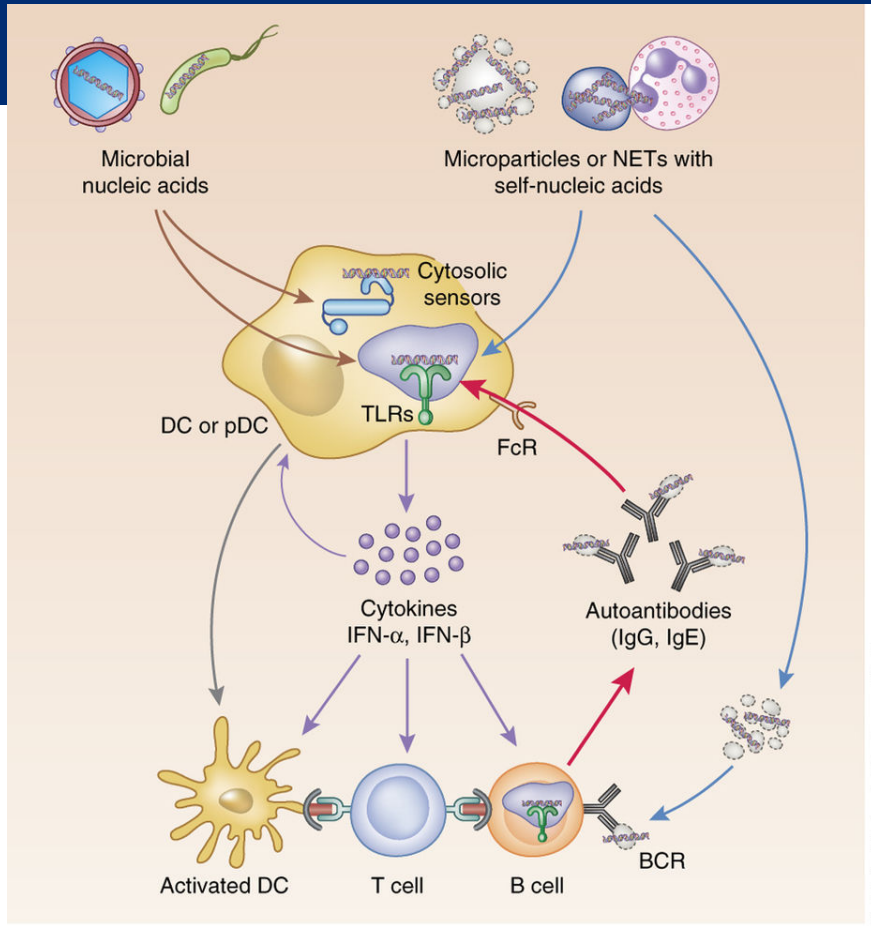
Cell death that leads to an immune response



Green, Douglas R., et al. "Immunogenic and tolerogenic cell death." Nature Reviews Immunology 9.5 (2009): 353-363.

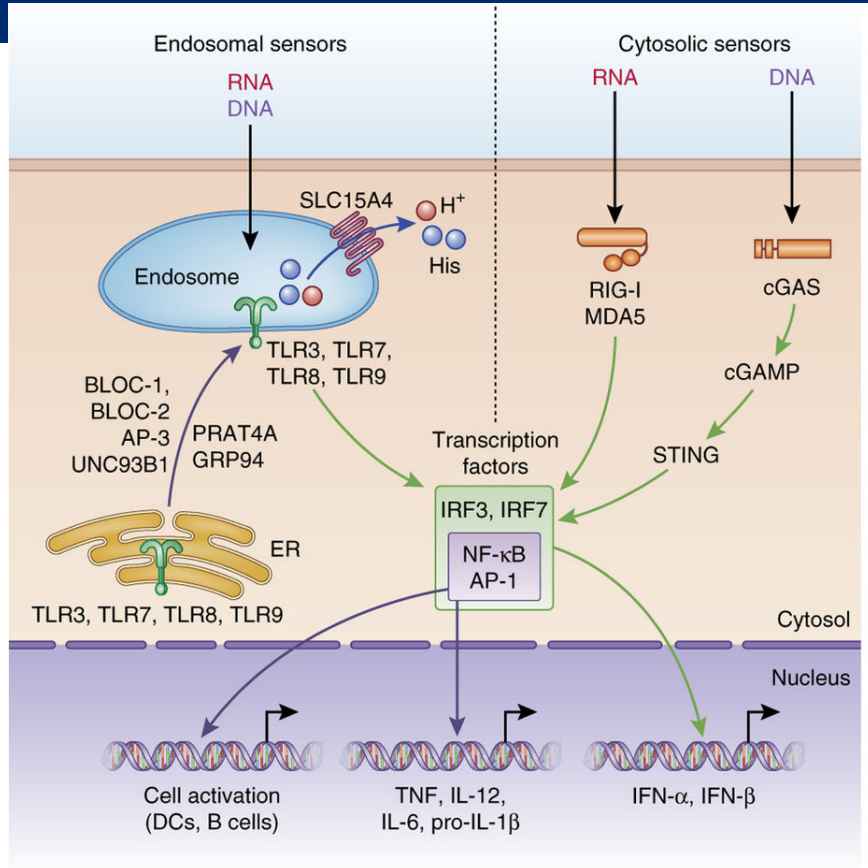
Nature Reviews | Immunology

Nucleic-acid sensing can lead to activation of autoimmune events



(Theofilopoulos, Argyrios N., Dwight H. Kono, and Roberto Baccala. "The multiple pathways to autoimmunity." *Nature immunology* 18.7 (2017): 716.)

TLR signaling of nucleic acids



Debbie Maizels/Springer Nature

(Theofilopoulos, Argyrios N., Dwight H. Kono, and Roberto Baccala. "The multiple pathways to autoimmunity." *Nature immunology* 18.7 (2017): 716.)

Trauma eliminates antigen segregation - SO

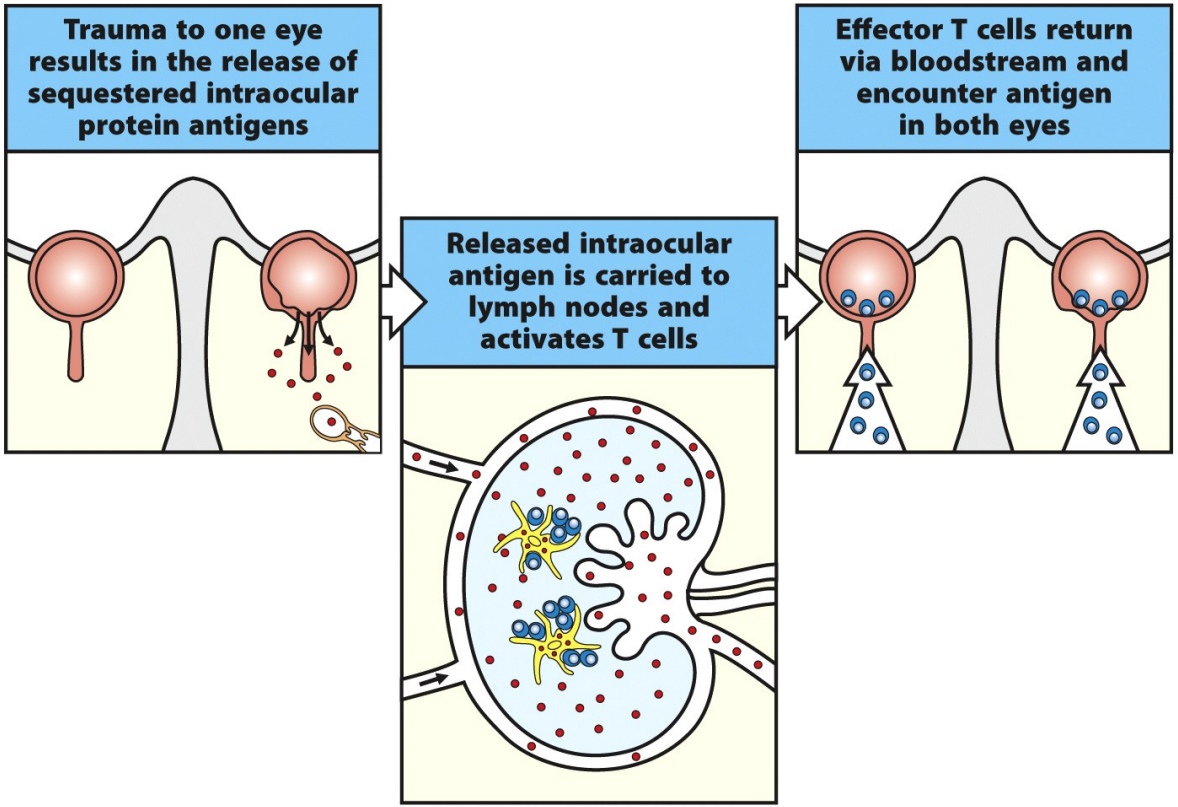


Figure 15.8 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Trauma eliminates antigen segregation - MS

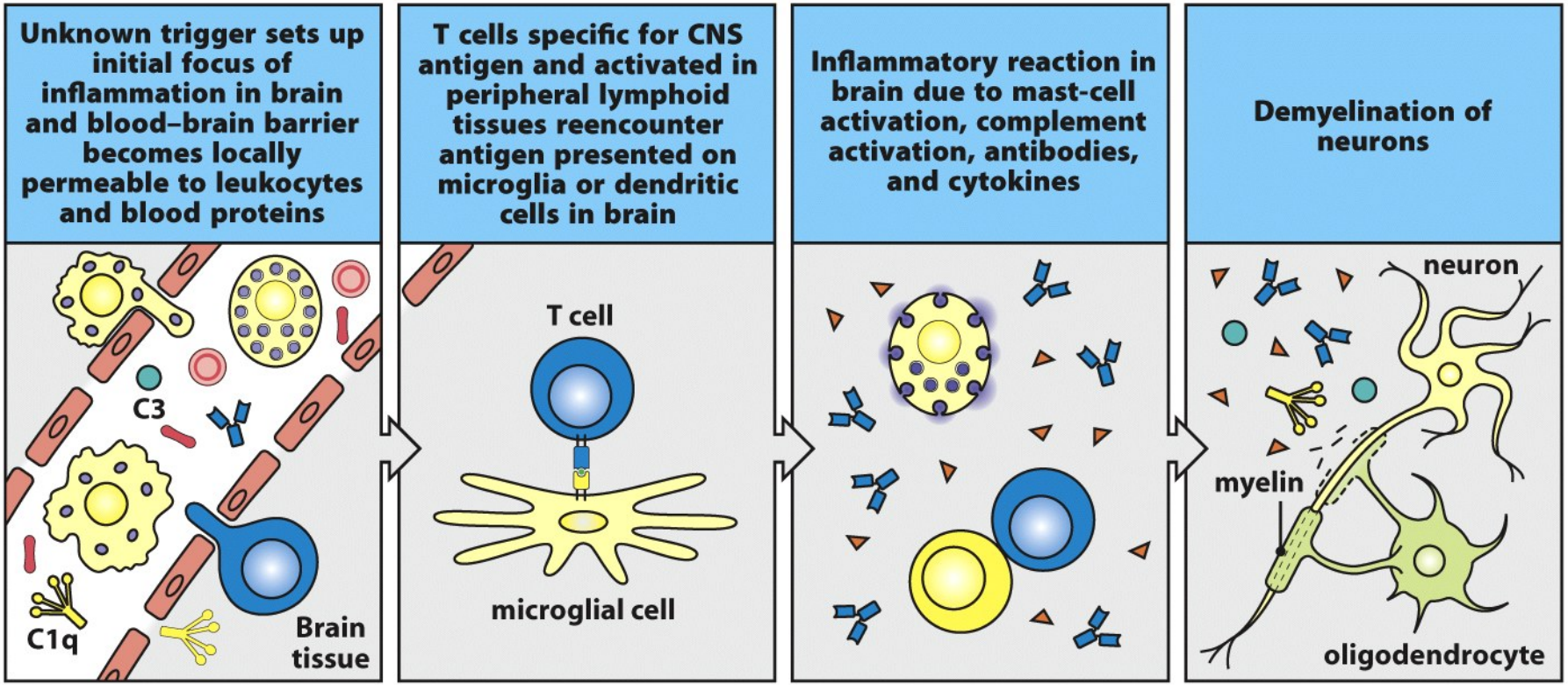


Figure 15.27 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Break Down of Peripheral Tolerance - RA

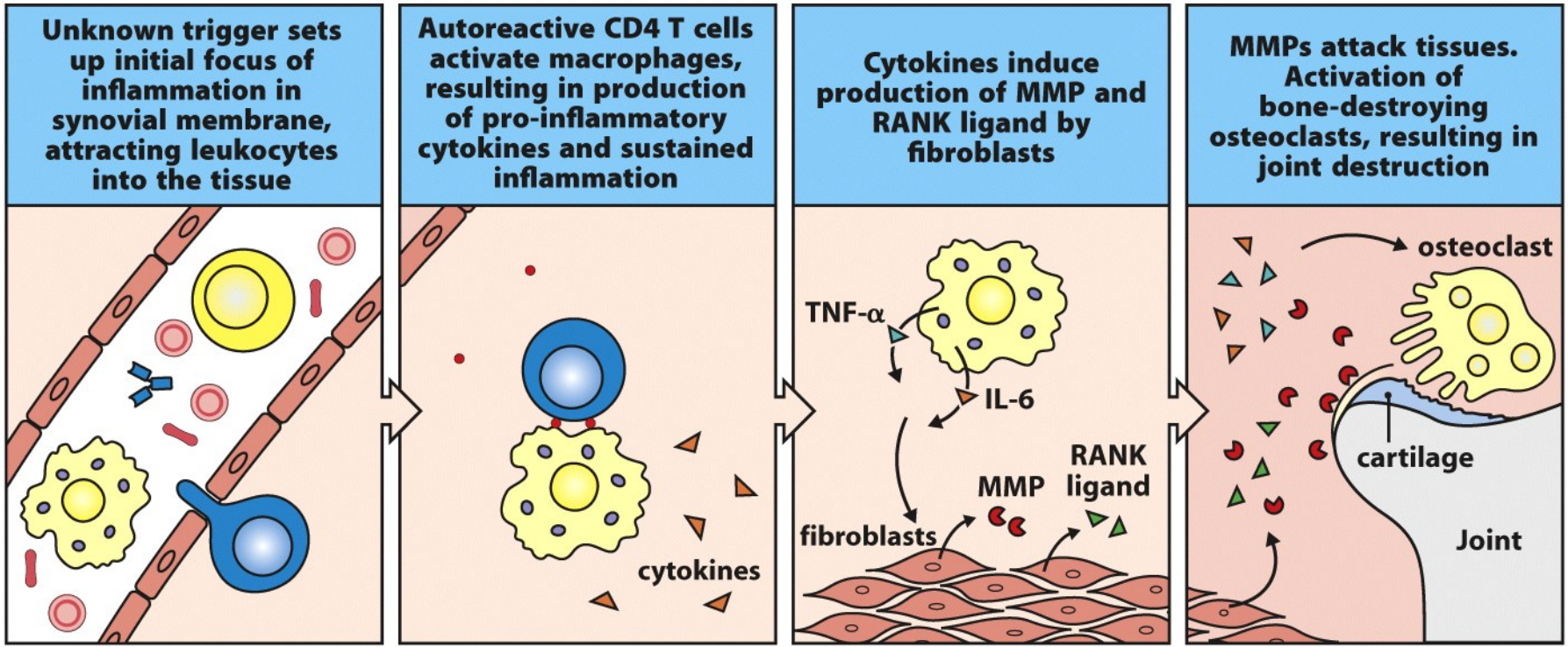


Figure 15.28 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

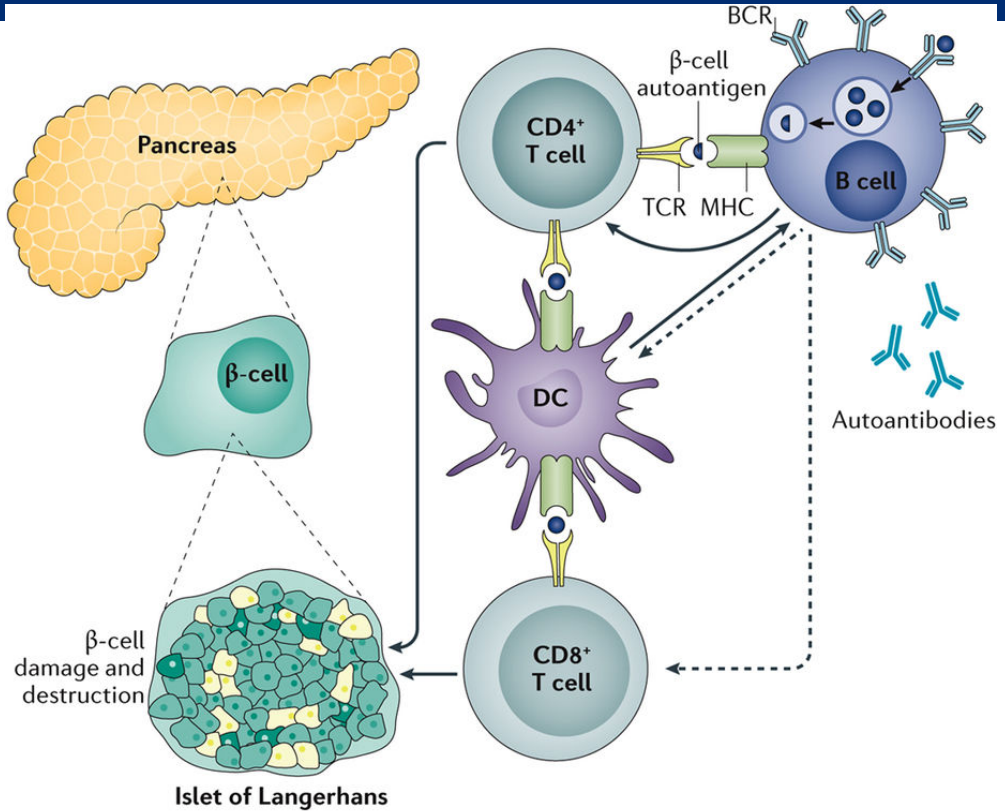
Genes related to Autoimmune Disorders

Single-gene traits associated with autoimmunity			
Gene	**Human disease**	**Mouse mutant or knockout**	**Mechanism of autoimmunity**
AIRE	APECED (APS-1)	Knockout	Decreased expression of self antigens in the thymus, resulting in defective negative selection of self-reactive T cells
CTLA4	Association with Graves' disease, type 1 diabetes and others	Knockout	Failure of T-cell anergy and reduced activation threshold of self-reactive T cells
FOXP3	IPEX	Knockout and mutation (*scurfy*)	Decreased function of CD4 CD25 regulatory T cells
FAS	ALPS	*lpr/lpr;gld/gld* mutants	Failure of apoptotic death of self-reactive B and T cells
C1q	SLE	Knockout	Defective clearance of immune complexes and apoptotic cells

 Figure 15.32 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Type 1 Diabetes and Peripheral Tolerance

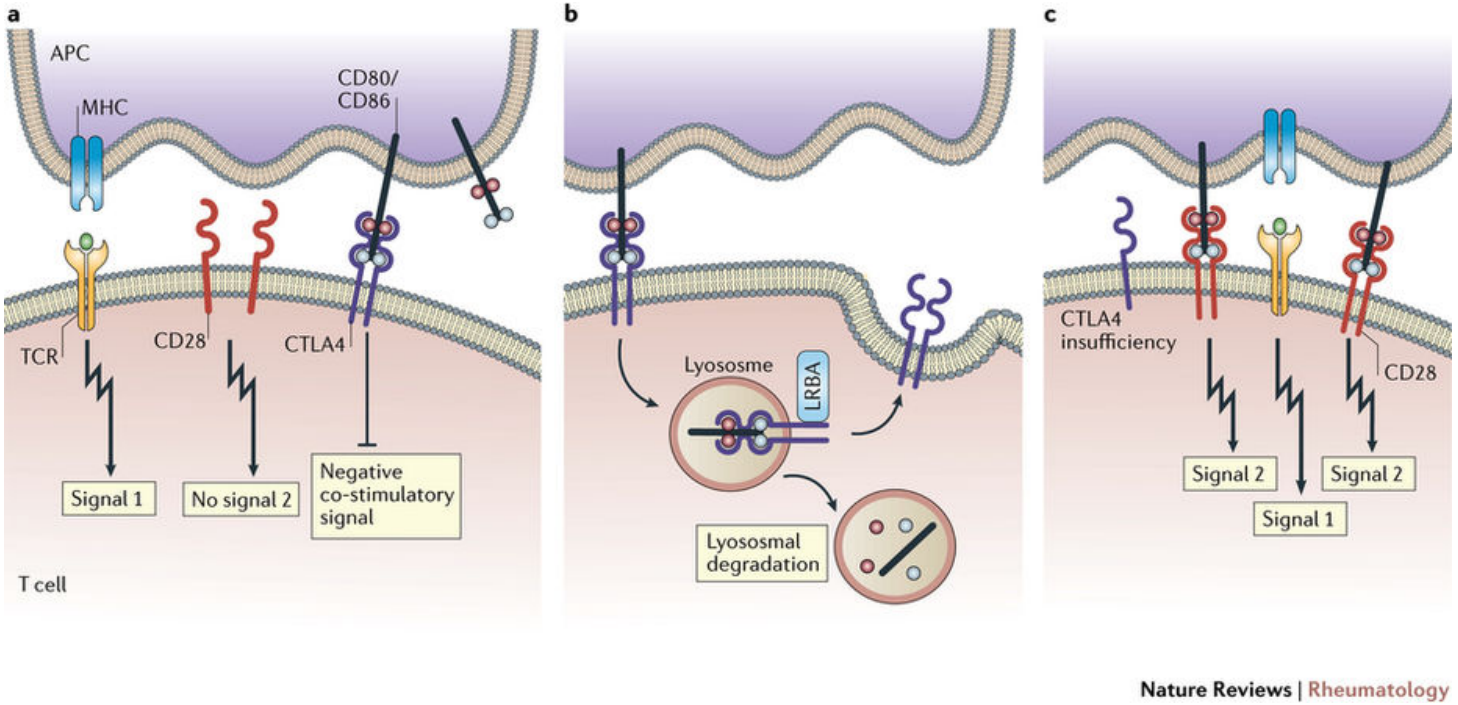
- Genetic Risk Factors
  - CTLA4



(Katsarou, A. et al. Type 1 diabetes mellitus. *Nat. Rev. Dis. Primers 3*, 17016 (2017))

Nature Reviews | Disease Primers

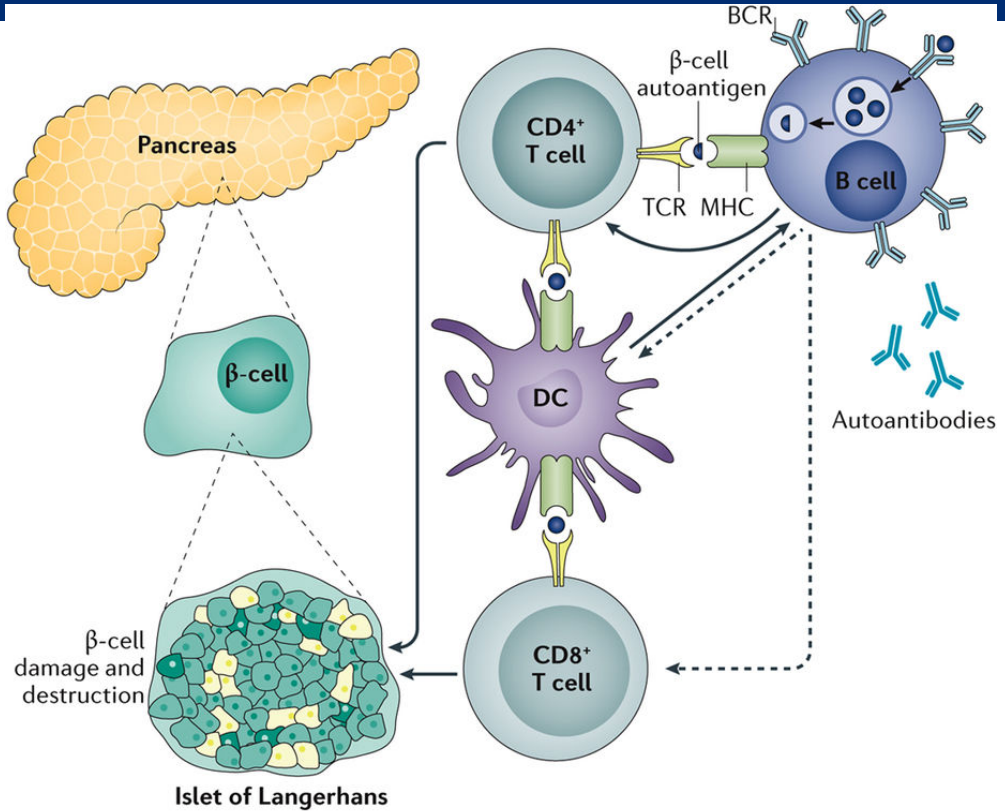
Problems with CTLA4 deficiency



Schmidt, Reinhold E., Bodo Grimbacher, and Torsten Witte. "Autoimmunity and primary immunodeficiency: two sides of the same coin?." *Nature Reviews Rheumatology* 14.1 (2018): 7.

Type 1 Diabetes and Peripheral Tolerance

- Genetic Risk Factors
  - CTLA4
  - IL2R
  - PTPN22
  - Insulin

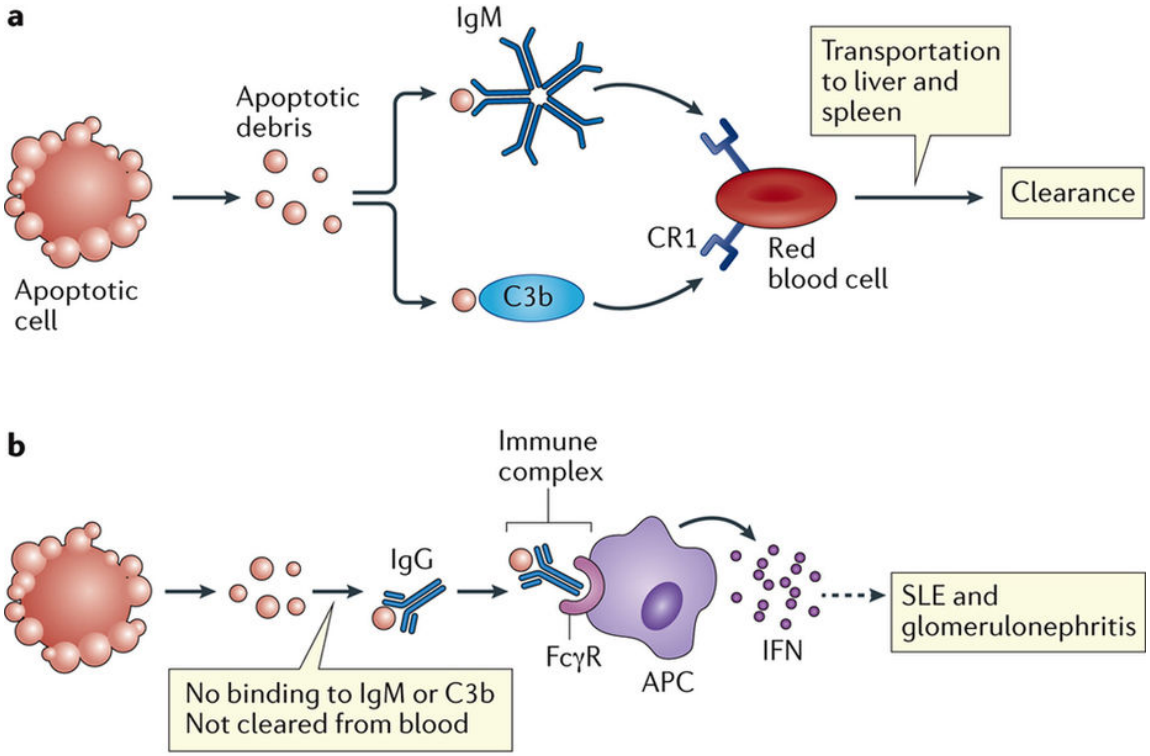


(Katsarou, A. et al. Type 1 diabetes mellitus. *Nat. Rev. Dis. Primers 3*, 17016 (2017))

Nature Reviews | Disease Primers

Defects in Removing Apoptotic Cells

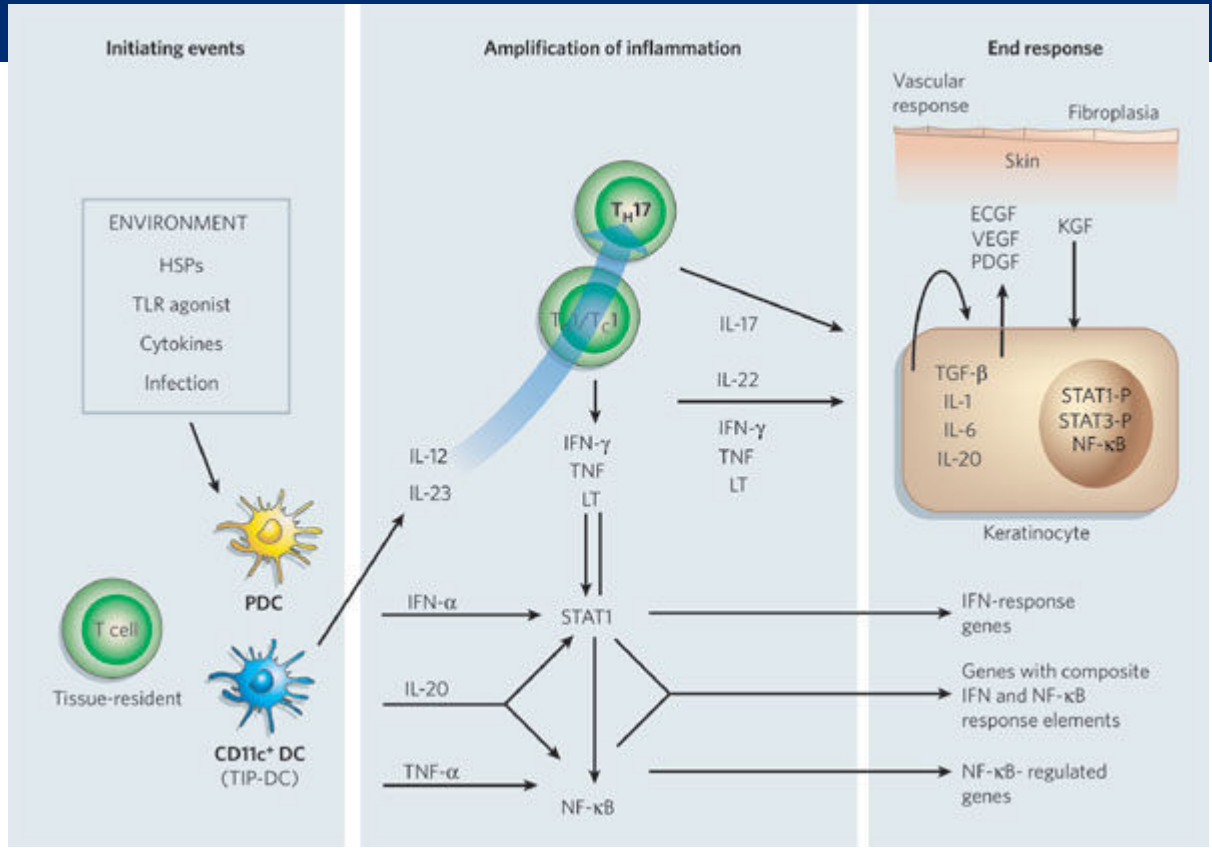
- Systemic lupus erythematosus
- IgM antibodies provide immunoregulation
- Defect in complement proteins



Schmidt, Reinhold E., Bodo Grimbacher, and Torsten Witte. "Autoimmunity and primary immunodeficiency: two sides of the same coin?." *Nature Reviews Rheumatology* 14.1 (2018): 7.

Initiation of Psoriasis

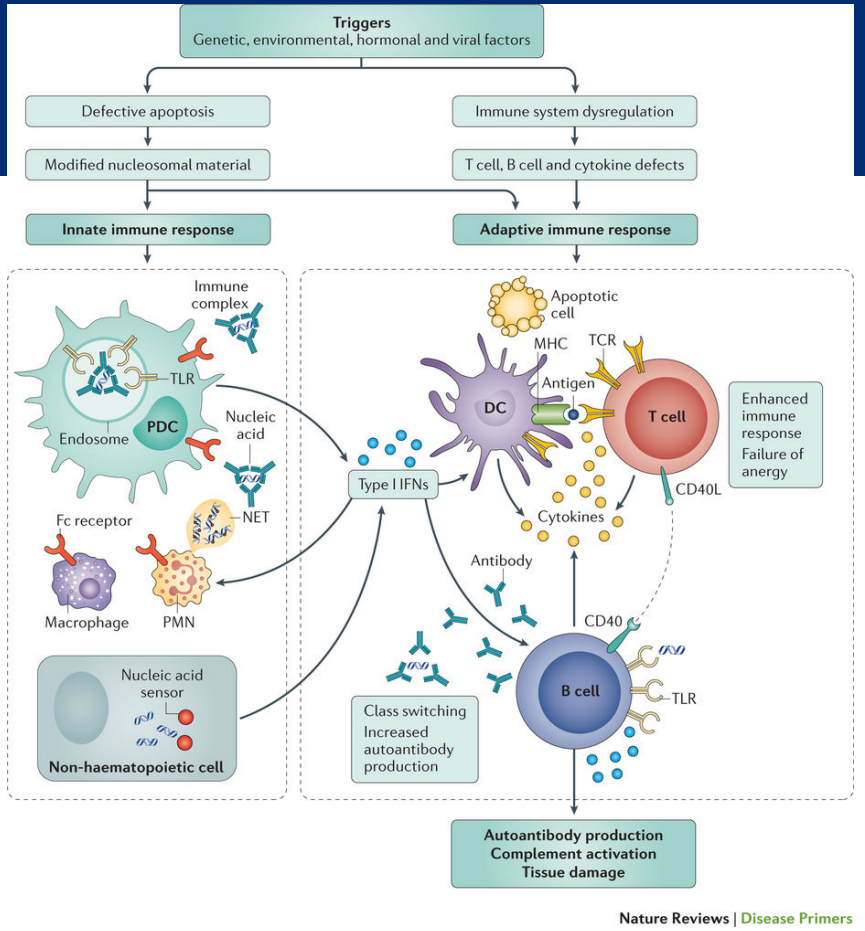
- Initial insult
  - Trauma
  - Infection
  - Medications
- Combination with Genetic Risk Factors:
  - HLA allele
  - CARD14
  - IL23/IL23 receptor



Lowes, Michelle A., Anne M. Bowcock, and James G. Krueger. "Pathogenesis and therapy of psoriasis." *Nature*445.7130 (2007): 866-873.

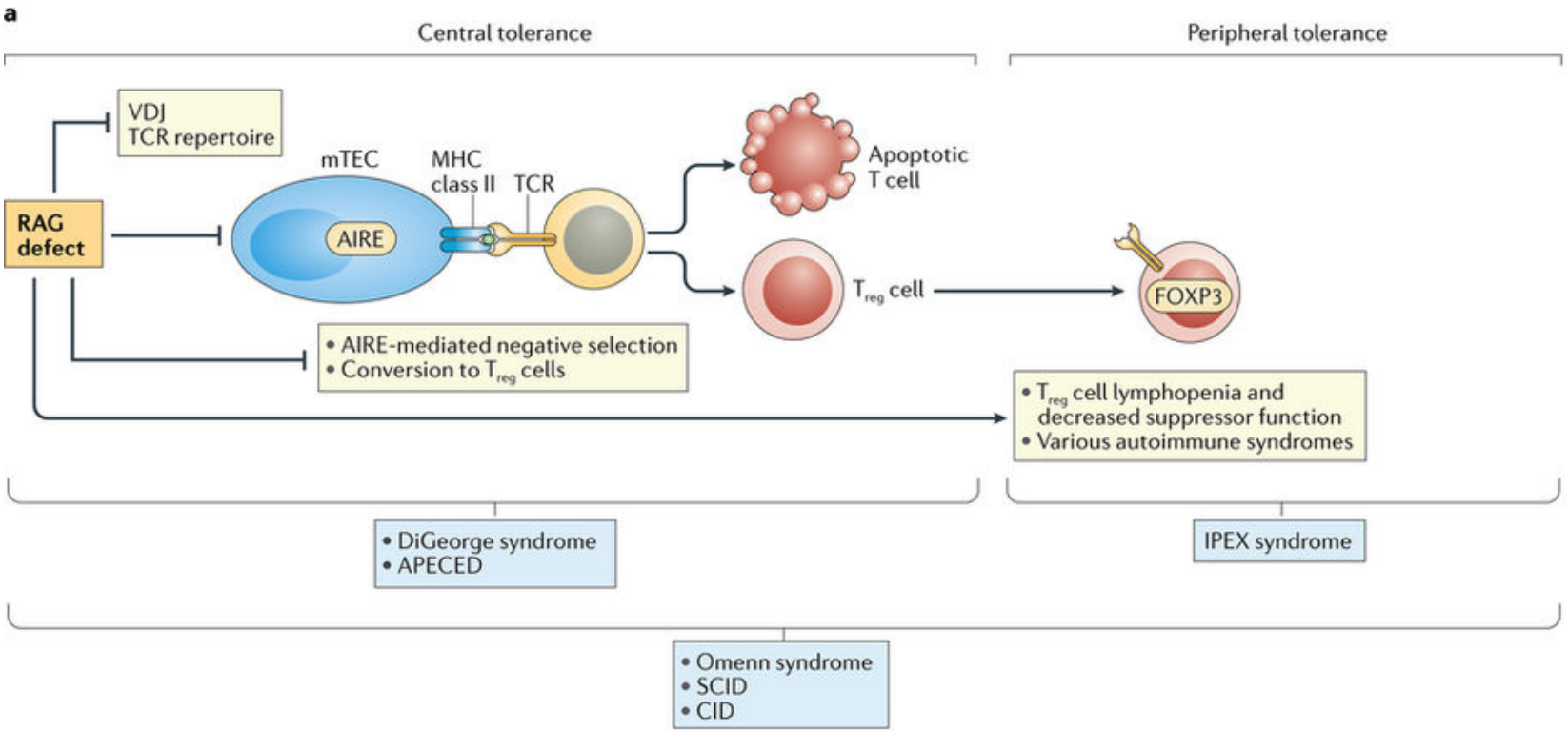
Insult & Genetic Susceptibility

- Grave's Disease
- Hashimoto's Thyroiditis
- Systemic lupus erythematosus



Smith, Terry J., and Laszlo Hegedüs. "Graves' disease." *New England Journal of Medicine* 375.16 (2016): 1552-1565.
(Kaul et al., Systemic lupus erythematosus, *Nature Reviews Disease Primers 2* (2016) 16039)

Immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX)



Schmidt, Reinhold E., Bodo Grimbacher, and Torsten Witte. "Autoimmunity and primary immunodeficiency: two sides of the same coin?." *Nature Reviews Rheumatology* 14.1 (2018): 7.

Regulatory T cells can be given to treat IBD

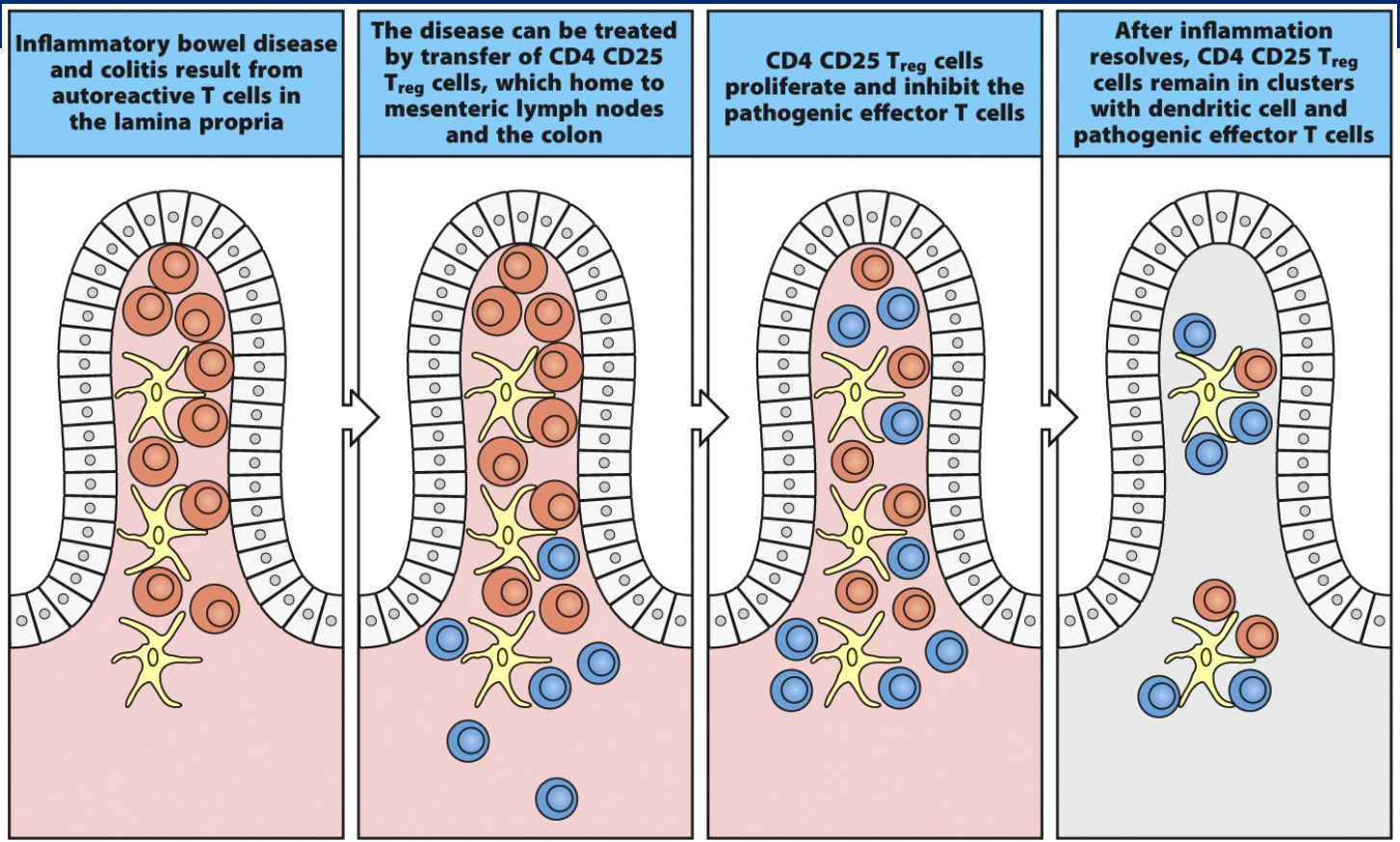


Figure 15.10 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Irregular Cytokine Expression Cause Auotimmunity

Defects in cytokine production or signaling that can lead to autoimmunity		
Defect	**Cytokine or intracellular signal**	**Result**
Overexpression	TNF-α	Inflammatory bowel disease, arthritis, vasculitis
	IL-2, IL-7, IL-2R	Inflammatory bowel disease
	IL-3	Demyelinating syndrome
	IFN-γ	Overexpression in skin leads to SLE
	STAT4	Inflammatory bowel disease
Underexpression	TNF-α	SLE
	IL-1 receptor agonist	Arthritis
	IL-10, IL-10R, STAT3	Inflammatory bowel disease
	TGF-β	Ubiquitous underexpression leads to inflammatory bowel disease. Underexpression specifically in T cells leads to SLE

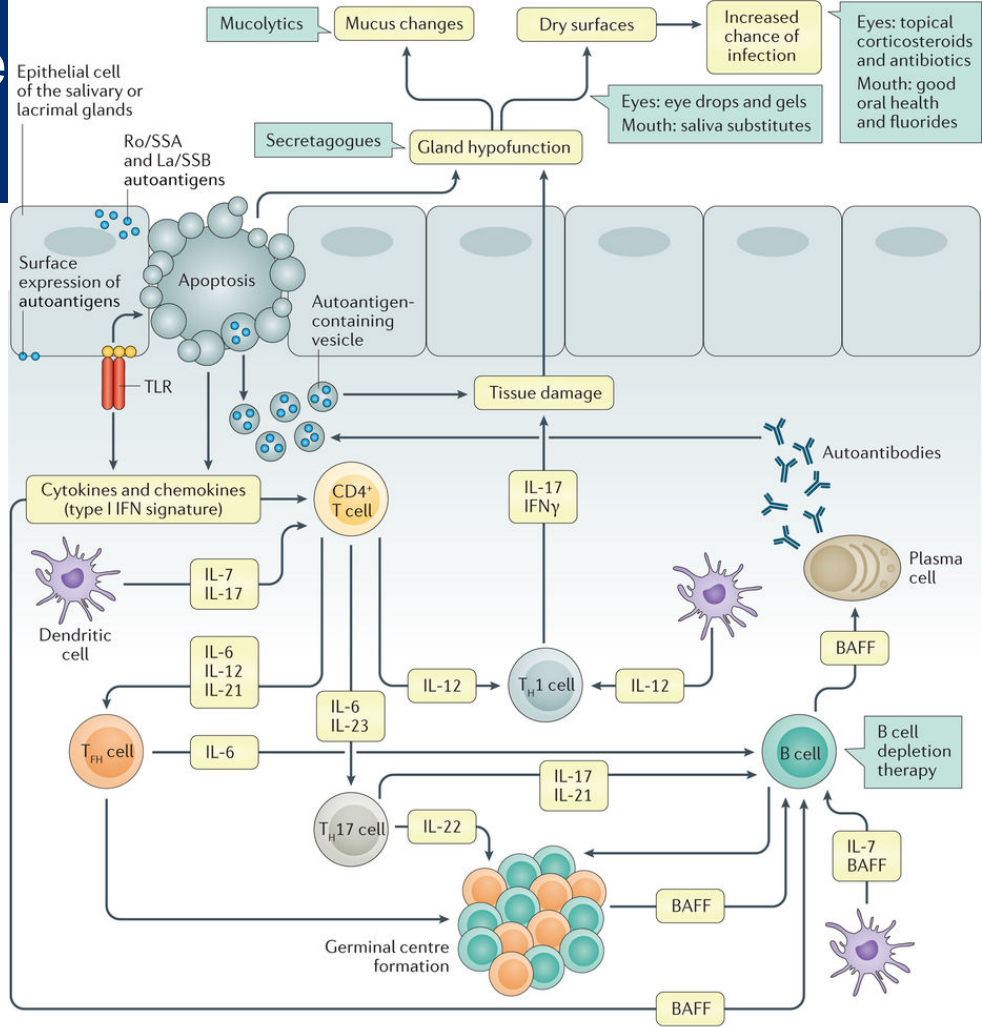
Figure 15.30 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Sjögren syndrome – An example of cytokine dysfunction

Salivary gland epithelial cells express:

- Human leukocyte antigen (HLA) class I
- CD40; a co-stimulatory protein
- Adhesion molecules
- FAS receptor
- Pro-inflammatory cytokines
- Many chemokines that attract T cells

Leads to vicious cycle

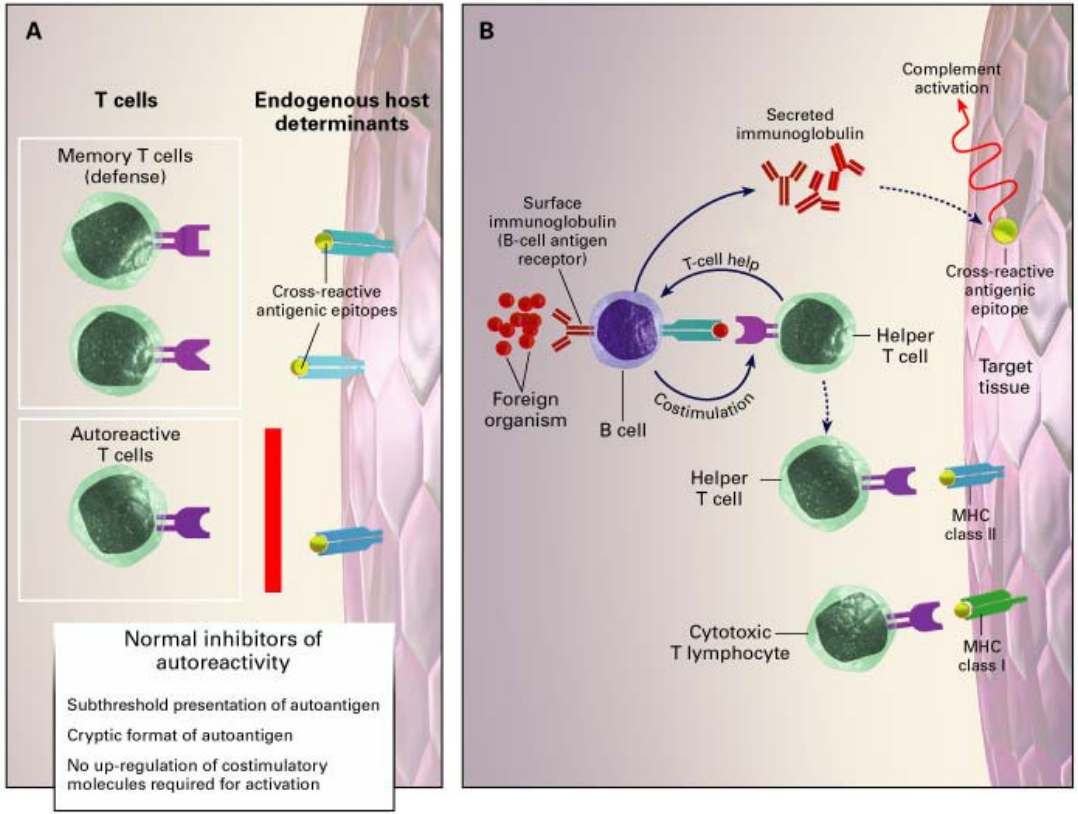


(Brito-Zeron et al., Sjögren syndrome, *Nature Reviews Disease Primers 3* (2016) 16047)

Molecular Mimicry

Pathogenic response leads to autoimmune response

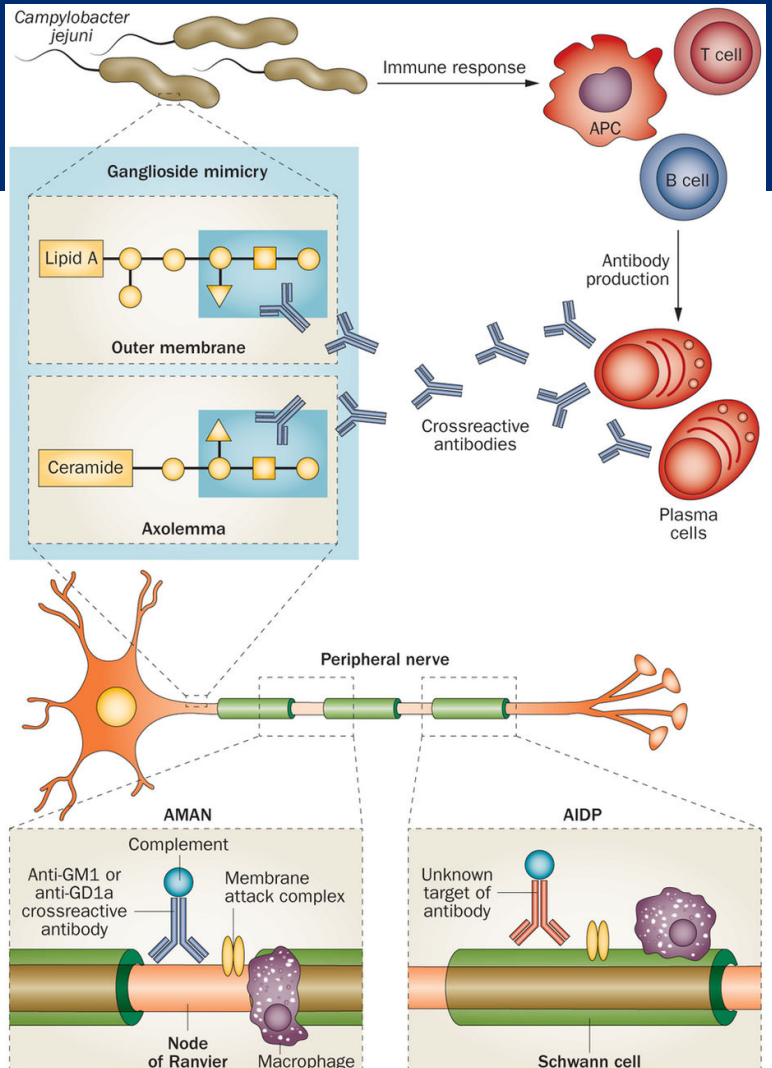
- Increases Total Antigen – Ignorance
- Increases Co-stimulation molecules – Peripheral Tolerance
- Reveal Cryptic Antigen – Antigen Sequestration



Albert, Lori J., and Robert D. Inman. "Molecular mimicry and autoimmunity." *New England Journal of Medicine* 341.27 (1999): 2068-2074.

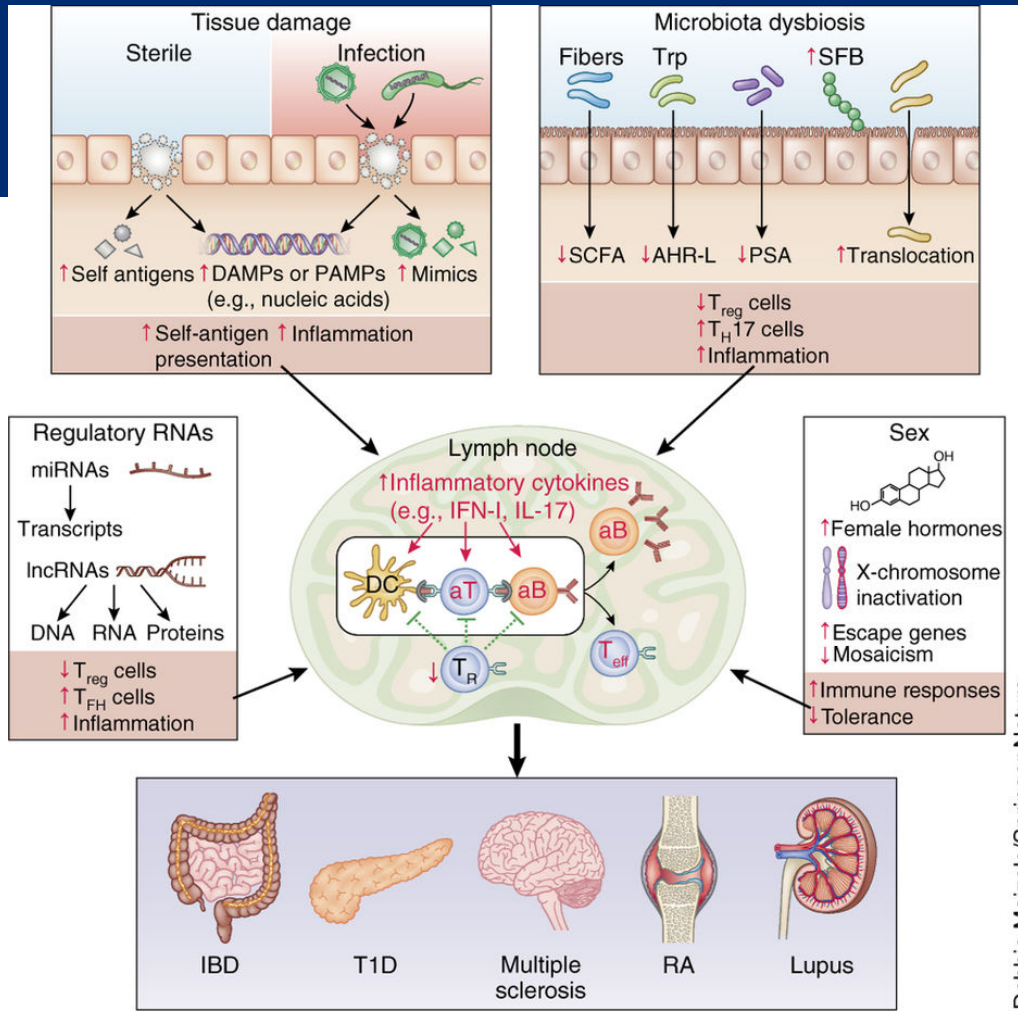
Guillain–Barré syndrome

- Symptoms: Pain, Fatigue, Limb weakness, Sensory disturbances, and Cranial nerve deficits
- Occurs after infectious disease
- 1/100,000 incidence



Van Den Berg, Bianca, et al. "Guillain-Barré syndrome: pathogenesis, diagnosis, treatment and prognosis." *Nature Reviews Neurology* 10.8 (2014): 469-482.

Risk Factors for Autoimmunity



(Theofilopoulos, Argyrios N., Dwight H. Kono, and Roberto Baccala. "The multiple pathways to autoimmunity." *Nature immunology* 18.7 (2017): 716.)

Failure of several mechanisms for tolerance can lead to Chron's Disease

A. Escape of central tolerance
B. Not sequester bacteria
C. Abnormal activity of Th1 and Th17 cells
D. Failure of Tregs
E. Pro-inflammatory mutation of NOD2 gene
F. Mutations on IL-23 gene of innate immune cells

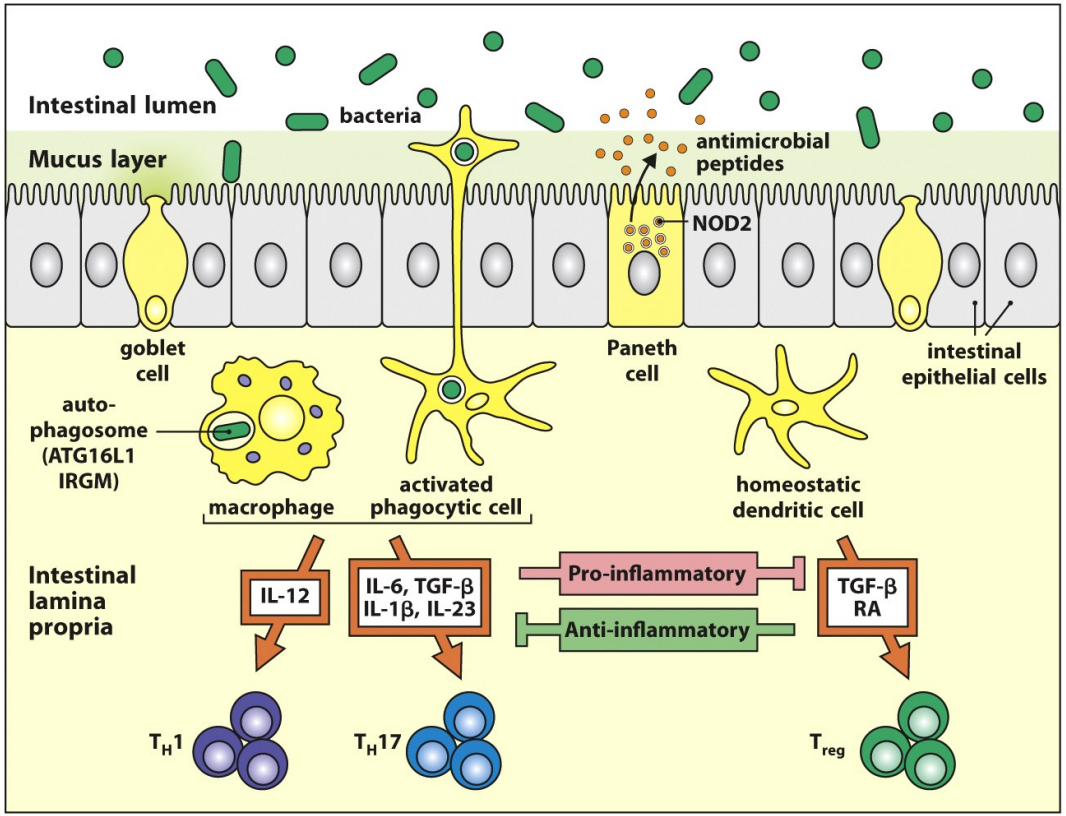


Figure 15.37 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Tolerance has implications for organ transplants

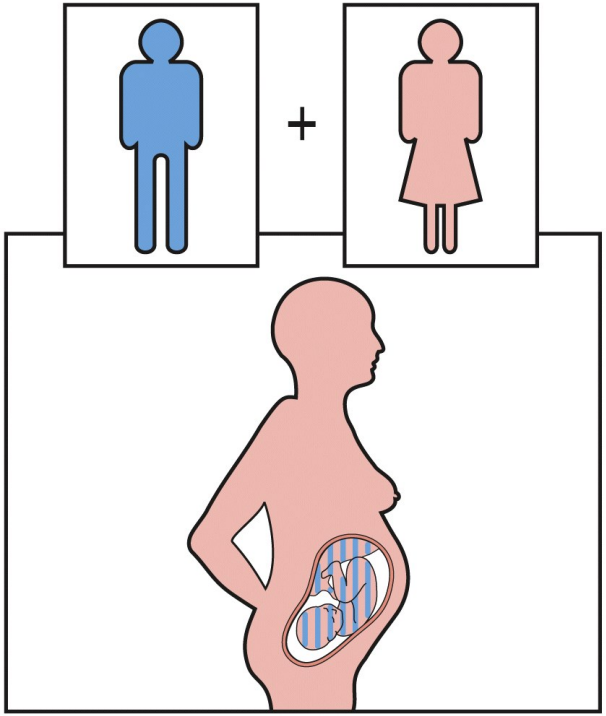
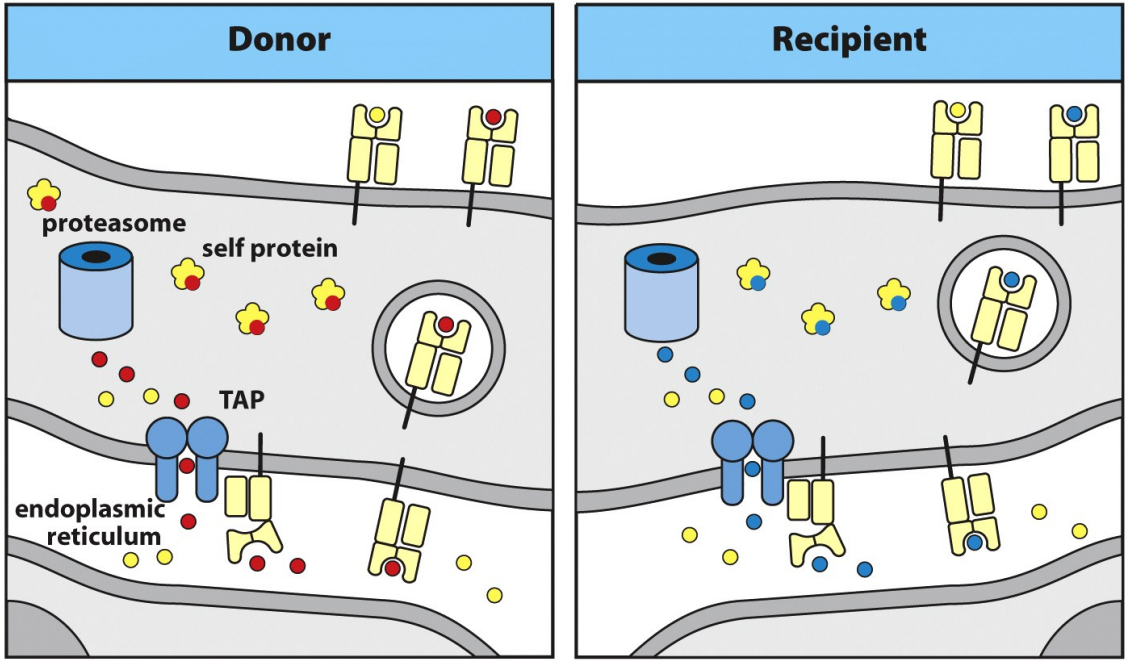


Figure 15.50 Janeway's Immunobiology, 8ed. (© Garland Science 2012)



Polymorphic self proteins that differ in amino acid sequence between individuals give rise to minor H antigen differences between donor and recipient

Figure 15.43 Janeway's Immunobiology, 8ed. (© Garland Science 2012)