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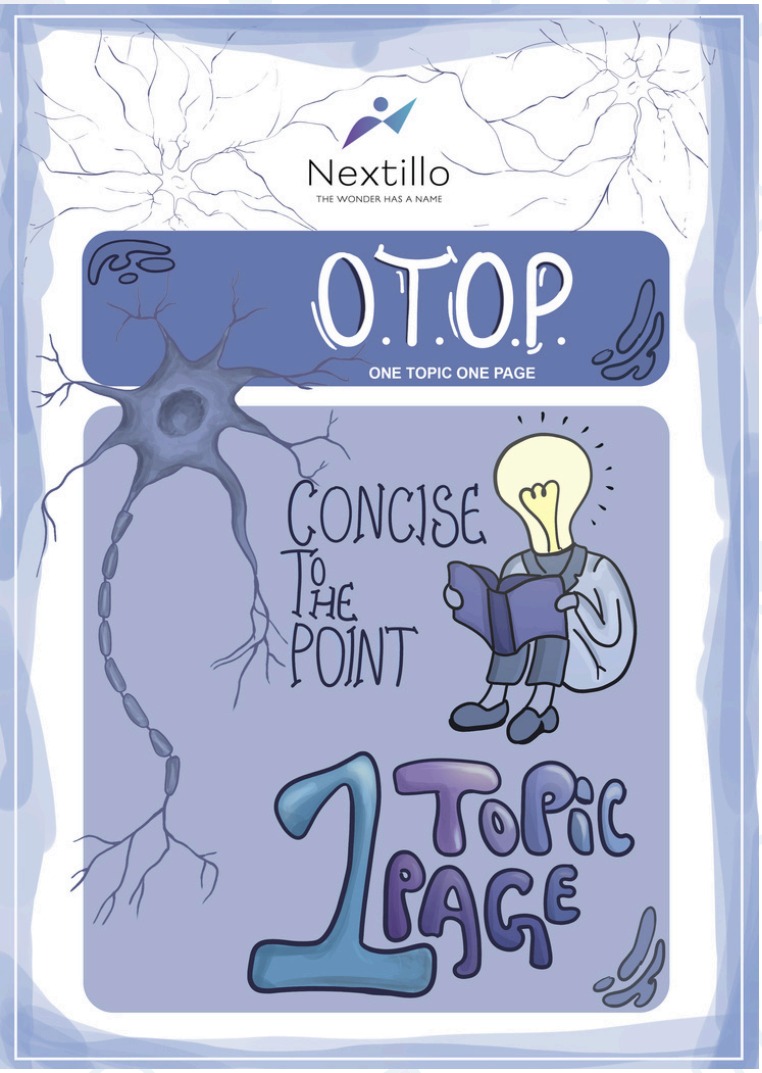

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MICROSOMAL & NON-MICRSOMAL ENZYMES

Both microsomal and non-microsomal enzymes are essential for maintaining cellular health, regulating metabolism, and protecting organisms from harmful substances. Microsomal enzymes, primarily localized in the endoplasmic reticulum, are crucial for drug metabolism and detoxification.

Microsomal enzymes:

- *Properties: The microsomal enzymes are mostly membrane-bound enzymes. They are involved in the drug metabolism and detoxification.*
- *Location: Primarily located in endoplasmic reticulum of cells.*
- *Examples: Cytochrome P450 enzymes (CYPs) are most commonly microsomal enzymes involved in drug metabolism. Other examples include CYP3A4, CYP2D6, CYP2C9, etc.*
- *Reaction : Microsomal enzymes catalyze the oxidation, reduction, and hydrolysis reactions of various endogenous and metabolise exogenous substances, including drugs, toxins, and hormones.*
- *Normally present: In the liver most commonly , but also found in intestines and lungs.*
- *Disorder associated: Genetic polymorphisms in microsomal enzymes, such as CYP2D6, can lead to the variable drug response and toxicity.*
- *Function: They contribute significantly to the drug interactions and variability in the drug response among individuals.*

Non-microsomal enzymes:

- *Properties: the non-microsomal enzymes are soluble enzymes found in cytoplasm or other cellular compartments outside endoplasmic reticulum.*
- *Location: they are distributed throughout cytoplasm and the other cellular compartments.*
- *Examples: like alcohol dehydrogenase, aldehyde dehydrogenase, acetylcholinesterase etc.*
- *Reaction: the non-microsomal enzymes catalyze oxidation, reduction, hydrolysis, and conjugation.*
- *Normally present : liver, kidneys, brain, and muscles.*
- *disorder associated: Genetic deficiencies of non-microsomal enzymes can lead to metabolic disorders such as the alcohol intolerance (due to deficiency of the enzyme alcohol dehydrogenase) or hereditary hemochromatosis (due to the mutations in the HFE gene).*
- *Function: Non-microsomal enzymes are involved in the fundamental metabolic processes such as alcohol metabolism, neurotransmitter degradation.*
- *They also participate in detoxification (to make non polar to polar compound to make it soluble) of endogenous and exogenous substances, but less commonly as compared to microsomal enzymes.*

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NON- HLA GENES

These genes are necessary in presenting antigens to the T-cells and strongly associated with autoimmune disorders.These genes encodes proteins involving in immune cell signaling, regulation, and function. Variation or mutation in non-HLA genes can cause disruption of immune tolerance, leading to the initiation and regulation of autoimmune responses.

CTLA4 (Cytotoxic T-Lymphocyte Associated Protein 4)

- *Function: it down regulates immune response by inhibiting T-cell activation.*
- *Associated Autoimmune Diseases: Graves disease and Hashimoto thyroiditis.*

PTPN22 (Protein Tyrosine Phosphatase, Non-Receptor Type 22)

- *Function: it regulates the T-cell activation and signaling.*
- *Associated Autoimmune Diseases: Rheumatoid arthritis, type 1 diabetes, systemic lupus erythematosus (SLE).*

IL2RA (Interleukin 2 Receptor Subunit Alpha)

- *Function: it encodes for a subunit of interleukin-2 receptor, which is crucial for the T-cell activation and proliferation.*
- *Associated Autoimmune Diseases: Type 1 diabetes, multiple sclerosis.*

IRF5 (Interferon Regulatory Factor 5)

- *Function: it regulates production of type I interferons and other immune-related genes.*
- *Associated Autoimmune Diseases: SLE, rheumatoid arthritis.*

IL23R (Interleukin 23 Receptor)

- *Function: it encodes for a subunit of interleukin-23 receptor, involved in Th17 cell differentiation and function.*
- *Associated Autoimmune Diseases: Crohn's disease, ulcerative colitis, psoriasis.*

STAT4 (Signal Transducer and Activator of Transcription 4)

- *Function: it Mediate the cellular response to various cytokines, including interleukin-12 and interferons.*
- *Associated Autoimmune Diseases: SLE, rheumatoid arthritis.*

TNFAIP3 (Tumor Necrosis Factor Alpha-Induced Protein 3)

- *Function: it is a negative regulator of nuclear factor-kappa B (NF-κB) signaling pathway, which is involved in inflammation.*
- *Associated Autoimmune Diseases: Rheumatoid arthritis, SLE.*

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INNATE V/S ADAPTIVE IMMUNITY

Innate immunity serves as the first line of defense, providing immediate protection and initiating adaptive responses. Adaptive immunity complements innate immunity, offering specific and long-lasting protection, with memory for enhanced defense upon re-exposure.

Innate Immunity

- *Function: Immediate defense against pathogens*
- *Recognizes common microbial patterns.*
- *Activates inflammation and recruits immune cells.*
- *Time of Response: Rapid, occurring within minutes to hours after pathogen invasion.*
- *Memory: Lacks immunological memory.*
- *Responses are the same upon repeated exposure.*
- *Types of Receptors: Pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs), NOD-like receptors (NLRs), and RIG-I-like receptors (RLRs).*
- *Examples: Phagocytes (neutrophils, macrophages),Dendritic cells,Natural killer (NK) cells,Complement proteins.*
- *Antibodies Involved: Innate immunity primarily relies on nonspecific mechanisms and does not involve antibodies.*

Adaptive Immunity

- *Function: Highly specific defense against pathogens.*
- *Recognizes antigens via antigen receptors.*
- *Generates immunological memory.*
- *Time of Response:Slower, taking days to weeks to mount a full response upon initial exposure. Memory response is rapid upon subsequent exposure.*
- *Memory: Exhibits immunological memory. Generates stronger and faster responses upon re-exposure to the same pathogen.*
- *Types of Receptors: Antigen receptors: B cell receptors (BCRs) on B cells and T cell receptors (TCRs) on T cells.*
- *Examples: B lymphocytes (B cells): Produce antibodies, involved in humoral immunity. T lymphocytes (T cells): Helper T cells, cytotoxic T cells, regulatory T cells, involved in cell-mediated immunity.*
- *Antibodies Involved: IgM, IgG, IgA, IgE, and IgD are various classes of antibodies involved in different immune responses.*

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HLA GENES

Human Leukocyte Antigen (HLA) genes are also known as Major Histocompatibility Complex (MHC) genes and are a group of genes located on chromosome 6 that encodes for proteins crucial for regulation of immune system. HLA genes play an important role in immune response by presenting antigens to the T cells, which are crucial for recognition of self and non-self antigens.

HLA-A, HLA-B, HLA-C:

- *Function: These genes encode MHC class I (MHC-I) molecules. They present antigenic peptides to cytotoxic T cells.*
- *Associated Autoimmune Diseases: ankylosing spondylitis, psoriasis, celiac disease, and Behcet's disease.*

HLA-DR, HLA-DP, HLA-DQ:

- *Function: These genes encode major histocompatibility complex class II (MHC-II) molecules. They present antigenic peptides to helper T cells.*
- *Associated Autoimmune Diseases:*

1. *HLA-DR2: Multiple sclerosis*
2. *HLA-DR3, HLA-DR4: Type 1 diabetes mellitus, rheumatoid arthritis*
3. *HLA-DQ2, HLA-DQ8: Celiac disease*

HLA-DRB1:

- *Function: it is a part of HLA-DR gene complex, which encodes for beta chain of the HLA-DR molecule.*
- *Associated Autoimmune Disease: rheumatoid arthritis.*

HLA-B27:

- *Function: it encodes a subunit of MHC-I.*
- *Associated Autoimmune Diseases: Strongly associated with sero negative arthropathies like ankylosing spondylitis, reactive arthritis, and other spondyloarthropathies.*

HLA-DQB1:

- *Function: it is a part of HLA-DQ gene complex, encodes beta chain of HLA-DQ molecule.*
- *Associated Autoimmune Diseases: celiac disease, particularly alleles HLA-DQB1.*

HLA-DRA:

- *Function: it encodes for alpha chain of HLA-DR molecule.*
- *Associated Autoimmune Diseases: Specific associations is unknown , but it plays an important role in the antigen presentation in autoimmune process.*

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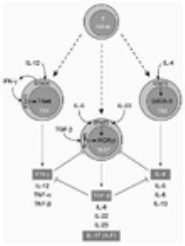
T- HELPER CELLS

T helper cells, or CD4+ T cells, are a subset of lymphocytes that play a crucial role in the adaptive immune response. They recognize antigenic peptides presented by major histocompatibility complex class II (MHC-II) molecules on antigen-presenting cells (APCs) and help coordinate the immune response. Here are the main types of T helper cells and their roles -

Th1 Cells:

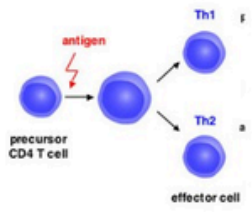
- *Defense Mechanism: Th1 cells primarily defend against intracellular pathogens, such as viruses and certain bacteria.*
- *Role in Disease: Th1 cells are associated with cell-mediated immunity and are involved in autoimmune diseases and inflammatory conditions.*
- *Products: Th1 cells produce cytokines such as interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α), and interleukin-2 (IL-2).*
- *Functions: They activate macrophages, promote cytotoxic T cell responses, and stimulate B cells to produce opsonizing antibodies (IgG).*



TH1, TH2, TH17 and their products

Th2 Cells:

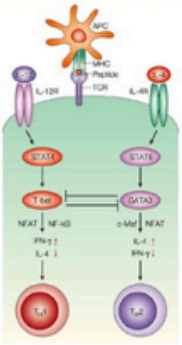
- *Defense Mechanism: Th2 cells are involved in defending against extracellular parasites, such as helminths.*
- *Role in Disease: Th2 cells are associated with allergic responses, asthma, and certain autoimmune diseases.*
- *Products: Th2 cells produce cytokines such as interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-13 (IL-13).*
- *Functions: They stimulate B cells to produce IgE antibodies and eosinophils for parasite defense.*



Response to Antigen

Th17 Cells:

- *Defense Mechanism: Th17 cells defend against extracellular bacteria and fungi, particularly at mucosal surfaces.*
- *Role in Disease: Th17 cells are implicated in autoimmune diseases, inflammatory bowel diseases, and tissue inflammation.*
- *Products: Th17 cells produce cytokines such as interleukin-17 (IL-17), interleukin-21 (IL-21), and interleukin-22 (IL-22).*
- *Functions: They recruit neutrophils and monocytes to sites of infection and promote tissue inflammation.*



Differentiation of TH 1 and TH 2

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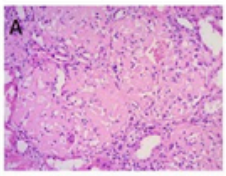
AMYLOIDOSIS

Amyloidosis refers to a group of diseases characterized by the extracellular deposition of insoluble proteinaceous fibrils known as amyloid. There are several types of amyloidosis, each associated with different precursor proteins and clinical manifestations. Here are the main types of amyloidosis includes-

AL Amyloidosis (Primary Amyloidosis):

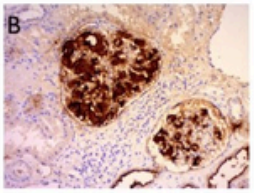
- *Precursor Protein: Immunoglobulin light chains (AL).*
- *Conditions: Associated with plasma cell dyscrasias, multiple myeloma.*
- *Clinical Significance: Leads to renal failure, cardiomyopathy, peripheral neuropathy, and hepatomegaly.*
- *Pathophysiology: Abnormal plasma cells produce monoclonal light chains, which misfold and deposit as amyloid fibrils in tissues.*



Renal amylodosis
A- H&E stained

AA Amyloidosis (Secondary Amyloidosis):

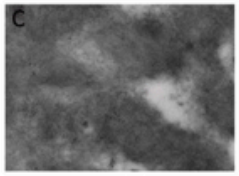
- *Precursor Protein: Serum amyloid A protein (SAA).*
- *Conditions: rheumatoid arthritis, inflammatory bowel dis., tuberculosis.*
- *Clinical Significance: affects kidneys, leading to proteinuria and renal failure, also involve organs, including liver, spleen, and heart.*
- *Pathophysiology: Chronic inflammation stimulates hepatic synthesis of SAA, which misfolds and deposits as amyloid fibrils in tissues.*



Response to Antigen

ATTR (Hereditary and Senile Systemic Amyloidosis):

- *Precursor Protein: Transthyretin (TTR).*
- *Conditions: hereditary (caused by mutations in the TTR gene) or senile (associated with wild-type TTR).*
- *Clinical Significance: Manifests mainly as cardiomyopathy or peripheral neuropathy.*
- *Pathophysiology: Mutations in TTR or age-related changes lead to misfolding of TTR, resulting in amyloid deposition in various tissues.*



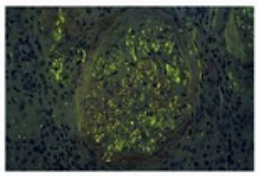
C- Electro micrograph show amyloid deposition

AApoAI and AApoAII Amyloidosis:

- *Precursor Protein: Apolipoprotein A-I (AApoAI) and Apolipoprotein A-II.*
- *Clinical Significance: renal involvement, cardiomyopathy, or neuropathy.*
- *Pathophysiology: Mutations or age-related changes in apolipoproteins.*

Beta-2 Microglobulin Amyloidosis:

- *Precursor Protein: Beta-2 microglobulin (β2M).*
- *Conditions: Associated with chronic renal failure in patients undergoing long-term hemodialysis.*
- *Clinical Significance: Deposits in musculoskeletal tissues, particularly joints, leading to carpal tunnel syndrome and destructive arthropathy.*
- *Pathophysiology: Accumulation of β2M due to impaired renal clearance leads to its misfolding and deposition as amyloid fibrils.*



Apple green birefringence under polarised light

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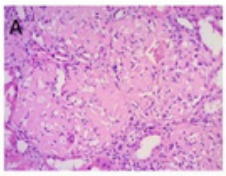

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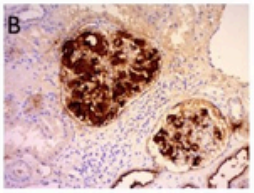

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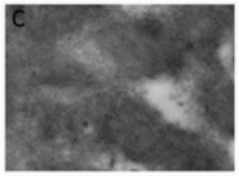

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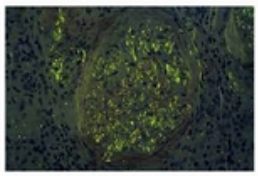

Apple green birefringence under polarised light