Hypersensitivity -2

- Dr Esraa Al-Fraihat
- The University of Jordan
- 3rd year medical students
- 2025/2026

DISEASES CAUSED BY ANTIGEN-ANTIBODY COMPLEXES (type III hypersensitivity)

- **Antibodies (typically IgG)**may cause disease by forming immune complexes that deposit in blood vessels.
- Antigen–antibody complexes are produced during normal immune responses.
- These complexes cause disease only under specific conditions.
- Disease occurs when complexes are formed in excessive amounts.
- Inefficient removal by phagocytes allows complexes to persist.
- Persistent immune complexes become deposited in tissues.

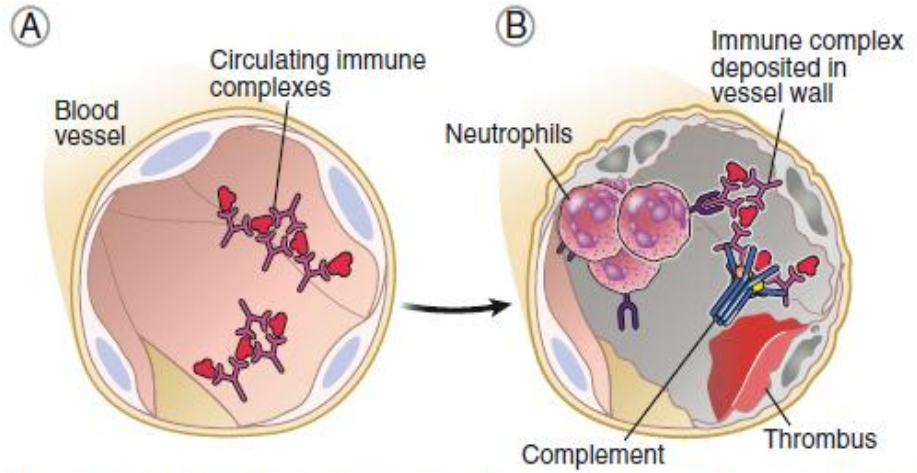


Fig. 11.9 Pathogenesis of immune complex–mediated diseases. Immune complexes are formed in the circulation and deposit in blood vessels, where they elicit complement- and Fc receptor–mediated inflammation.

Pathogenic Properties and Sites of Immune Complex Deposition

- Complexes containing **positively charged antigens** are particularly pathogenic.
- Positively charged antigens bind avidly to **negatively charged basement** membranes.
- Immune complexes usually deposit in blood vessels.
- Vessels with high-pressure plasma filtration are especially affected.
- Renal glomeruli and joint synovium are common sites.

Systemic Nature of Immune Complex Diseases

- Immune complex diseases tend to be **systemic**.
- Vessels in **any organ may** be affected.
- Kidneys and joints are particularly susceptible.
- This differs from antibody-mediated diseases targeting specific tissues.
- **Widespread vasculitis** is a characteristic manifestation.

Mechanism of Tissue Injury in Immune Complex Disease

- Deposited immune complexes activate **complement via antibody Fc regions.**
- Fc regions bind Fc receptors on **neutrophils.**
- Neutrophils become activated at the site of deposition.
- Activated neutrophils release proteases and reactive oxygen species.
- **Inflammation within vessel walls** is called vasculitis.

Vascular and Renal Consequences

- Vasculitis may cause **local hemorrhage**.
- **Thrombosis may** occur in inflamed vessels leading to **ischemic tissue injury.**
- Immune complexes in kidney glomeruli **cause glomerulonephritis**.
- Glomerulonephritis may **impair filtration** and cause r**enal failure.**

Immune complex disease	Antibody specificity	Clinicopathologic manifestations
Systemic lupus erythematosus	DNA, nucleoproteins, others	Nephritis, arthritis, vasculitis
Polyarteritis nodosa	In some cases, microbial antigens (e.g., Hepatitis B virus surface antigen); most cases unknown	Vasculitis
Post-streptococcal glomerulonephritis	Streptococcal cell wall antigen(s)	Nephritis
Serum sickness (clinical and experimental)	Various protein antigens	Systemic vasculitis, nephritis, arthritis
Arthus reaction (experimental)	Various protein antigens	Cutaneous vasculitis

Fig. 11.10 Immune complex diseases (type III hypersensitivity). Examples of human diseases caused by the deposition of immune complexes, as well as two experimental models. In the diseases, immune complexes are detected in the blood or in the tissues that are the sites of injury. In all the disorders, injury is caused by complement-mediated and Fc receptor–mediated inflammation.

Serum Sickness

- Serum sickness was the first immune complex disease studied.
- It occurred after **treatment with antitoxin-containing serum** from immunized animals.
- Patients **developed fever, rashes, and arthritis**.
- Antibodies were produced against **injected animal proteins**.
- Immune complexes formed and deposited **systemically.**

- **The Arthus Reaction**
- The Arthus reaction is **a localized** immune complex reaction.
- It is induced by subcutaneous injection of a protein antigen into a previously immunized individual.
- Local immune complex formation causes localized vasculitis.

Immune Complex Diseases in Autoimmunity and Infection

- Antibodies may be specific for self antigens or microbial antigens.
- In systemic lupus erythematosus, immune complexes contain self DNA and anti-DNA antibodies.
- These complexes deposit in blood vessels of multiple organs.
- Streptococcal infections can initiate immune complex disease (poststreptococcal glomerulonephritis) .
- Chronic viral (hepatitis) and parasitic (malaria) infections may also cause immune complex vasculitis.

Diseases Caused by T Lymphocytes - type IV hypersensitivity

- T lymphocytes play a central role in chronic immunologic diseases.
- Inflammation is a prominent component.
- Many effective therapies inhibit recruitment and activity of T lymphocytes.
- Tissue injury results from T lymphocyte-mediated mechanisms.
- These diseases differ from immune complex–mediated diseases.

Etiology of T Lymphocyte–Mediated Diseases

- Major causes include **autoimmunity and exaggerated or persistent responses to antigens.**
- Autoimmune reactions target cellular antigens with **restricted tissue distribution.**
- These diseases tend to be organ-specific rather than systemic.
- **Environmental antigens** can induce **contact sensitivity (poisen ivy, drugs and nickle)**.
- Chemicals modify self proteins, creating neoantigens recognized by T lymphocytes.

T Lymphocyte Responses to Microbes and Superantigens

- Tissue injury may accompany T lymphocyte responses to microbes.
- In tuberculosis, T lymphocyte responses develop against protein antigens of *Mycobacterium tuberculosis*.
- The response becomes chronic because infection is difficult to eradicate.
- Granulomatous inflammation causes tissue injury.
- Certain microbial toxins act as superantigens and activate large numbers of T lymphocytes.

Mechanisms of T Lymphocyte–Mediated Tissue Injury

- Tissue injury is caused mainly by inflammation induced by **cytokines**.
- **Cytokines** are produced primarily by **CD4 positive** T lymphocytes.
- Some injury is caused by killing of host cells by **CD8 positive** cytotoxic T lymphocytes.
- These mechanisms normally eliminate cell-associated microbes.
- The same mechanisms cause tissue injury in disease

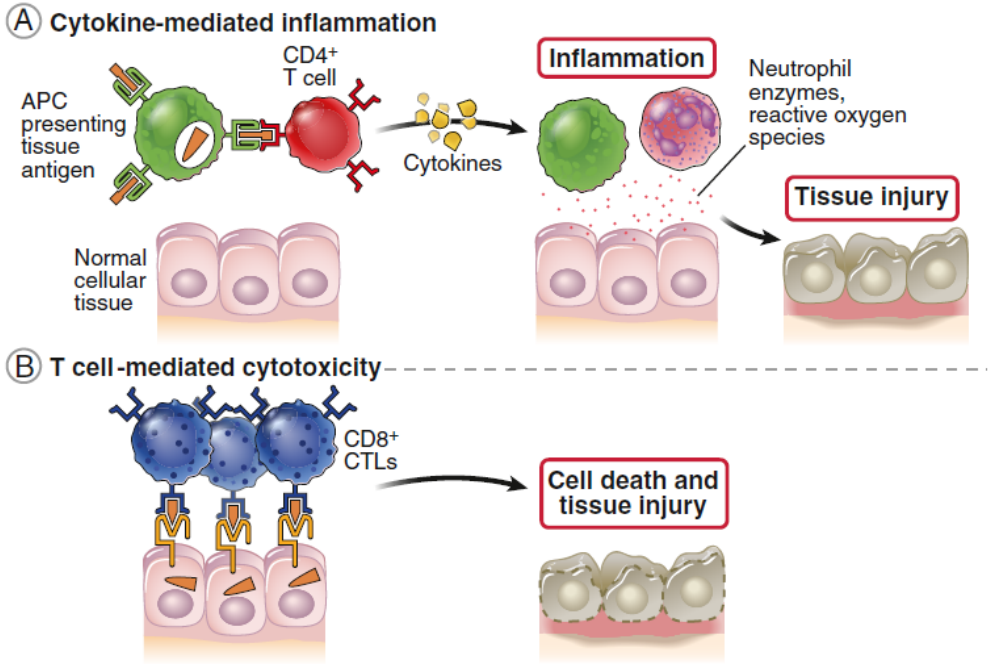


Fig. 11.11 Mechanisms of Tcell—mediated tissue injury (type IV hypersensitivity). T cells may cause tissue injury and disease by two mechanisms. **A,** Inflammation triggered by cytokines produced mainly by $CD4^+$ T cells in which tissue injury is caused by activated macrophages and neutrophils. **B,** Direct killing of target cells is mediated by $CD8^+$ cytotoxic T lymphocytes (CTLs). *APC,* Antigen-presenting cell.

T Helper Cell Subsets and Cytokines

- Th1 cells are a major source of interferon gamma.
- Interferon gamma is the principal macrophage-activating cytokine.
- Th17 cells are responsible for recruitment of leukocytes.
- Recruited leukocytes include neutrophils.
- Activated macrophages and neutrophils cause most tissue damage.

Delayed-Type Hypersensitivity: Mechanism

- Delayed-type hypersensitivity is a T lymphocyte-mediated reaction.
- It occurs 24 to 48 hours after antigen challenge.
- The delay reflects time required for circulating effector T lymphocytes to home to the site.
- At the site, T lymphocytes recognize antigen and secrete cytokines, inducing inflammation, increased vascular permeability, and leukocyte recruitment.

Pathology and Example of Delayed-Type Hypersensitivity

- Delayed-type hypersensitivity shows infiltrates of T lymphocytes and monocytes.
- Edema and fibrin deposition result from cytokine-induced vascular permeability.
- Tissue damage is caused mainly by macrophages activated by T lymphocytes.
- Delayed-type hypersensitivity reactions are used to **assess prior antigen exposure.**
- A skin reaction to **purified protein derivative (PPD)** indicates past or active mycobacterial infection

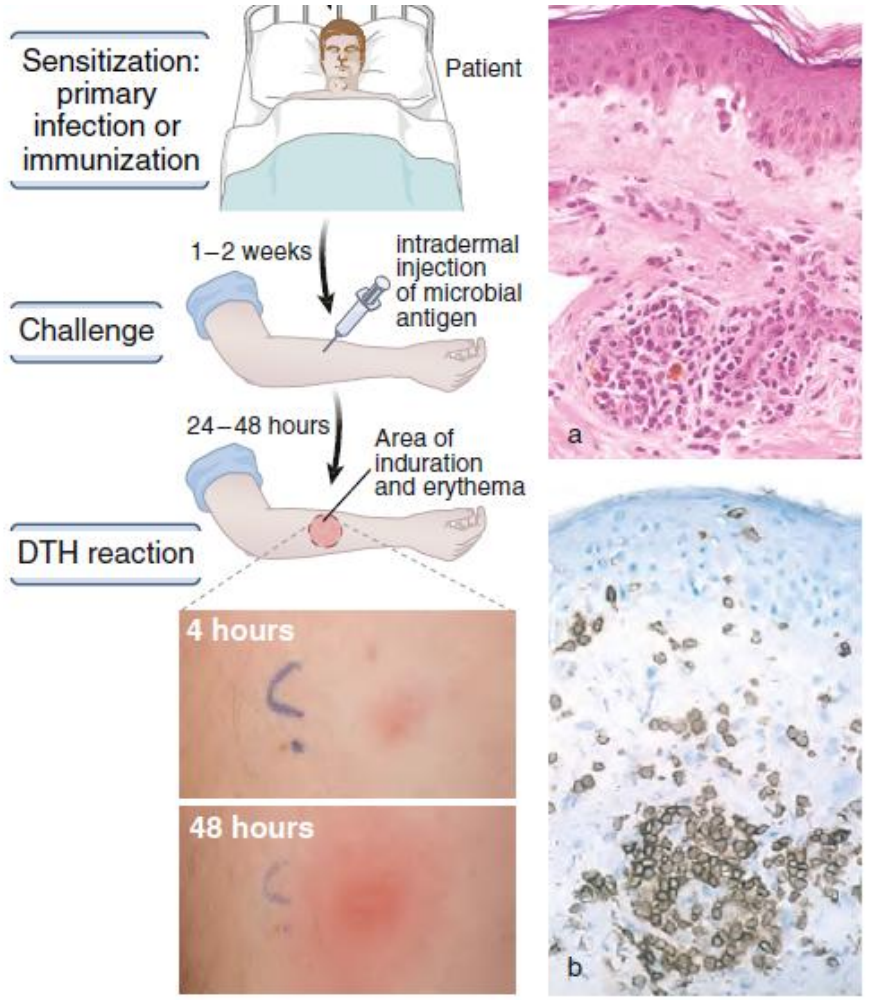


Fig. 11.12 Delayed-type hypersensitivity reaction in the skin. **A,** Individuals may be sensitized to an antigen (e.g., mycobacterial protein) by infection or vaccination. Subsequent cutaneous challenge with the antigen elicits a visible reaction (erythema, swelling) within 48 hours. **B,** A biopsy sample of the reaction shows peri-

Examples and Therapy of T Lymphocyte–Mediated Diseases

- Many organ-specific autoimmune diseases are caused by T lymphocytes and are chronic and progressive due to long-lived memory T lymphocytes.
- Examples include **type 1 diabetes**, **autoimmune myocarditis**, **multiple sclerosis**, **rheumatoid arthritis**, **psoriasis**, and **inflammatory bowel disease**.
- Therapy is designed to reduce inflammation and inhibit T lymphocyte activation; anti-inflammatory steroids have been the mainstay of treatment.

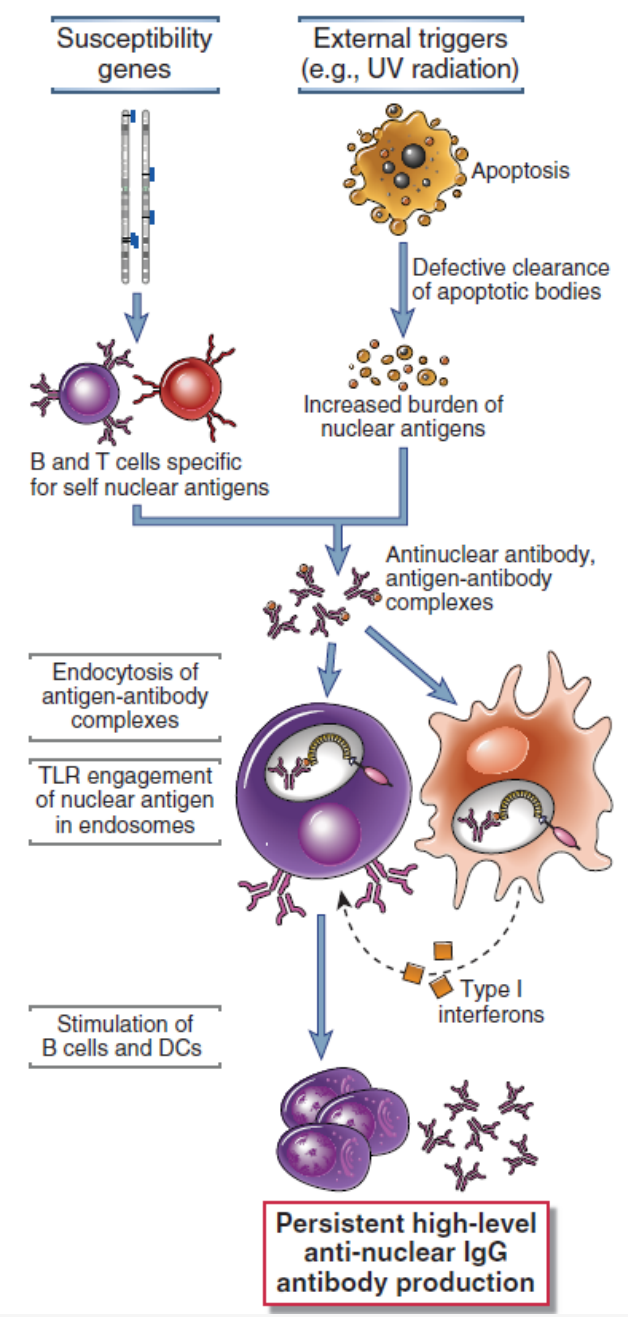
- Targeted therapies include monoclonal antibodies that block **tumor necrosis factor**, **interleukin-6 receptor**, **interleukin-17**, **interleukin-23**, and **interleukin-12 and interleukin-23**.
- Additional treatments include **Janus kinase inhibitors**, drugs that block costimulators such as **B7**, **B cell depletion with anti-CD20**, and experimental approaches using **regulatory T lymphocytes** or **interleukin-2** to expand regulatory T lymphocytes.

Disease	Specificity of pathogenic T cells	Clinicopathologic manifestations
Rheumatoid arthritis	Unknown antigens in joint	Inflammation of synovium and erosion of cartilage and bone in joints
Type 1 diabetes	Pancreatic islet antigens	Impaired glucose metabolism, vascular disease
Crohn's disease	Unknown, ? role of intestinal microbes	Inflammation of the bowel wall; abdominal pain, diarrhea, hemorrhage
Psoriasis	Unknown	Chronic skin inflammation
Multiple sclerosis	Myelin proteins	Demyelination in the central nervous system, sensory and motor dysfunction
Contact sensitivity (e.g. poison ivy, drug reaction)	Modified skin proteins	DTH reaction in skin, rash
Chronic infections (e.g., tuberculosis)	Microbial proteins	Chronic (e.g., granulomatous) inflammation

Fig. 11.13 Human T cell–mediated diseases. Diseases in which T cells play a dominant role in causing tissue injury; antibodies and immune complexes may also contribute. Note that rheumatoid arthritis and type 1 diabetes are autoimmune disorders. Crohn's disease, an inflammatory bowel disease, is likely caused by reactions against microbes in the intestine and may have a component of autoimmunity. The other diseases are caused by reactions against foreign (microbial or environmental) antigens. In most of these diseases, the role of T cells is inferred from the detection and isolation of T cells reactive with various antigens from the blood or lesions, and from the similarity with experimental models in which the involvement of T cells has been established by a variety of approaches. The specificity of pathogenic T cells has been defined in animal models and in some of the human diseases. Although multiple sclerosis (MS) has long been considered a T cell–mediated disease, the most successful therapy for MS is depletion of B cells. Viral hepatitis and toxic shock syndrome are disorders in which T cells play an important pathogenic role, but these are not considered examples of hypersensitivity. *DTH,* Delayed-type hypersensitivity.

Systemic Lupus Erythematosus

- Chronic **multisystem** autoimmune disease predominantly **affects women** with a female to male ratio 10:1.
- Manifestations: rashes arthritis and glomerulonephritis, involvement of blood cells and the central nervous system.
- Autoantibodies including **antinuclear antibodies ANA p**articularly antibodies against **double stranded DNA.**
- **Immune complexes** formed by these antibodies circulate and deposit in tissues (glomerulonephritis arthritis and small vessel vasculitis).



Pathogenesis and Therapy of SLE

- **Loss of tolerance** is self reactive B and T lymphocytes.
- **HLA DR2, HLA DR3** and **complement deficiency** as C1q C2 and C4 increase genetic susceptibility.
- UV light exposure induces apoptosis and release of nuclear antigens stimulate autoreactive lymphocytes.
- Plasmacytoid dendritic cells produce increased **IFN a** which amplifies immune activation.
- Antibodies against INF a, B cell depletion with anti CD20 antibodies and blockade of B cell growth factor BAFF are treatment options.

Rheumatoid Arthritis

- A chronic inflammatory disease involving small and large joints.
- Characterized by synovial inflammation **with progressive destruction of cartilage and bone.**
- Mediated by **CD4 positive Th 1 and Th 17 cells**, **activated B cell**, plasma cells **and macrophages**.
- **TNF, IL-1, IL- 6, IL 17 and IFN-γ** are also detected in synovial fluid.
- These immune processes produce the characteristic joint damage seen in rheumatoid arthritis.

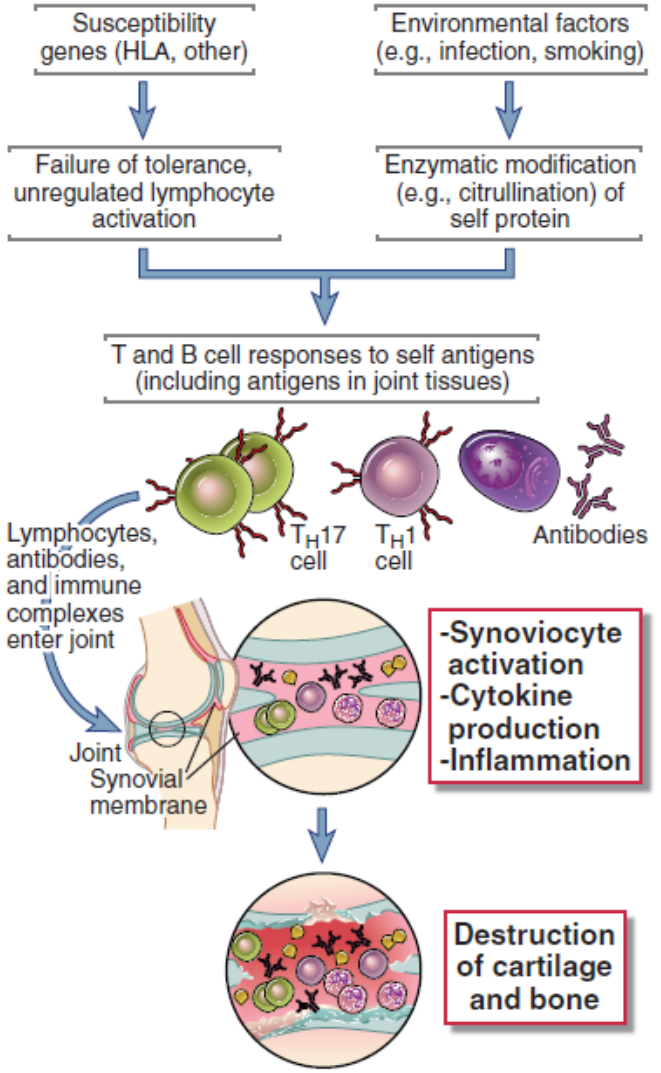


FIGURE 18–10 A model for the pathogenesis of rheumatoid arthritis. According to this hypothesis, citrullinated proteins induced by environmental stimuli elicit T cell and antibody responses in genetically susceptible individuals. The T cells and antibodies enter joints, respond to the self proteins, and cause tissue injury mainly by cytokine secretion and perhaps also by antibody-dependent effector mechanisms. Protein modifications other than citrullination may lead to the same result.

Pathogenesis and Therapy of Rheumatoid Arthritis

- **HLA DR4** associated with increased genetic susceptibility.
- Environmental factors induce modification of self proteins leading to loss of tolerance and immune activation.
- **Activated T cells** induce the release of proteolytic **enzymes and RANK ligand** which **increases osteoclast mediated bone destruction.**
- **Rheumatoid factor** and antibodies against cyclic citrullinated peptides **Anti- CCP** are important diagnostic markers.
- Therapies target TNF, IL-1, IL-6, B7 costimulatory pathways, IL-17 and CD 20 on B cells.

Diabetes Mellitus

- A metabolic disease caused by immune mediated destruction of insulin producing beta cells in the pancreas.
- Usually begins in childhood or adolescence and is characterized by hyperglycemia and ketoacidosis.
- Pancreatic islets show lymphocytic infiltration and beta cell necrosis known as insulitis.
- Autoantibodies against islet cells and insulin are detectable and predict disease development.

Pathogenesis and Therapy of Type 1 Diabetes

- **HLA DR3, DR4, DQ2 and DQ8** alleles are associated with increase genetic susceptibility.
- Destruction is mediated **by CD4 positive Th1cells CD8 positive** cytotoxic T cells, **TNF** and **IL-1**.
- Environmental factors including **viral infections** may initiate immune responses against beta cells.
- New therapies focus on inducing immune tolerance using islet antigen peptides and regulatory T cells.

Multiple Sclerosis and Experimental Autoimmune Encephalomyelitis

- An autoimmune disease of the central nervous system characterized by inflammation and demyelination (white matter).
- **CD4 positive Th1 and Th17** react against myelin antigens in the brain and spinal cord, **macrophage** activation leads to destruction of myelin and impaired nerve conduction.
- Experimental autoimmune encephalomyelitis is an animal model induced by immunization with myelin antigens and demonstrates T cell mediated demyelination.

Pathogenesis and Therapy of MS and EAE

- **HLA DR2** and **polymorphisms affecting T cell regulation** increase susceptibility.
- **Myelin specific T cells** migrate into the central nervous system where they release cytokines and recruit additional immune cells.
- Treatment options: administration of β-interferon, antibody against VLA-4 integrins, and fingolimod (FTY720) interfering with leukocyte migration to CNS,.
- B cell depletion and experimental tolerance induction using myelin basic protein are also useful options.