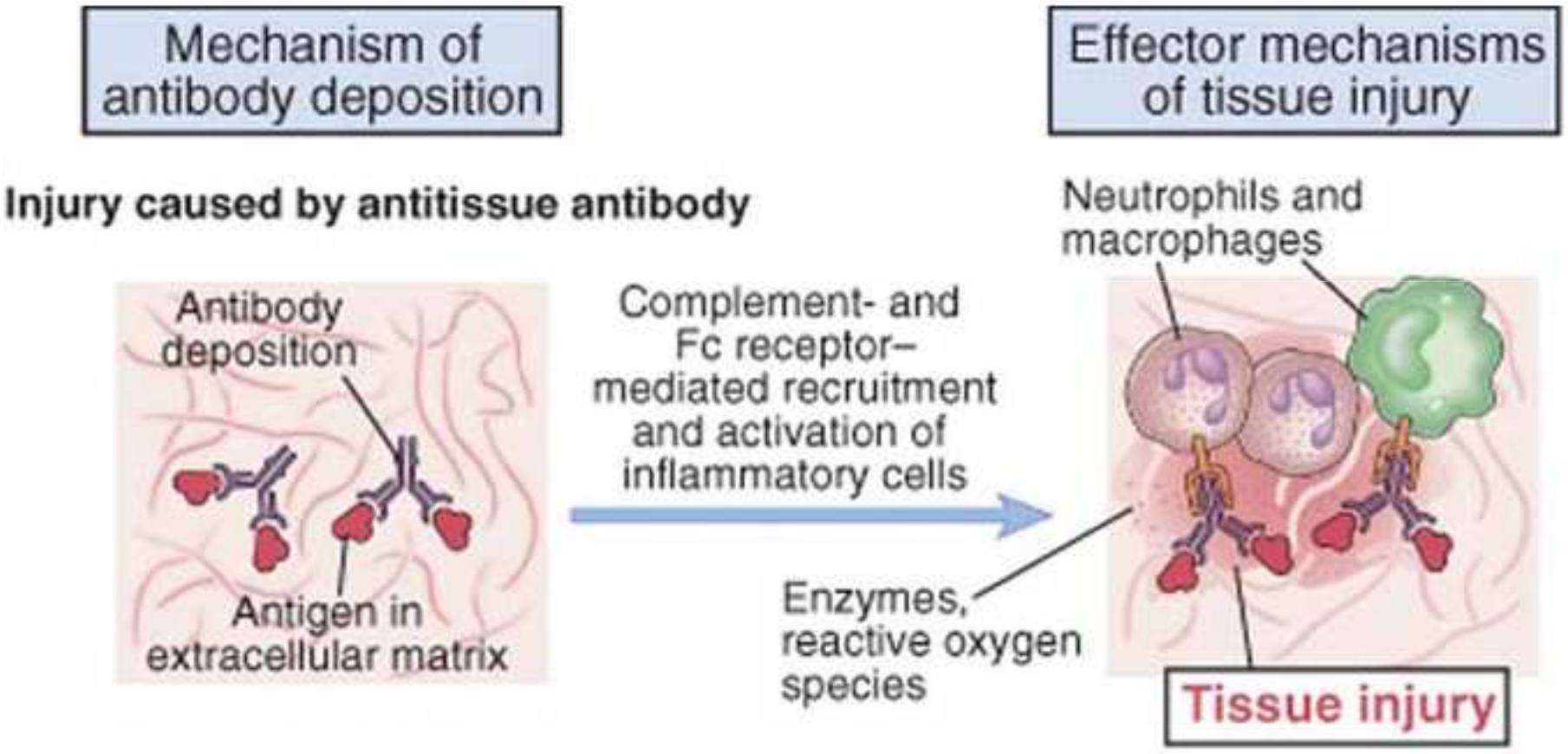
Immunopathology and autoimmunity

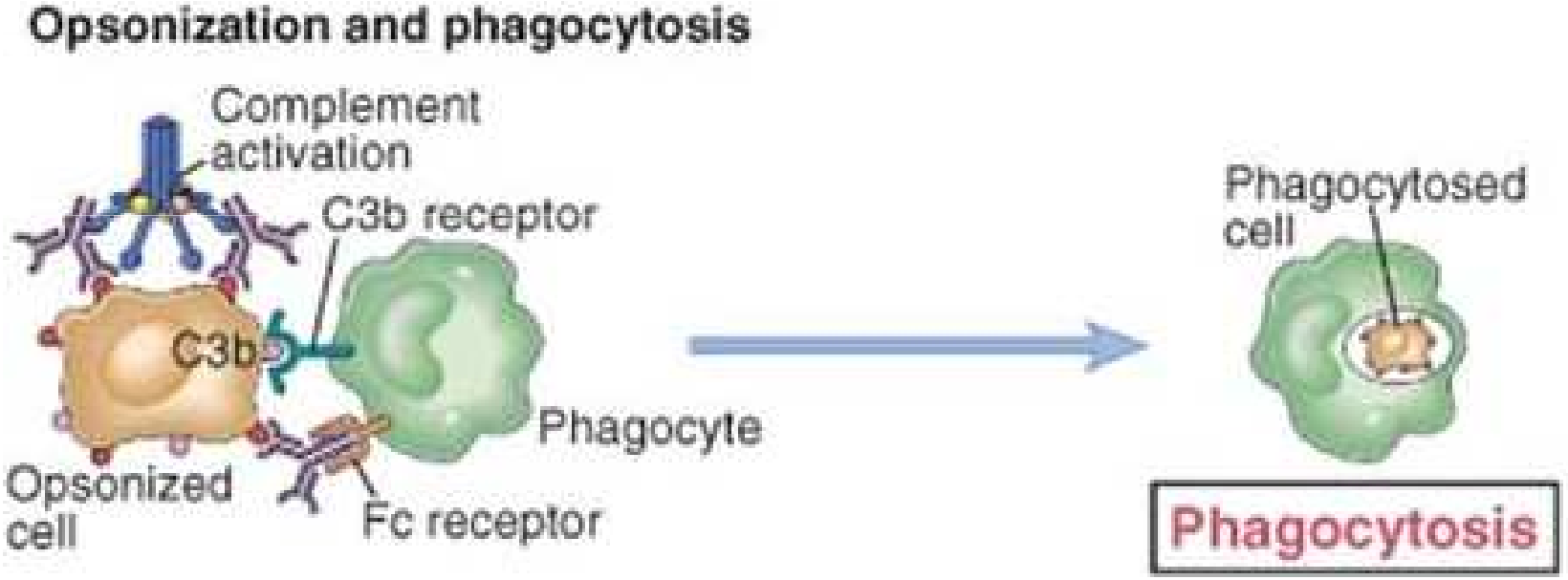
Immune-mediated tissue damage (hypersensitivity, HS)

Type of hypersensitivity	Pathologic immune mechanisms	Mechanisms of tissue injury and disease
Immediate hypersensitivity: Type I	IgE antibody	Mast cells and their mediators (vasoactive amines, lipid mediators, cytokines)
Antibody mediated: Type II	IgM, IgG antibodies against cell surface or extracellular matrix antigens	Opsonization and phagocytosis of cells Complement- and Fc receptor-mediated recruitment and activation of leukocytes (neutrophils, macrophages) Abnormalities in cellular functions, e.g., hormone receptor signaling
Immune complex mediated: Type III	Immune complexes of circulating antigens and IgM or IgG antibodies	Complement- and Fc receptor-mediated recruitment and activation of leukocytes
T cell mediated: Type IV	1. $CD4^+$ T cells (delayed-type hypersensitivity) 2. $CD8^+$ CTLs (T cell-mediated cytolysis)	1. Macrophage activation, cytokine-mediated inflammation 2. Direct target cell killing, cytokine-mediated inflammation

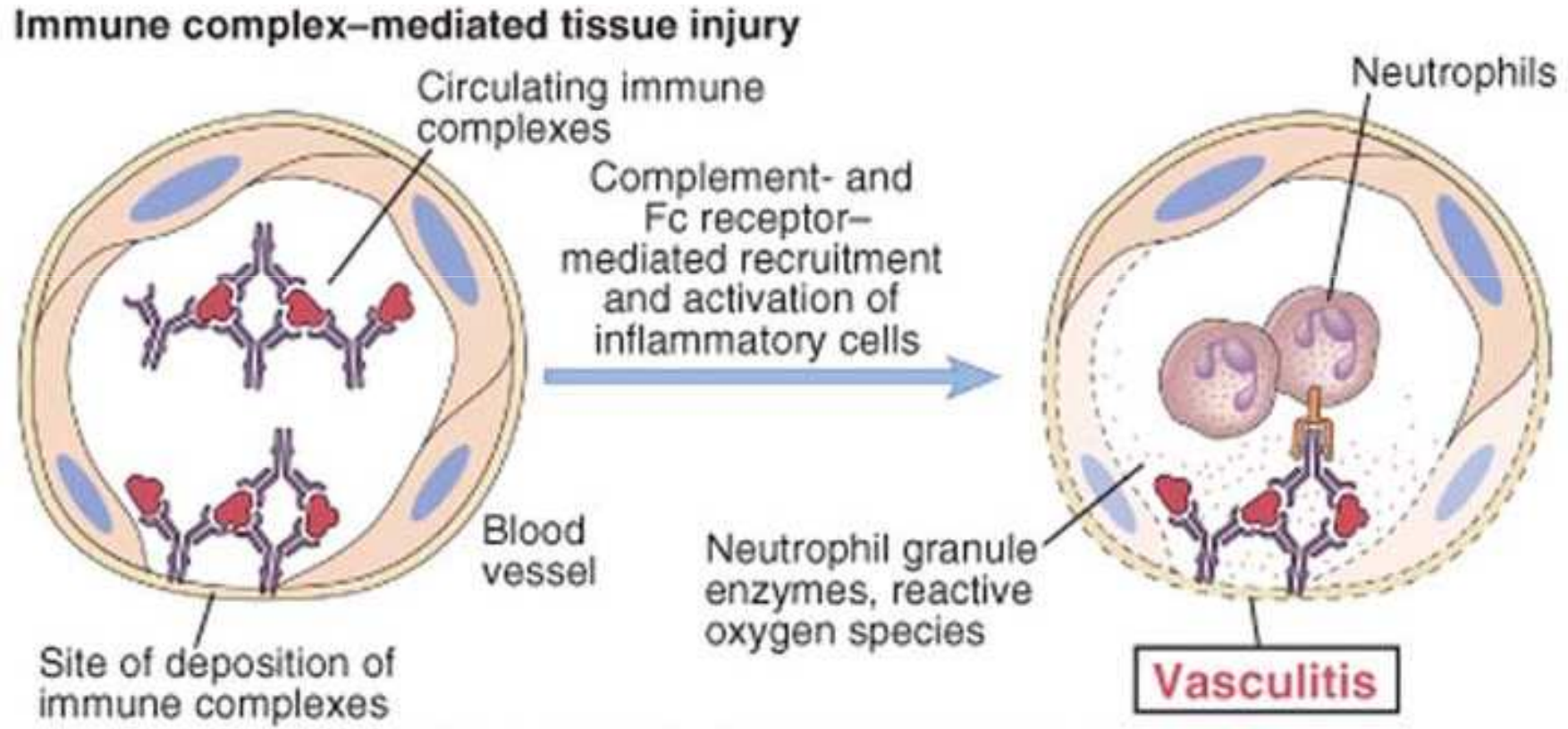
Tissue damage caused by antibodies (type 2 HS)



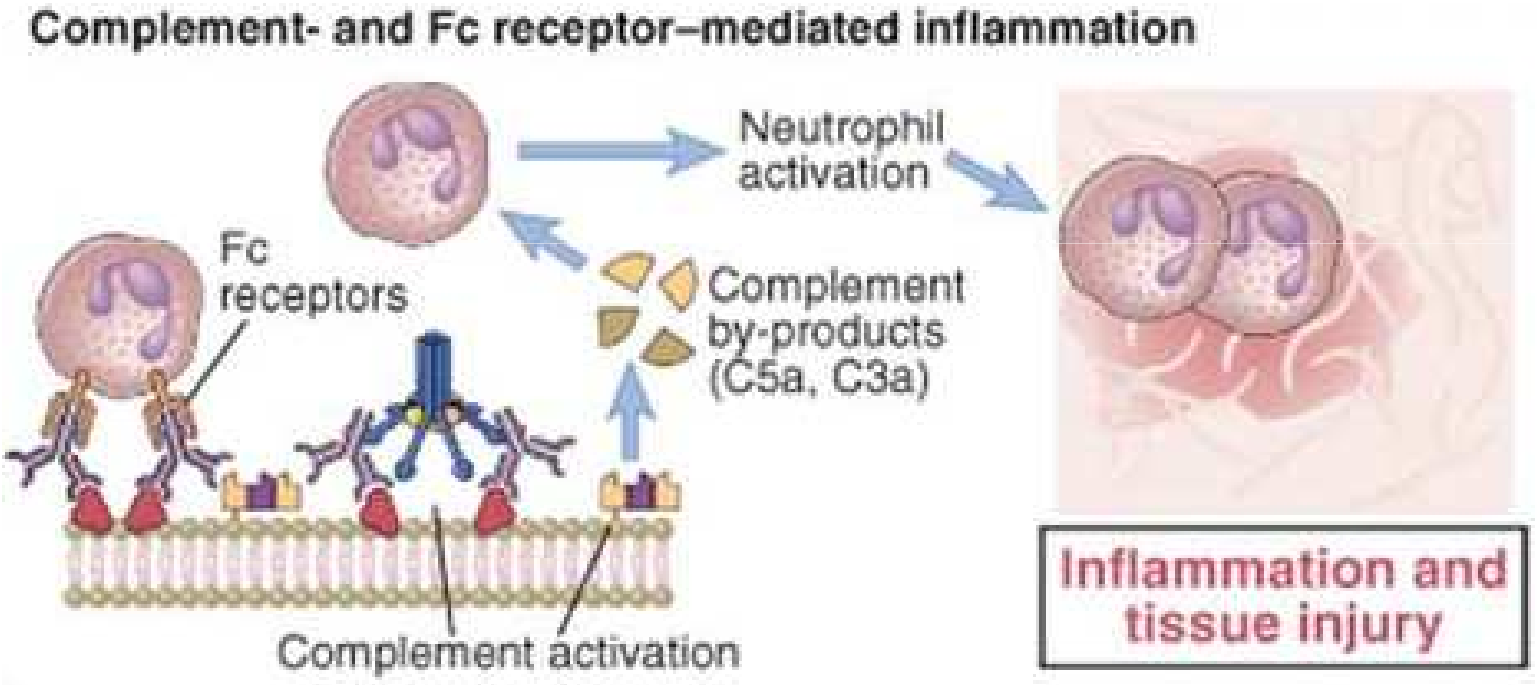
Cellular destruction after “opsonization” (type 2 HS)



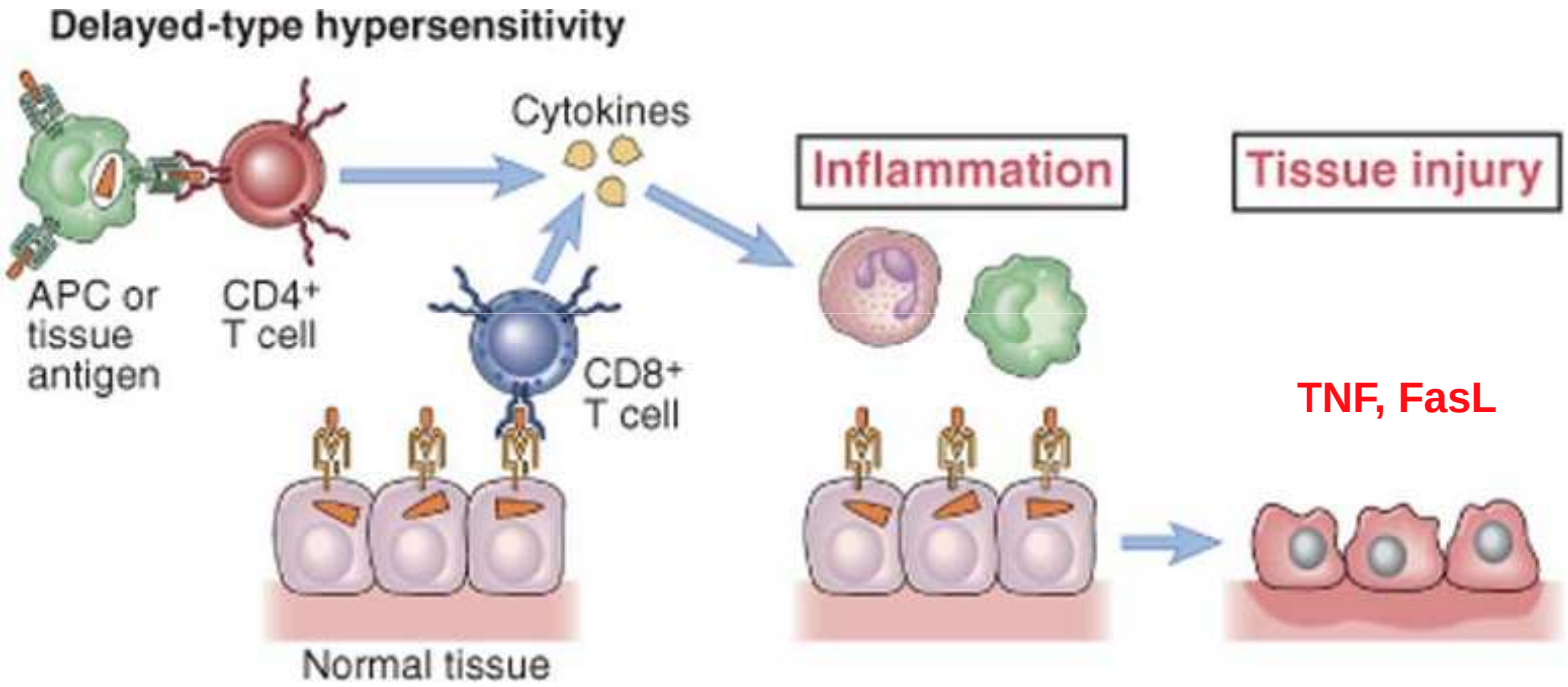
Tissue damage caused by immunocomplexes (type 3 HS)



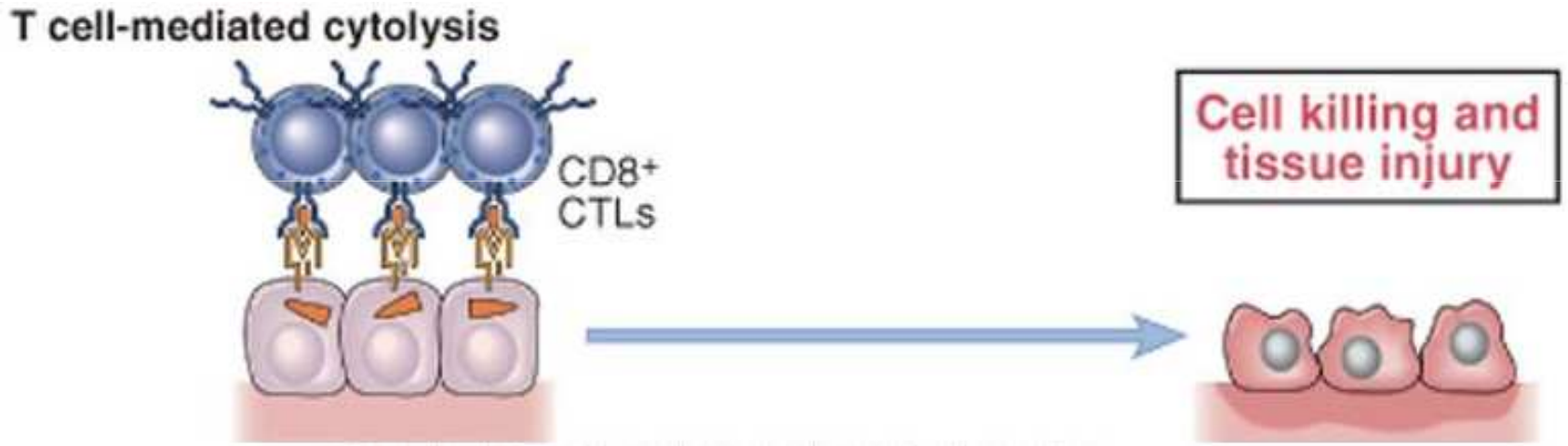
Tissue damage caused by complement (type 3 HS)



Tissue damage caused by cytokines (type 4 HS)



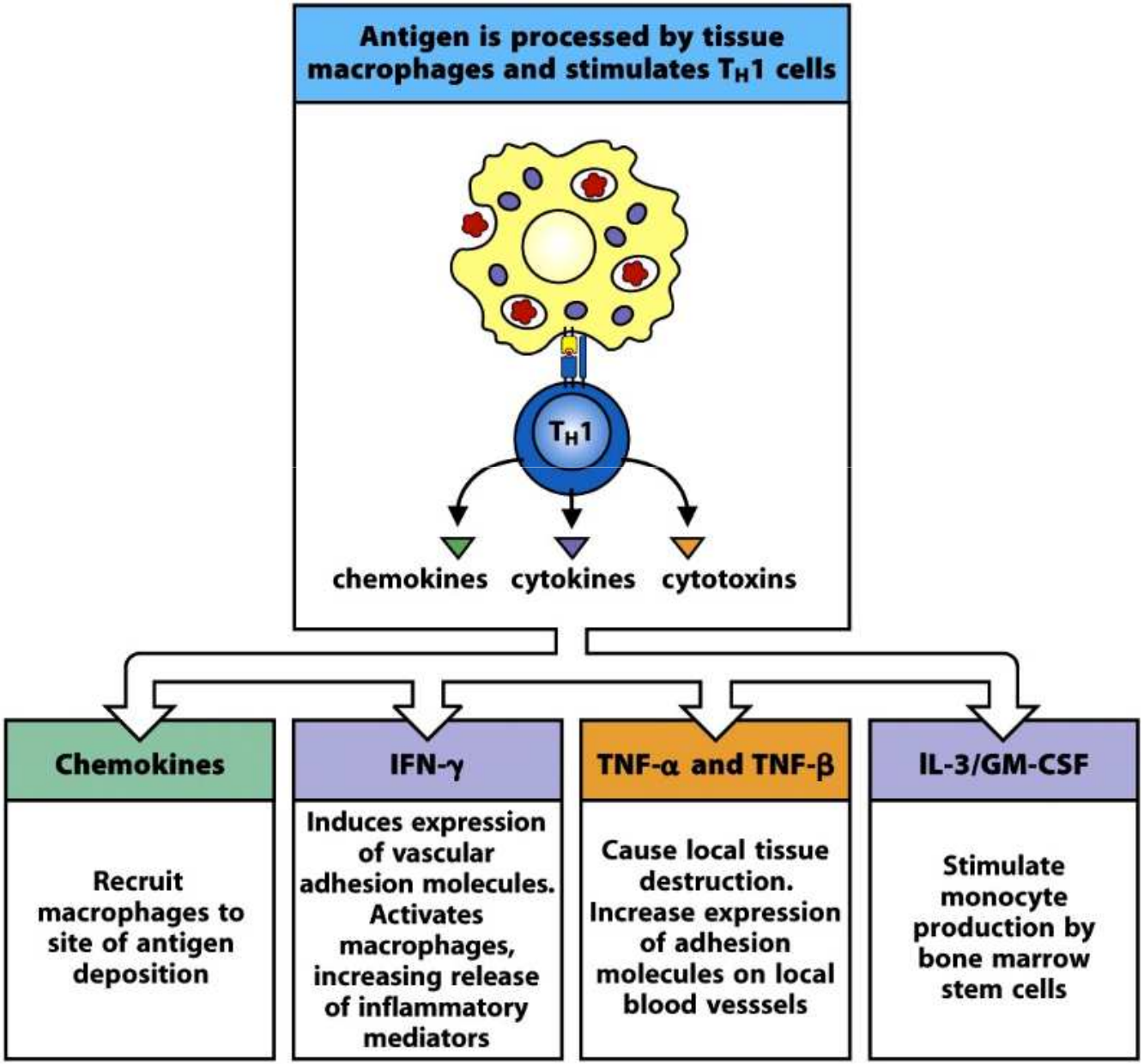
Tissue damage caused by CTL (type 4 HS)



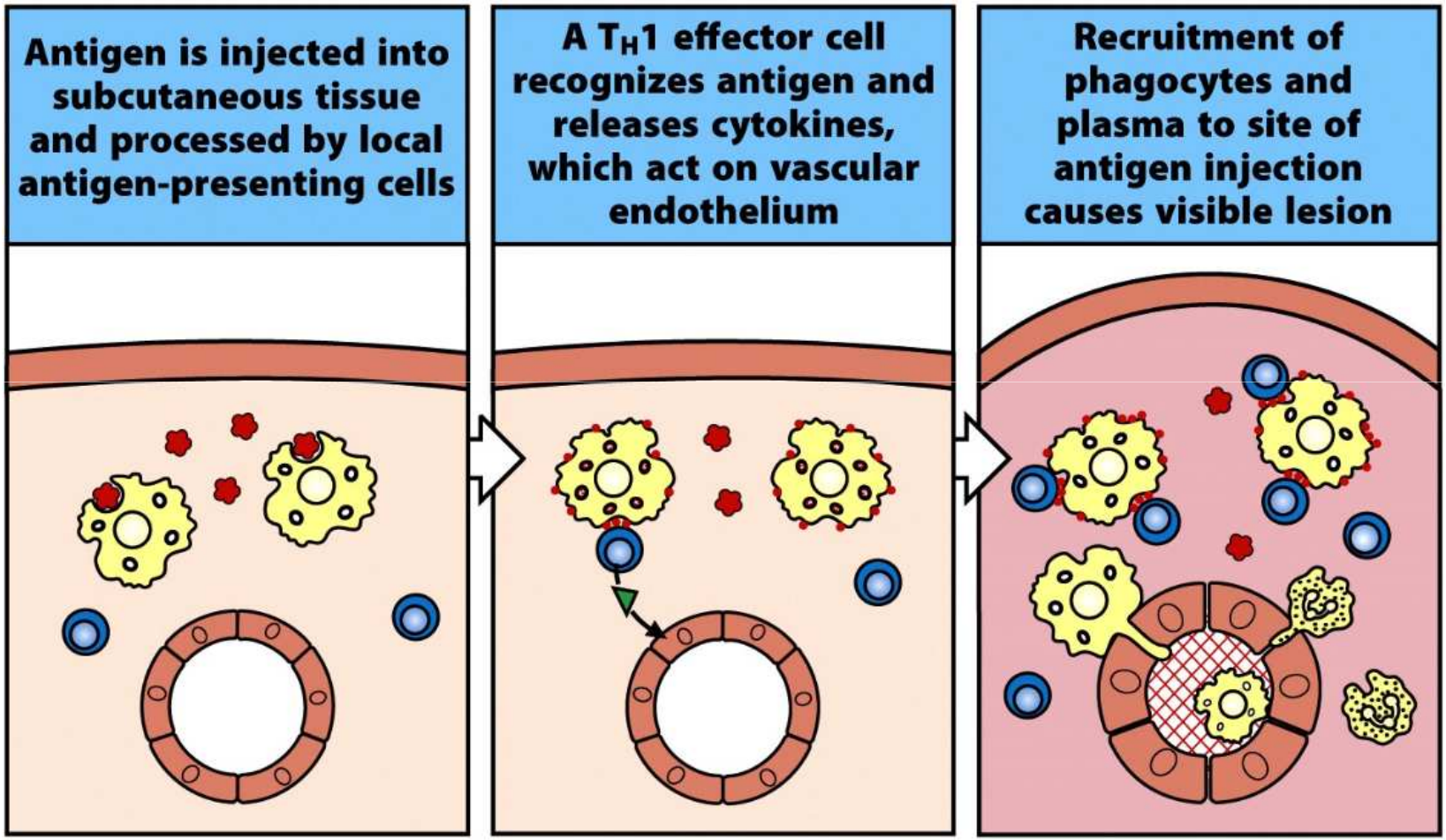
Delayed-type hypersensitivity (DTH) - (type 4 HS)

Type IV hypersensitivity reactions are mediated by antigen-specific effector T cells		
Syndrome	**Antigen**	**Consequence**
Delayed-type hypersensitivity	Proteins: Insect venom Mycobacterial proteins (tuberculin, lepromin)	Local skin swelling: Erythema Induration Cellular infiltrate Dermatitis
Contact hypersensitivity	Haptens: Pentadecacatechol (poison ivy) DNFB Small metal ions: Nickel Chromate	Local epidermal reaction: Erythema Cellular infiltrate Vesicles Intraepidermal abscesses
Gluten-sensitive enteropathy (celiac disease)	Gliadin	Villous atrophy in small bowel Malabsorption

DTH: tissue damage caused by Th1 lymphocytes



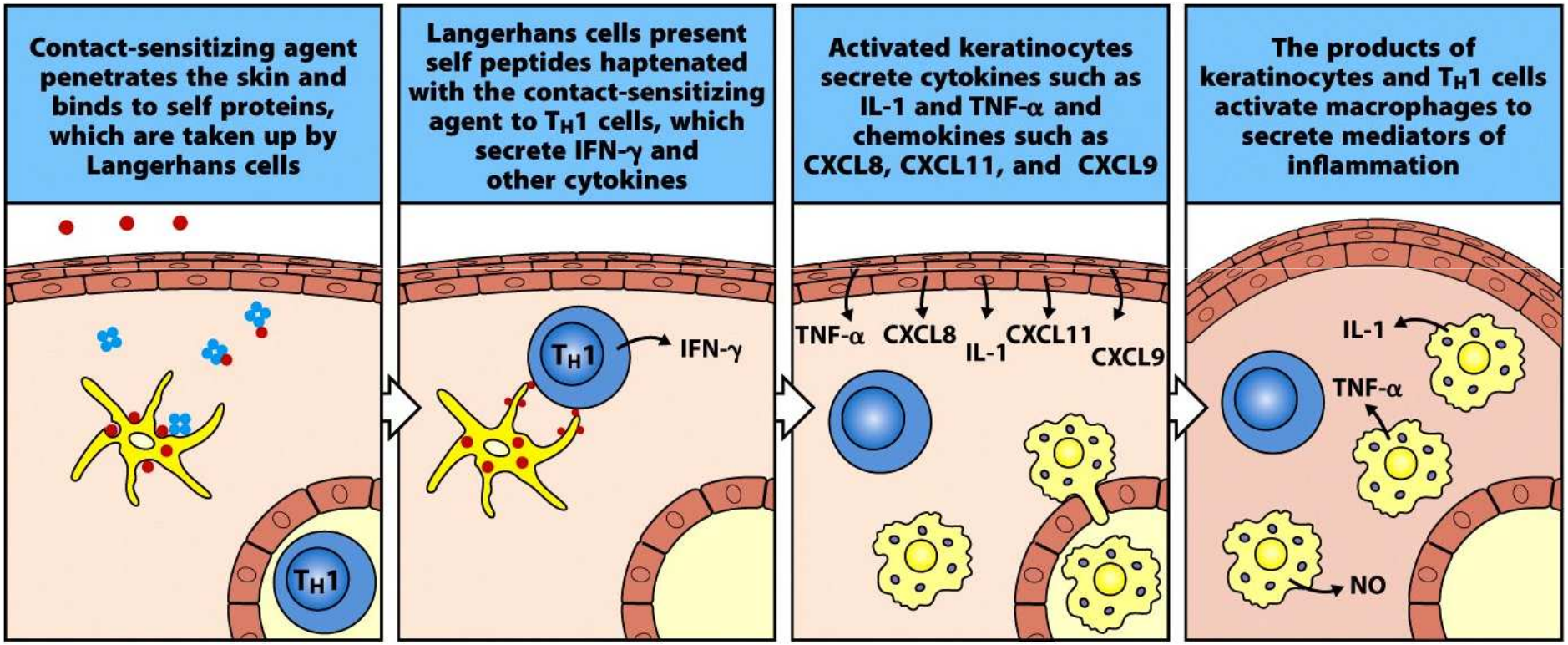
DTH: tissue damage caused by Th1 lymphocytes



Delayed-type hypersensitivity (DTH) movie

QuickTime™ and a
H.264 decompressor
are needed to see this picture.

DTH triggered by contact-sensitizing agents

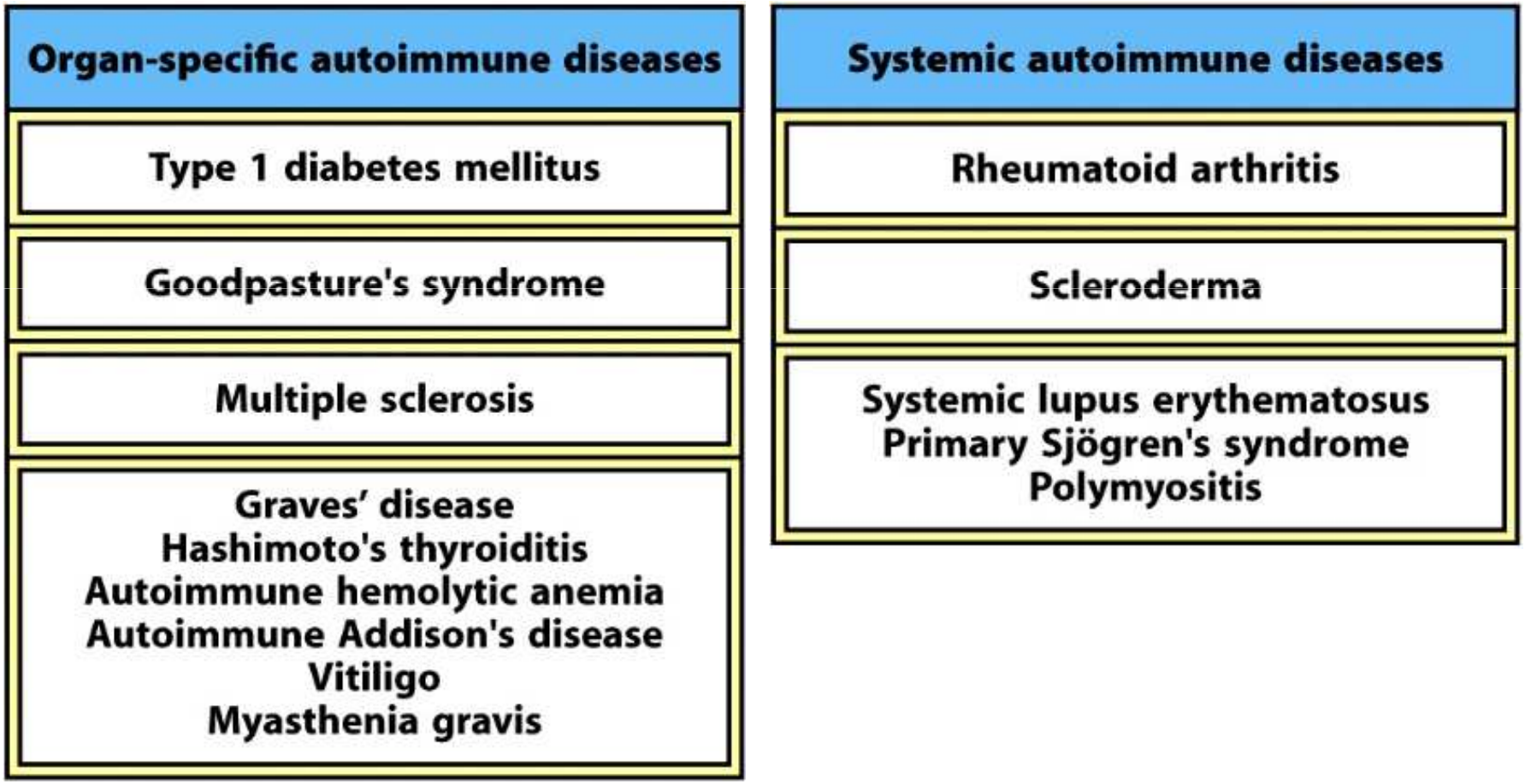


Autoinflammatory diseases

Disease (common abbreviation)	Clinical features	Inheritance	Mutated gene	Protein (alternative name)
Familial Mediterranean fever (FMF)	Periodic fever, serositis (inflammation of the pleural and/or peritoneal cavity), arthritis, acute-phase response	Autosomal recessive	*MEFV*	Pyrin (marenostrin)
TNF-receptor associated periodic syndrome (TRAPS) (also known as familial Hibernian fever)	Periodic fever, myalgia, rash, acute-phase response	Autosomal dominant	*TNFRSF1A*	TNF-α 55 kDa receptor (TNFR-I)
Pyogenic arthritis, pyoderma gangrenosum and acne (PAPA)		Autosomal dominant	*PTSTPIP*	CD2-binding protein 1
Muckle–Wells syndrome	Periodic fever, urticarial rash, joint pains, conjunctivitis, progressive deafness	Autosomal dominant	*CIAS1*	Cryopyrin
Familial cold auto inflammatory syndrome (FCAS) (familial cold urticaria)	Cold-induced periodic fever, urticarial rash, joint pains, conjunctivitis			
Chronic infantile neurologic, cutanean articular syndrome (CINCA)	Neonatal onset recurrent fever, urticaria rash, chronic arthropathy, facia dysmorphia, neurologic involvement		*CIAS1*	Cryopyrin
Hyper-IgD syndrome (HIDS)	Periodic fever, elevated IgD levels, lymphadenopathy	Autosomal recessive	*MVK*	Mevalonate synthase
Blau syndrome	Granulomatous inflammation of skin, eye, and joints	Autosomal dominant	*NOD2 (CARD15)*	NOD2 (CARD15)
Crohn's disease	Granulomatous inflammatory bowel disease, sometimes eye, skin, and joint granulomata	Complex trait		

Autoimmunity

Organ-specific and systemic autoimmune diseases



Systemic Lupus Erythematosus (SLE)

- **1:700 women 20-50 years old, women/men 10:1,**
- **rash, erithema (butterfly), arthritis, glomerulonephritis, vasculitis**

- **anti-nuclear auto-antibodies (DNA released by apoptotic cells)**
- **relapses triggered by sunlight (UV), infections**

- **damage caused by immuno-complexes**

- **DR2, DR3**

Type-1 diabetes mellitus (T1D)

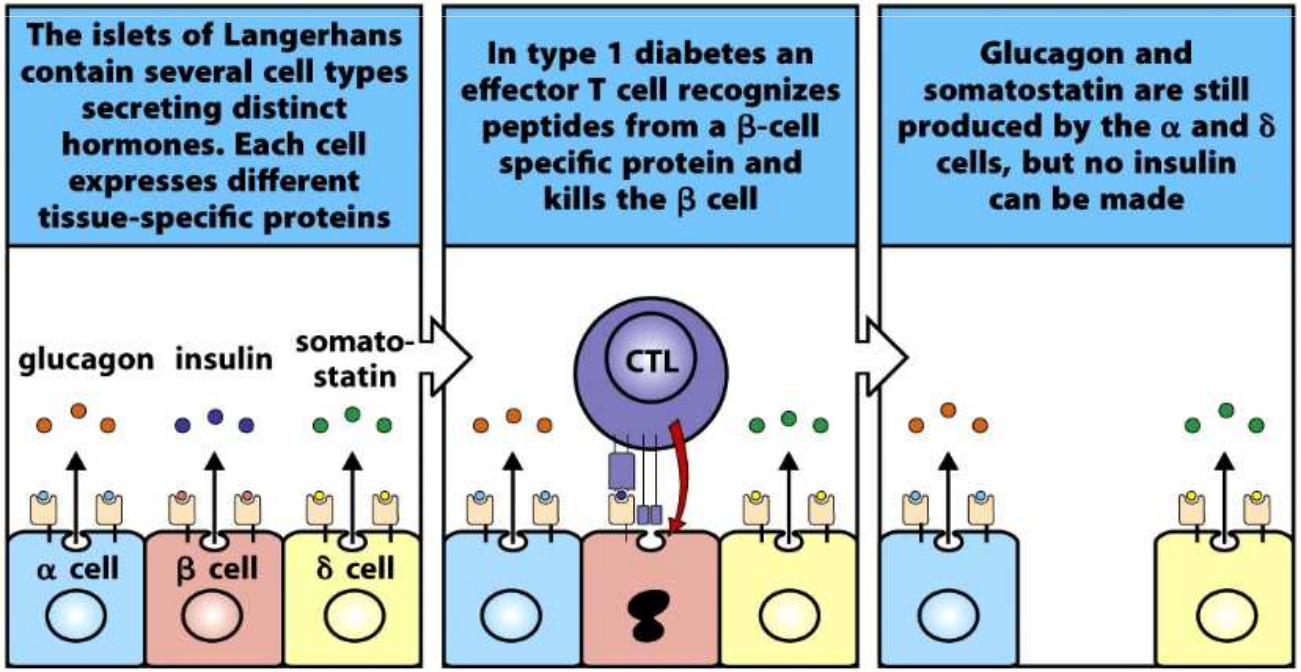
Insulin-dependent diabetes mellitus (IDDM)

- 1:50, peak incidence 10-15 years old

- Hyperglycemia, ketoacidosis
- Complications: atherosclerosis, ischemic necrosis of limbs, retina, kidney

- destruction of pancreatic insulin-producing beta cells (islets of Langerhans) mediated by CTL, anti-islet autoantibodies, cytokines (TNF, FasL, IL-1)

- DR3, DR4, DQ2, DQ8



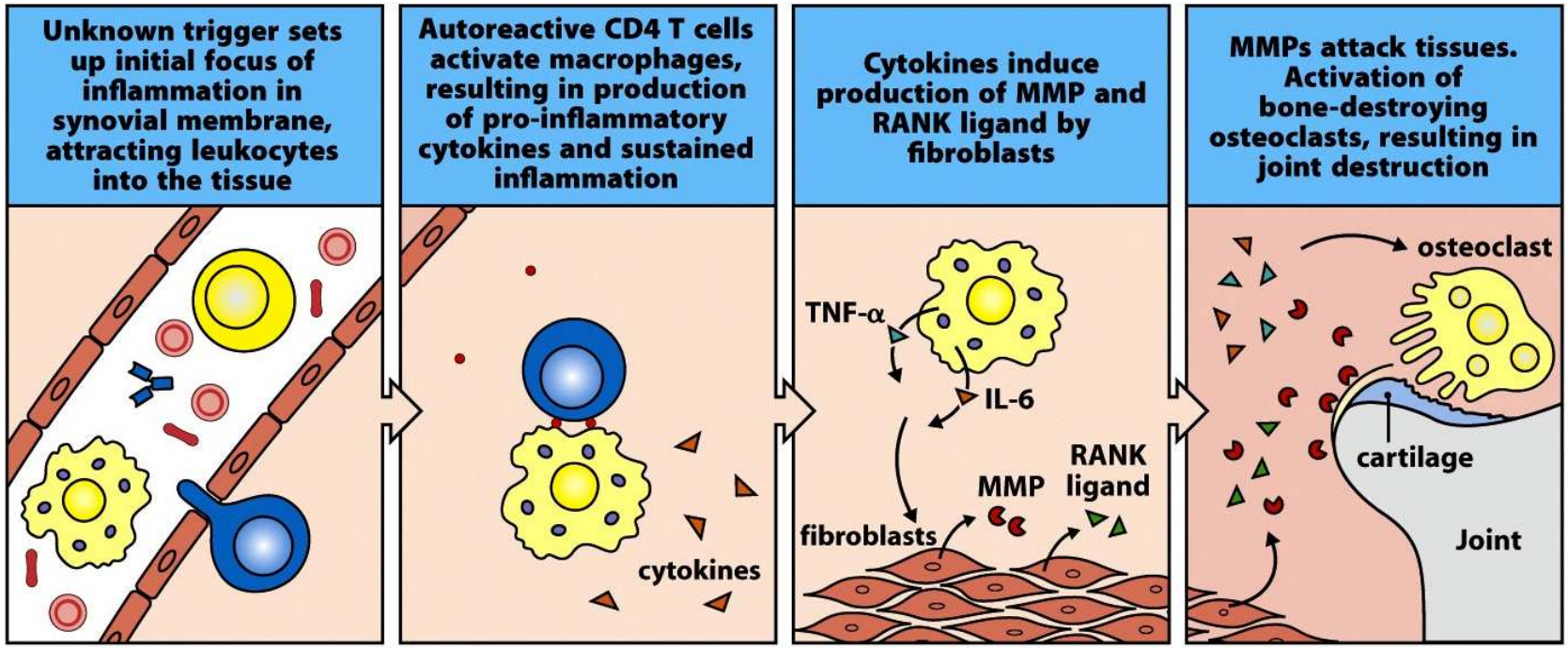
Rheumatoid arthritis

- arthritis of fingers, elbows, knees, ankles, shoulders

- inflammation (T, B lymphocytes, macrophages) of the synovium of joints
- destruction of joint cartilage and bone
- systemic vasculitis by immunocomplexes (reumathoid factors)

- bone, cartilage damage caused by cytokines (TNF, IL-6), proteases (MMP)
- activation of osteoclasts (RANKL)

- DR4



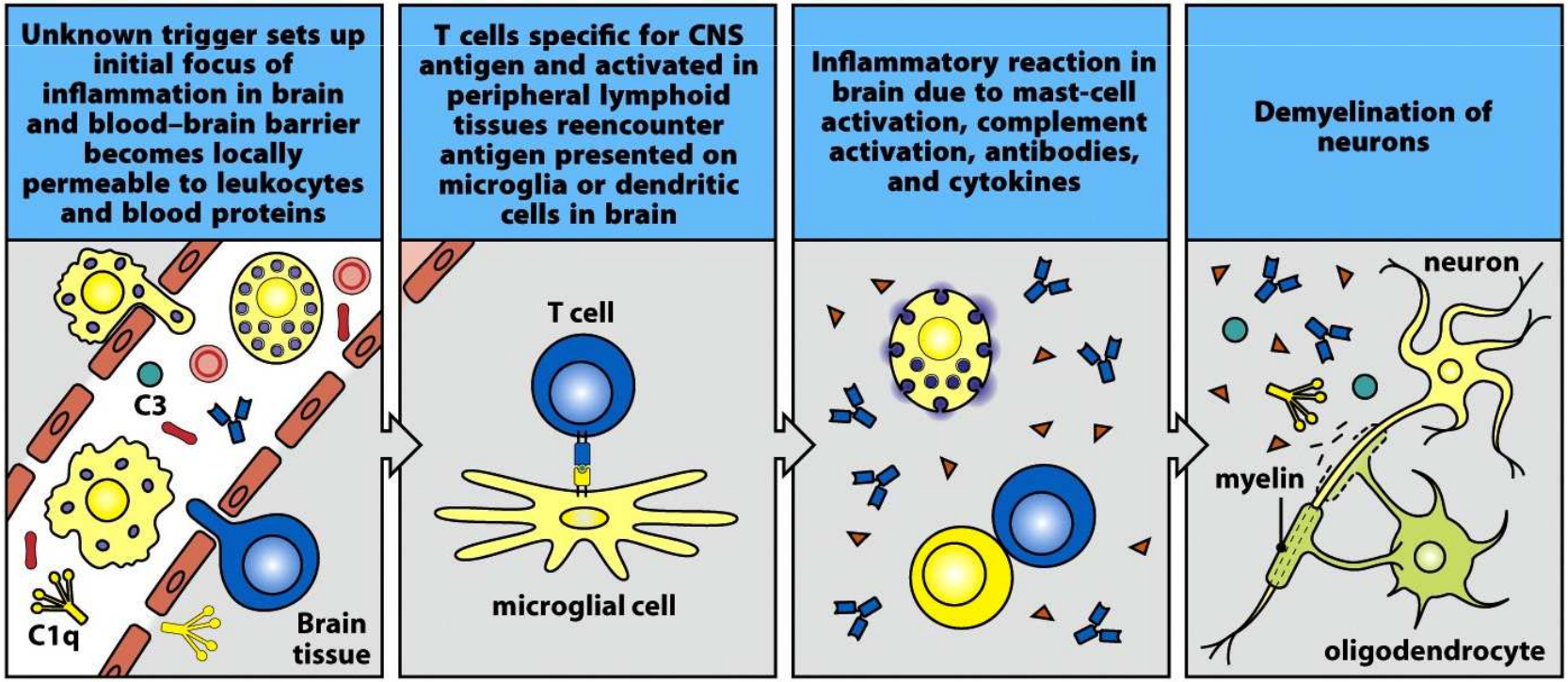
Multiple Sclerosis (MS)

- weakness, paralysis, ocular symptoms, sensory dysfunctions

- inflammation of the white matter, demyelination

- damage caused by myelin basic protein (MBP)-reactive T lymphocytes
- cytokines (INF gamma, IL-2)

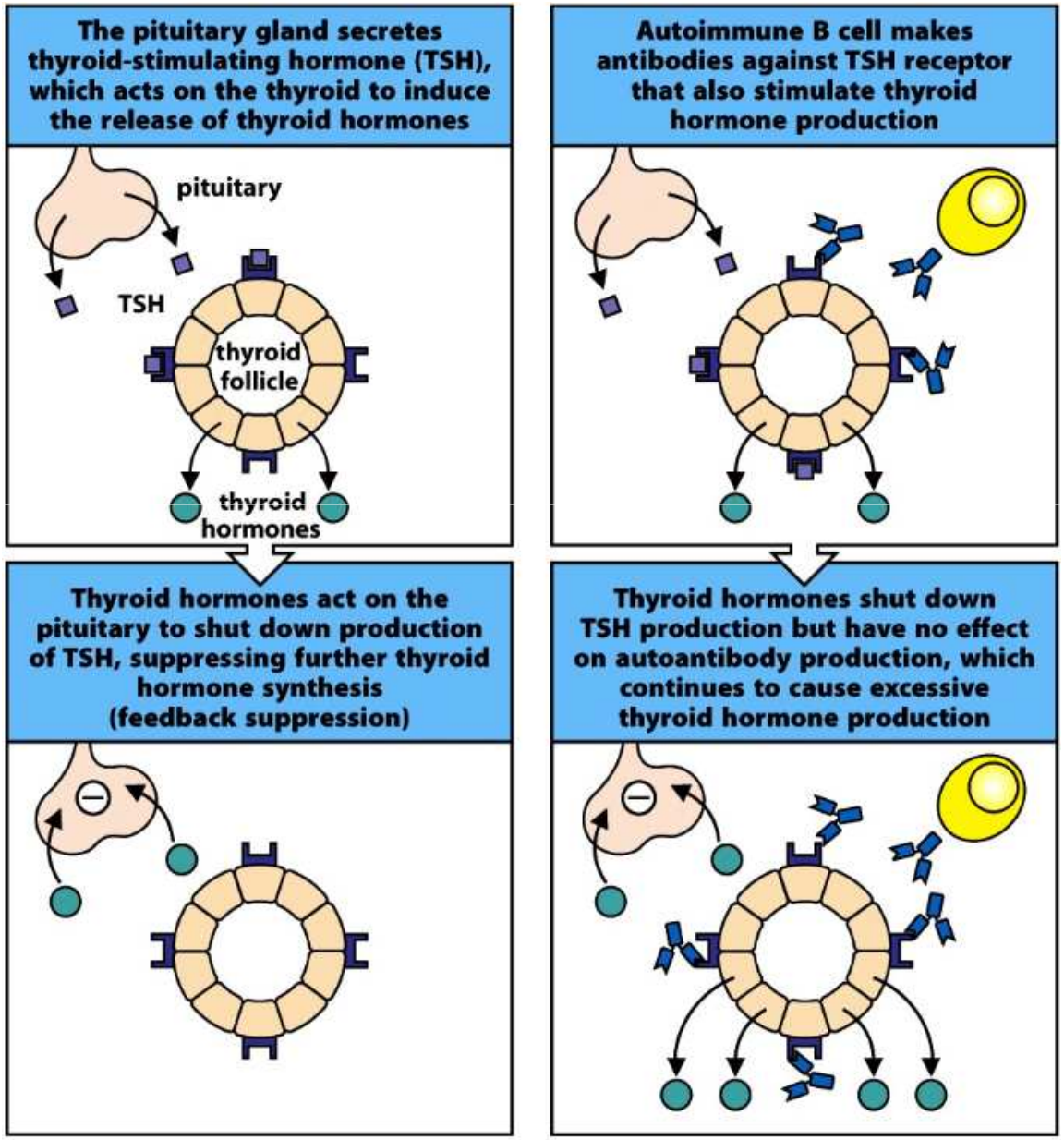
- DR2



Grave's disease

- **Hypethyroidism**

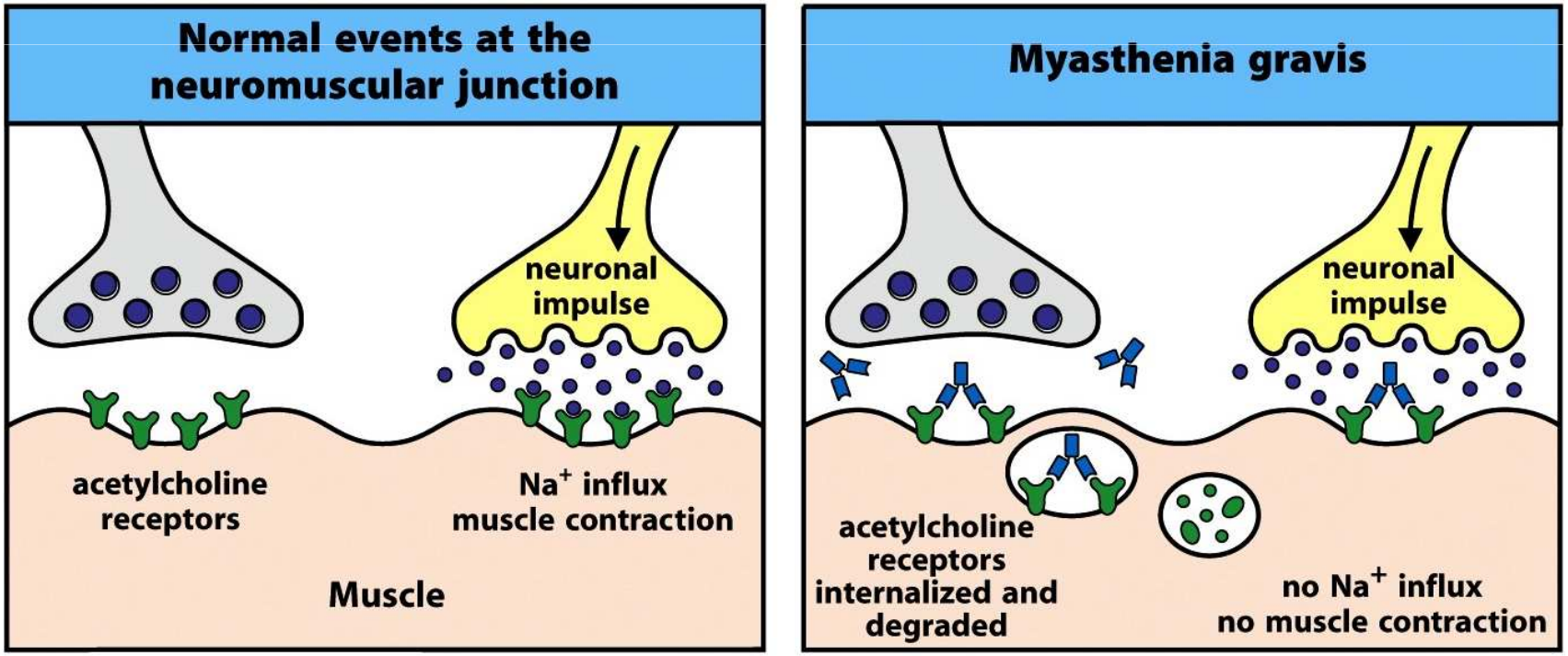
- **anti-TSHR autoantibodies**



Myastenia gravis

- chronic muscolar weakness, neurotransmission blockade

- autoantibodies against the nicotin receptor for acetylcholine



Diseases caused (mainly) by auto-antibodies

Disease	Target antigen	Mechanisms of disease	Clinicopathologic manifestations
Autoimmune hemolytic anemia	Erythrocyte membrane proteins (Rh blood group antigens, I antigen)	Opsonization and phagocytosis of erythrocytes	Hemolysis, anemia
Autoimmune thrombocytopenic purpura	Platelet membrane proteins (gpIIb:IIIa integrin)	Opsonization and phagocytosis of platelets	Bleeding
Pemphigus vulgaris	Proteins in intercellular junctions of epidermal cells (epidermal cadherin)	Antibody-mediated activation of proteases, disruption of intercellular adhesions	Skin vesicles (bullae)
Vasculitis caused by ANCA	Neutrophil granule proteins, presumably released from activated neutrophils	Neutrophil degranulation and inflammation	Vasculitis
Goodpasture's syndrome	Noncollagenous protein in basement membranes of kidney glomeruli and lung alveoli	Complement- and Fc receptor-mediated inflammation	Nephritis, lung hemorrhage
Acute rheumatic fever	Streptococcal cell wall antigen; antibody cross-reacts with myocardial antigen	Inflammation, macrophage activation	Myocarditis, arthritis
Myasthenia gravis	Acetylcholine receptor	Antibody inhibits acetylcholine binding, down-modulates receptors	Muscle weakness, paralysis
Graves' disease (hyperthyroidism)	TSH receptor	Antibody-mediated stimulation of TSH receptors	Hyperthyroidism
Insulin-resistant diabetes	Insulin receptor	Antibody inhibits binding of insulin	Hyperglycemia, ketoacidosis
Pernicious anemia	Intrinsic factor of gastric parietal cells	Neutralization of intrinsic factor, decreased absorption of vitamin B_{12}	Abnormal erythropoiesis, anemia

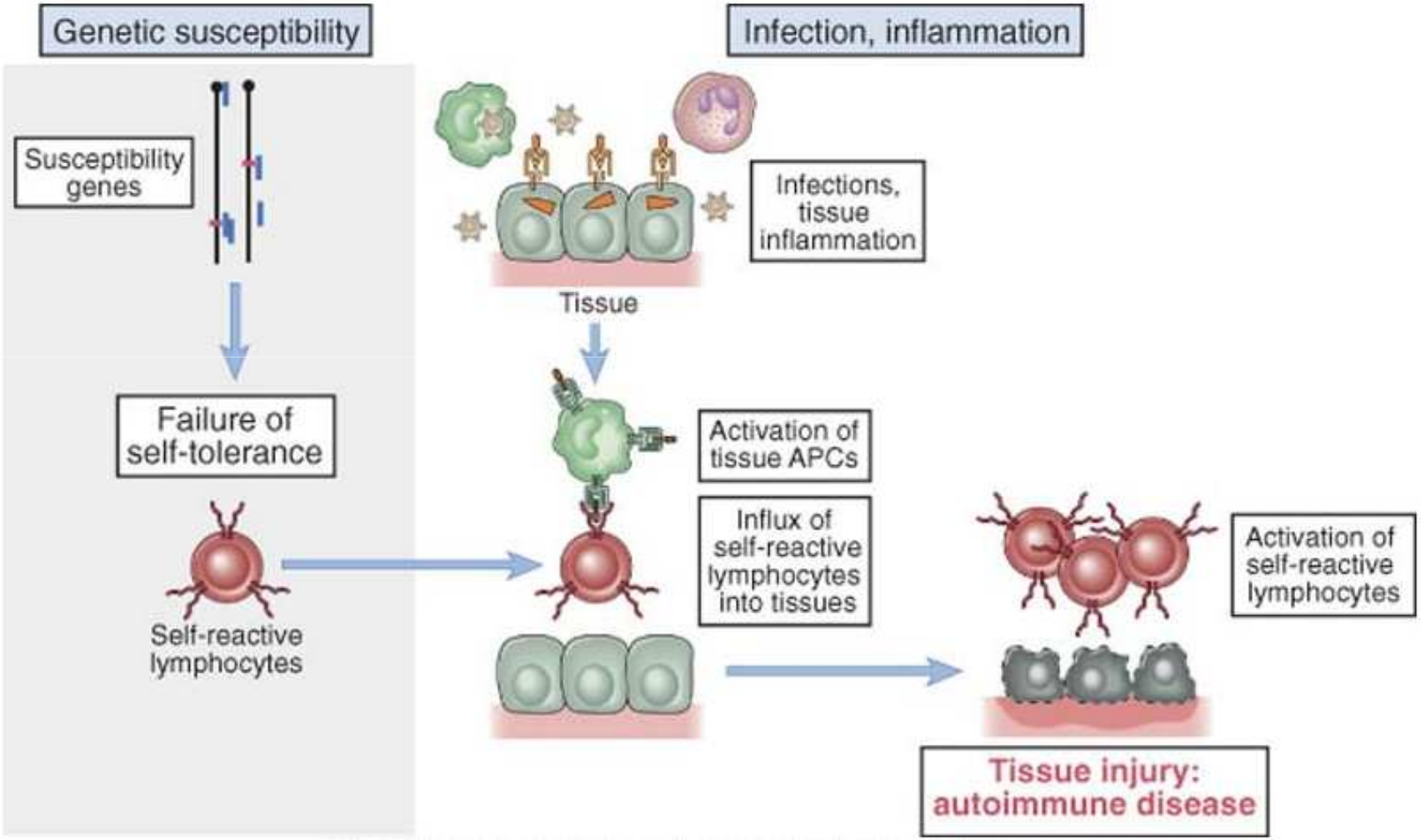
Diseases caused (mainly) by immunocomplexes

Disease	Antigen involved	Clinicopathologic manifestations
Systemic lupus erythematosus	DNA, nucleoproteins, others	Nephritis, arthritis, vasculitis
Polyarteritis nodosa	Hepatitis B virus surface antigen	Vasculitis
Poststreptococcal glomerulonephritis	Streptococcal cell wall antigen(s); may be "planted" in glomerular basement membrane	Nephritis
Serum sickness	Various proteins	Arthritis, vasculitis, nephritis

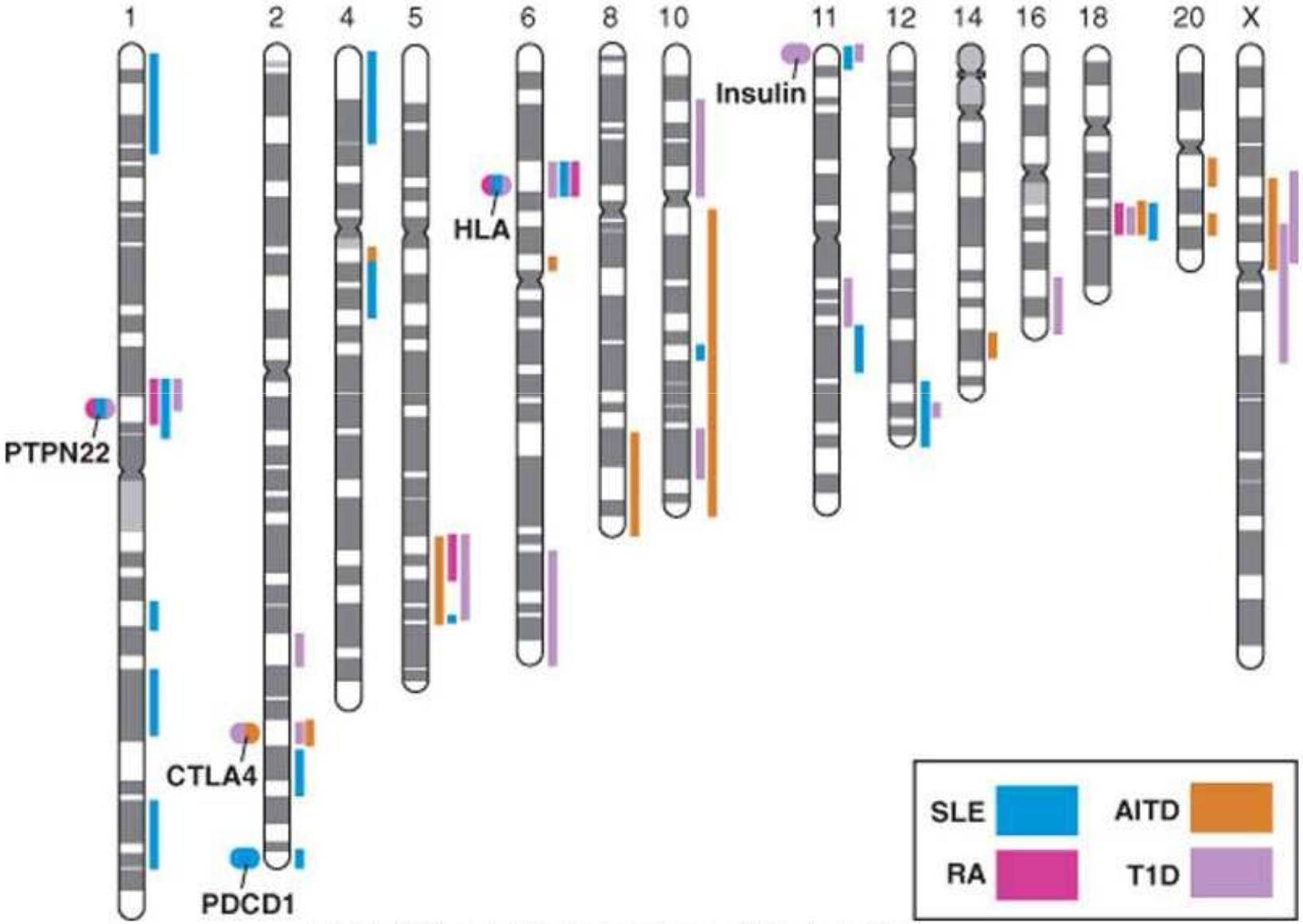
Diseases caused (mainly) by cytotoxic T lymphocytes

Disease	Specificity of pathogenic T cells	Human disease	Animal models
Type I (insulin-dependent) diabetes mellitus	Islet cell antigens (insulin, glutamic acid decarboxylase, others)	Yes; specificity of T cells not established	NOD mouse, BB rat, transgenic mouse models
Rheumatoid arthritis	Unknown antigen in joint synovium	Yes; specificity of T cells and role of antibody not established	Collagen-induced arthritis, others
Multiple sclerosis, experimental autoimmune encephalomyelitis	Myelin basic protein, proteolipid protein	Yes; T cells recognize myelin antigens	EAE induced by immunization with CNS myelin antigens; TCR transgenic models
Inflammatory bowel disease (Crohn's, ulcerative colitis)	Unknown	Yes	Colitis induced by depletion of regulatory T cells, knockout of IL-10
Peripheral neuritis	P2 protein of peripheral nerve myelin	Guillain-Barre syndrome	Induced by immunization with peripheral nerve myelin antigens
Autoimmune myocarditis	Myocardial proteins	Yes (post-viral myocarditis); specificity of T cells not established	Induced by immunization with myosin or infection by Coxsackie virus

Genetic and environmental factors in autoimmunity



Susceptibility loci for autoimmune diseases



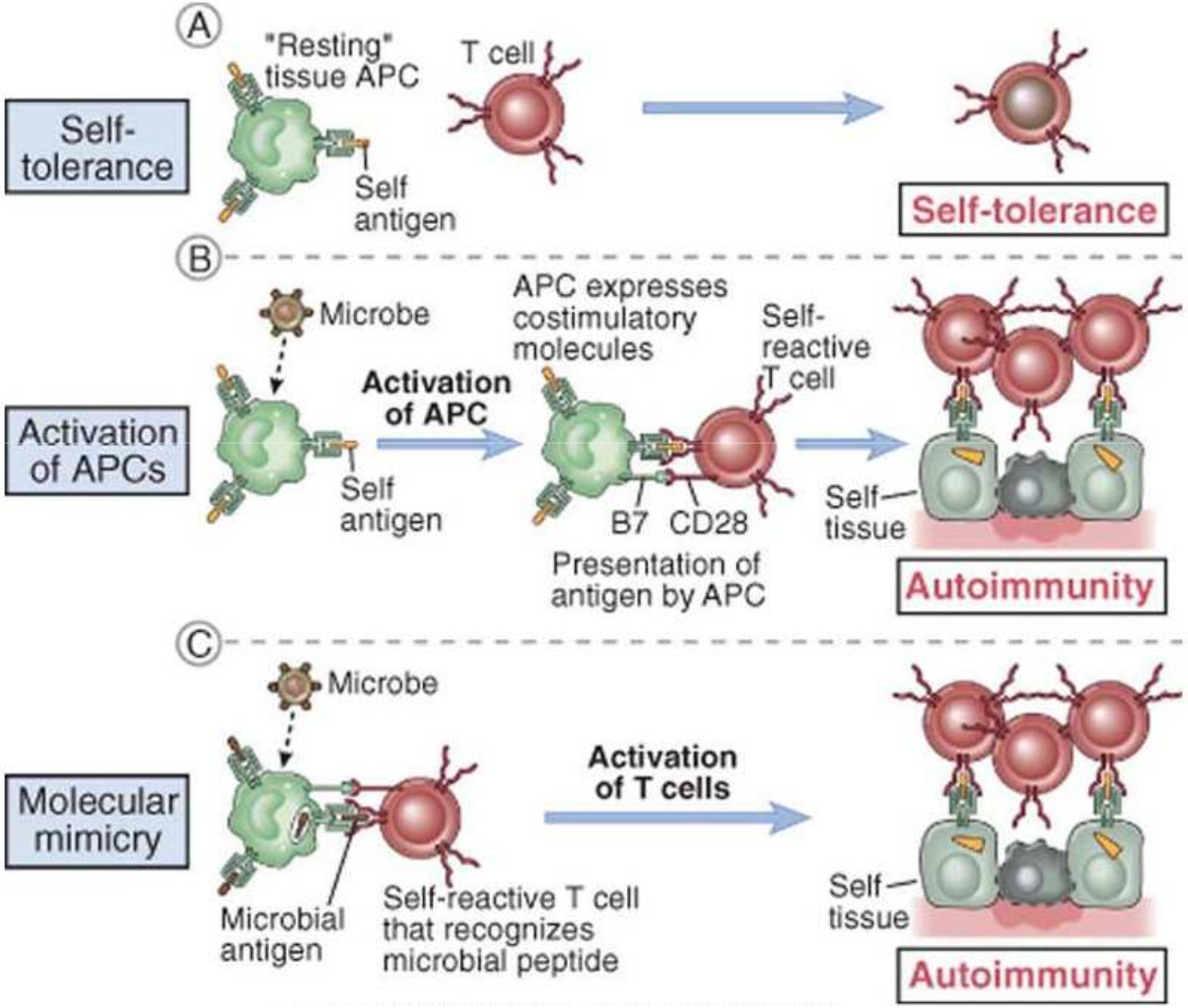
HLA-linkage and autoimmune diseases

Disease	HLA allele	Relative risk*
Rheumatoid arthritis	DR4	4
Insulin-dependent diabetes mellitus	DR3 DR4 DR3/DR4 heterozygote	5 5-6 25
Multiple sclerosis	DR2	4
Systemic lupus erythematosus	DR2/DR3	5
Pemphigus vulgaris	DR4	14
Ankylosing spondylitis	B27	90-100

Gene mutations that result in autoimmunity

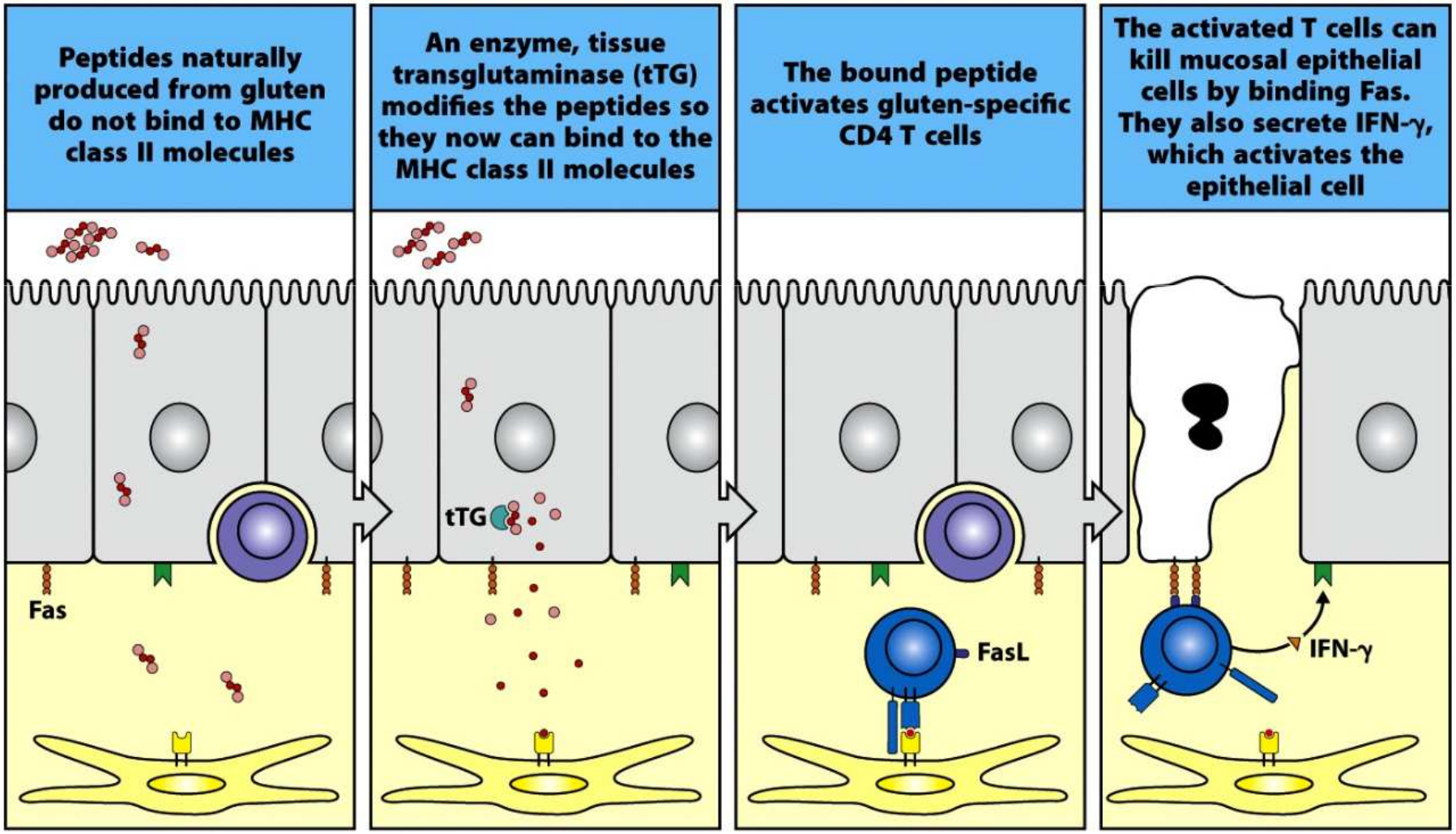
Gene	Phenotype of mutant or knockout mouse	Mechanism of failure of tolerance	Human disease?
AIRE	Destruction of endocrine organs by antibodies, lymphocytes	Failure of central tolerance	Autoimmune polyendocrine syndrome (APS)
C4	SLE	Defective clearance of immune complexes; failure of B cell tolerance?	SLE
CTLA-4	Lymphoproliferation; T cell infiltrates in multiple organs, especially heart; lethal by 3-4 weeks	Failure of anergy in $CD4^+$ T cells	CTLA-4 polymorphisms associated with several autoimmune diseases
Fas/FasL	Anti-DNA and other autoantibodies; immune complex nephritis; arthritis; lymphoproliferation	Defective deletion of anergic self-reactive B cells; reduced deletion of mature $CD4^+$ T cells	Autoimmune lymphoproliferative syndrome (ALPS)
FoxP3	Multi-organ lymphocytic infiltrates, wasting	Deficiency of regulatory T cells	IPEX **Immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome**
IL-2; IL-2Rα/β	Inflammatory bowel disease; anti-erythrocyte and anti-DNA autoantibodies	Defective development, survival or function of regulatory T cells	None known
SHP-1 **phosphatase**	Multiple autoantibodies	Failure of negative regulation of B cells	None known
PTPN22 **phosphatase**	Increased lymphocyte proliferation, antibody production	Reduced inhibition by tyrosine phosphatase?	PTPN22 polymorphisms are associated with several autoimmune diseases

Role of microbial infections in autoimmunity

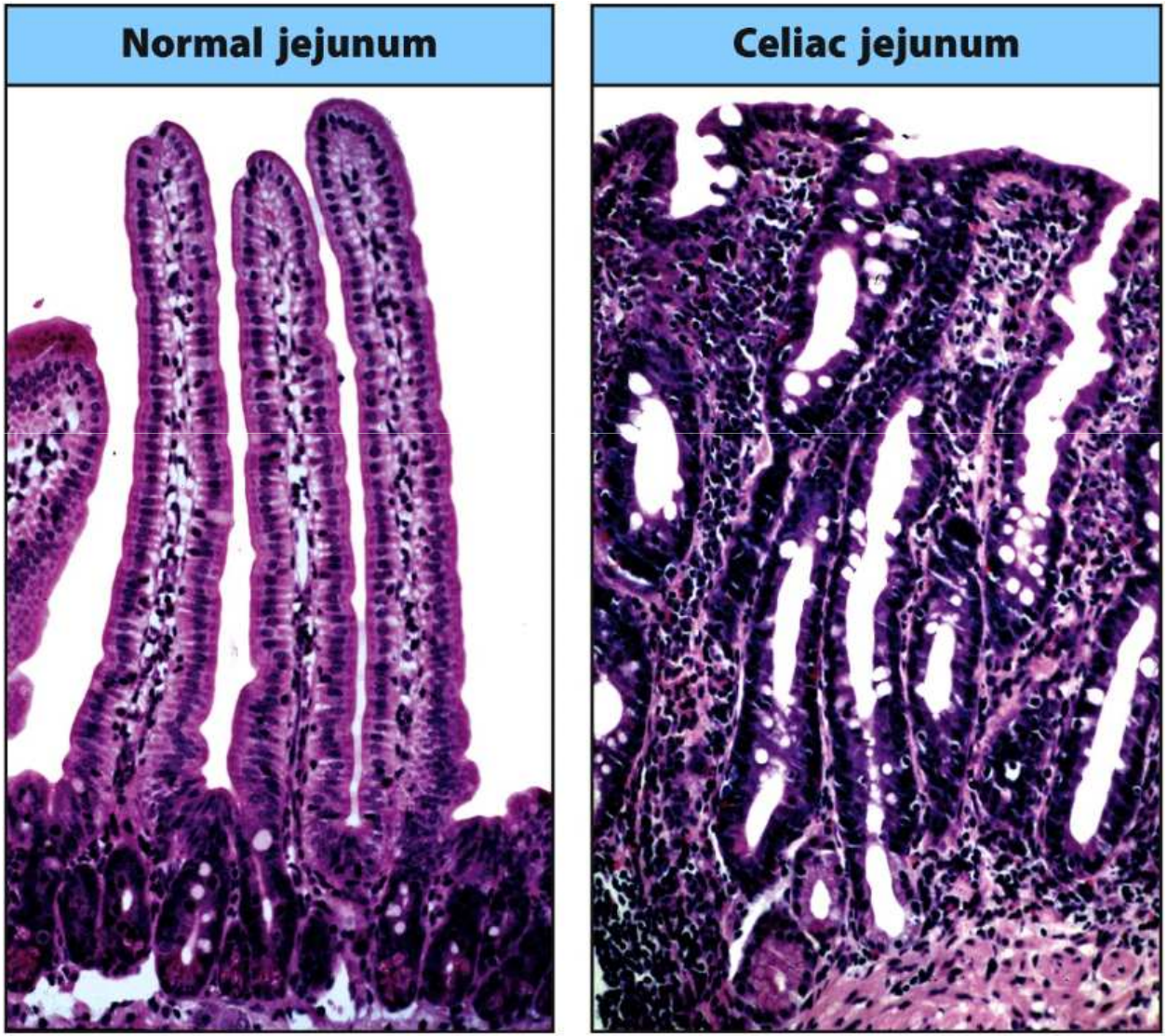


Celiac disease (Sprue)

Antigen: gliadin (a protein form gluten)



Pathological features of celiac disease



Destruction of villi, lymphocyte infiltration