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Chapter 15

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad Chapter 15

Basic sciences Immunology

Immune system response Innate VS Adaptive immune response Innate (non-specific system) Adaptive (acquired system) Components

1. Anatomical and physiological barriers
2. Inflammatory response with leakage of antibacterial serum proteins (acute-phase proteins) and phagocytic cells
3. Phagocytosis by neutrophils and macrophages
4. Complement system Components
5. Cell-mediated response effected by T cells
6. Humeral immune response effected by B cells Properties
7. Rapid: responds within minutes to infection
8. No antigenic specificity, i.e. the same molecules and cells respond to range of pathogens
9. No memory, i.e. the response does not change after repeated exposure
10. Preformed or rapidly formed components Properties
11. Slow: response over days to weeks
12. Antigenic specificity i.e. each cell is a programmed genetically to respond to a single antigen
13. Immunological memory, i.e. on repeated the response is faster, stronger and qualitatively different
14. Diversity: ability to recognize and respond to a vast number of different antigens
15. Self/non-self-recognition: i.e. lack of response (tolerance) to self-antigens but response to foreign antigens

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Overview of blood cell types involved in the innate immune response Cell type Functions and properties Neutrophil Primary phagocytic cell in acute inflammation Granules contain myeloperoxidase and lysozyme Most common type of white blood cell Multi-lobed nucleus

Basophil Releases histamine during allergic response Granules contain histamine and heparin Expresses IgE receptors on the cell surface Bi-lobed nucleus Mast cell Present in tissues and are similar in function to basophils but derived from different cell lines Granules contain histamine and heparin Expresses IgE receptors on the cell surface Eosinophil Defends against protozoan and helminthic infections Bi-lobed nucleus Monocyte Differentiates into macrophages Kidney shaped nucleus Macrophage Involved in phagocytosis of cellular debris and pathogens Acts as an antigen presenting cell Major source of IL-1 Natural killer cell Induce apoptosis in virally infected and tumour cells Dendritic cell Acts as an antigen presenting cell, but have no cytotoxic potential.

Macrophages Overview • Macrophages are a type of antigen-presenting cell, defined as a lymphocyte that is able to phagocytose debris, toxins, cells or pathogens. • Origin: Monocytes migrate to tissue and differentiate into macrophages. • Activated by γ-interferon. • Has a long life in tissues, which differentiates it from a circulating blood monocyte • Important cellular component of granulomas (eg, TB, sarcoidosis), where they may fuse to form giant cells. Tissue-specific subtypes • Osteoclasts (bone) • Kupffer cells (liver) • Microglia (brain and spinal cord) • Histiocytes (connective tissue) A patient undergoes liver biopsy, which shows ↑ phagocytes with kidney-shaped nuclei. What are these cells called? Kupffer cells (the names of macrophages can differ in each tissue) What signaling molecule activates macrophages? γ-interferon

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Important macrophage forms in various Diseases • Lipid laden macrophage (Foam cells) = Hyperlipidemia & Atherosclerotic plaques. • Hemosiderin laden macrophage(Heart failure cells) = CHF. • Macrophages containing debris from ingested Lymphocytes (Tingible body macrophage) = Benign reactive lymphadenitis. • Macrophages containing PAS +ve, gram +ve rod shaped bacilli within Lamina propria in small intestine = Whipple Disease. • Iron trapped in Macrophages in Bone marrow = Anemia of chronic disease. • Macrophages containing Carbon pigment along pleural lymphatics = Anthracosis. • Tissue paper like macrophage = Gaucher disease.

Pathogenesis of atherosclerosis

1. Chronic stress on the endothelium
2. Endothelial dysfunction, which leads to Invasion of inflammatory cells (mainly monocytes and lymphocytes) through the disrupted endothelial barrier Adhesion of platelets to the damaged vessel wall → platelets release inflammatory mediators (e.g., cytokines) and platelet-derived growth factor (PDGF) PDGF stimulates migration and proliferation of smooth muscle cells (SMC) in the tunica intima and mediates differentiation of fibroblasts into myofibroblasts
3. Inflammation of the vessel wall
4. Macrophages and SMCs ingest cholesterol from oxidized LDL and transform into foam cells.

5. Foam cells accumulate to form fatty streaks (early atherosclerotic lesions).
6. Lipid-laden macrophages and SMCs produce extracellular matrix (e.g., collagen) → development of a fibrous plaque (atheroma)
7. Inflammatory cells in the atheroma (e.g., macrophages) secrete matrix metalloproteinases → weakening of the fibrous cap of the plaque due to the breakdown of extracellular matrix → minor stress ruptures the fibrous cap
8. Calcification of the intima (the amount and pattern of calcification affect the risk of complications)
9. Plaque rupture → exposure of thrombogenic material (e.g., collagen) → thrombus formation with vascular occlusion or spreading of thrombogenic material Foam cells • Foam cells are a feature of atherosclerotic plaques and are essentially lipid-laden macrophages. • They may also be seen as a reaction to: silicone leakage around breast implants, and inhaled organic antigens. MRCPUK exam- Jan-2018: You are examining tissue biopsied from around a leaking silicone breast implant. It is rich in foam cells. What is the cell lineage of foam cells? • Macrophage The lipid A component of bacterial lipopolysaccharide (LPS) binds to CD14 on macrophages, which can trigger septic shock

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Fibroblasts • The most common cell type in connective tissue • Origin: derived from mesenchymal stem cells • Found in the interstitial spaces of organs. • Histological features: spindle-shaped cells arranged in a branching pattern • Function: synthesis and organization of the extracellular matrix (ECM) and collagen plays a critical role in wound healing play a critical role in an immune response to a tissue injury. They are early players in initiating inflammation in the presence of invading microorganisms. Tissue damage stimulates fibrocytes and induces the mitosis of fibroblasts. Responsible for forming the cap over an atherosclerotic plaque. • Pathologic fibrosis is characterized by uncontrolled fibroblast activation that results in exaggerated and persistent ECM accumulation and remodeling.

Immunoglobulins The table below summarises the characteristics of the 5 types of immunoglobulin found in the body: Type Frequency Shape Notes IgG 75% Monomer • comprises the majority of circulating antibody in serum • the major antibody produced in the secondary immune response. • Enhance phaGocytosis of bacteria and viruses • half-life: 7-23 days • Fixes classical complement • can bind to NK cells for antibody-dependent cytotoxicity (ADCC). • the only antibody that can cross the placenta and enter the fetal circulation • Most abundant isotype in blood serum • Gamma is the type of heavy chain found in IgG. IgA 15% Monomer/ dimer • Found in secretions such as saliva, tears and mucous • made primarily in the mucosal-associated lymphoid tissues (MALT). • Provides localized protection on mucous membranes • The Fc portion of secretory IgA binds to components of mucous and contributes to the ability of mucous to trap microbes. • Most commonly produced immunoglobulin in the body (but blood serum concentrations lower than IgG) • half-life ≈ 5 days • Transported across the interior of the cell via transcytosis • can activate the alternative complement pathway. (IgA ≈ Alternate) • Low levels of IgA are associated with an increased incidence of Coeliac Disease. • Alpha is the type of heavy chain found in IgA.

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Type Frequency Shape Notes IgM 10% Pentamer • First immunoglobulins to be secreted in response to an infection (primary response) • Fixes classical complement pathway (most efficient) • Anti-A, B blood antibodies (note how they cannot pass to the fetal circulation, which could of course result in haemolysis) • Monomeric forms of IgM are found on the surface of Blymphocytes as B-cell receptors or sIg. • half-life: about 5 days • Mu is the type of heavy chain found in IgM. IgD 1% Monomer • Involved in activation of B cells (as a surface receptor on B cells) • may play a role in eliminating B-lymphocytes generating selfreactive autoantibodies. • Delta is the type of heavy chain found in IgD. • Hyper-IgD is associated with periodic fever (attacks of fever every 4-8 weeks, with each attack lasting 3-7 days) IgE 0.1% Monomer • produced by plasma cells • Mediates type 1 hypersensitivity reactions • Binds to Fc receptors found on the surface of mast cells and basophils • Provides immunity to parasites such as helminths • Least abundant isotype in blood serum • half-life of 2 days • IgE may protect external mucosal surfaces by promoting inflammation, enabling IgG, complement proteins, and leucocytes to enter the tissues. • Cross linking of cell-bound IgE by antigen triggers the release of vasodilators for an inflammatory response. • The Fc portion of IgE made against parasitic worms and arthropods can bind to eosinophils enabling opsonization. This is a major defense against parasitic worms and arthropods. • Epsilon is the type of heavy chain found in IgE. • Raised IgE levels are a normal finding in 2.5% Blood transfusion • Rhesus antibodies are IgG , whereas ABO antibodies are IgM Commonly recognized immunoglobulin changes in liver disease (usually accompanied by a decrease in albumin) are: • lgG ↑in: chronic active hepatitis, cryptogenic cirrhosis • lgM ↑in: 1° biliary cirrhosis, alcoholic cirrhosis • lgA ↑in: alcoholic cirrhosis. Each day an average adult produces approximately 3gm of antibodies, about two-thirds of this IgA Acute organ rejection is due to anti-IgG antibodies to the human leukocyte antigen (HLA) incompatible tissues with primary activation of T cells.

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Immunoglobulins (antibodies) have two functional parts: the Fc region and the Fab region • Fc region Contains the constant region Formed by heavy (H) chains Recognizes and binds complement (IgG, IgM) • Fab region Contains the variable region Formed by light (L) chains and heavy (H) chains Recognizes and binds to antigens Immunoglobulins and complement fixation • IgA can fix complement via the alternative pathway • IgG and IgM can fix complement via the classical pathway through the Fc portion of the immunoglobulin

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Protein analysis: Gamma globulins • Hypergammaglobulinaemia Causes of polyclonal hypergammaglobulinaemia Artefactual, e.g. prolonged venous stasis before venepuncture Haemoconcentration secondary to dehydration Chronic infection, e.g. TB, infective endocarditis, leishmaniasis Autoimmune disease, e.g. SLE, rheumatoid arthritis Ulcerative colitis and Crohn's disease Sarcoidosis Hepatic disease. Causes of monoclonal hypergammaglobulinaemia Multiple myeloma, Waldenstrom's macroglobulinaemia and heavy

chain disease Leukaemia, lymphoma or carcinoma Bence Jones proteinuria 'Benign' paraproteinaemia Amyloidosis. • Agammaglobulinemia (e.g., Bruton agammaglobulinemia) • Hypogammaglobulinemia (low IgG) Nephrotic syndrome Drug-induced reactions Acquired humoral and congenital immunodeficiencies

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Immunoglobulins: therapeutics Basics • formed from large pool of donors (e.g. 5,000) • IgG molecules with a subclass distribution similar to that of normal blood • half-life of 3 weeks Uses • primary and secondary immunodeficiency • idiopathic thrombocytopenic purpura

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• myasthenia gravis • Guillain-Barre syndrome • Kawasaki disease • toxic epidermal necrolysis • pneumonitis induced by CMV following transplantation • low serum IgG levels following haematopoietic stem cell transplant for malignancy • dermatomyositis • chronic inflammatory demyelinating polyradiculopathy

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Leukotrienes Overview • mediators of inflammation and allergic reactions • secreted by leukocytes • formed from arachidonic acid by action of lipoxygenase • it is thought that the NSAID induced bronchospasm in asthmatics is secondary to the express production of leukotrienes due to the inhibition of prostaglandin synthetase Function • cause bronchoconstriction, • mucous production (an important consideration in the pathophysiology of bronchial asthma) • increase vascular permeability, attract leukocytes • leukotriene D4 has been identified as the SRS-A (slow reacting substance of anaphylaxis) which causes bronchial wall and intestinal smooth muscle contraction

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Acute phase proteins Acute phase proteins • CRP • procalcitonin • ferritin • fibrinogen • alpha-1 antitrypsin • caeruloplasmin • serum amyloid A, serum amyloid P • haptoglobin • complement Negative acute phase proteins • During the acute phase response, the liver decreases the production of other proteins (sometimes referred to as negative acute phase proteins). Examples include: albumin transthyretin (formerly known as prealbumin) transferrin retinol binding protein cortisol binding protein

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ANCA • There are two main types of anti-neutrophil cytoplasmic antibodies (ANCA):

1. cytoplasmic (cANCA) and
2. perinuclear (pANCA) • For the exam, remember: cANCA - Wegener's granulomatosis pANCA - Churg-Strauss syndrome + others (see below) cANCA • most common target serine proteinase 3 (PR3) • some correlation between cANCA levels and disease activity •

Wegener's granulomatosis, positive in > 90% In Wegener's, the level of PR3 antibody and ANCA titre are related to disease activity and the antibodies typically disappear when the disease is in remission. • microscopic polyangiitis, positive in 40% pANCA • most common target is myeloperoxidase (MPO) • cannot use level of pANCA to monitor disease activity • associated with immune crescentic glomerulonephritis (positive in c. 80% of patients) • microscopic polyangiitis, positive in 50-75% • Churg-Strauss syndrome, positive in 60% • primary sclerosing cholangitis, positive in 60-80% • Wegener's granulomatosis, positive in 25% • Other causes of positive ANCA (usually pANCA) inflammatory bowel disease (UC > Crohn's) connective tissue disorders: RA, SLE, Sjogren's autoimmune hepatitis MRCP-part-1-Jan-2018 exam: Which one of the following statements is true regarding cytoplasmic anti-neutrophil cytoplasmic antibodies (cANCA)? • Associated with Wegener's granulomatosis

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Rheumatoid factor (see rheumatology)

Antibodies and immunological markers Marker Associated condition Antinuclear antibodies (ANA) • Younger women often have low (ANAs) • increase with age • ANA positivity with antiphospholipid antibody syndrome (APL) suggests secondary APL, ie in association with a connective tissue disease. • The common tests used for detecting and screening ANAs are indirect immunofluorescence and enzyme-linked

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Marker Associated condition immunosorbent assay (ELISA). • Although positive titres of 1:160 or higher are strongly associated with autoimmune disorders, they are also found in 5% of healthy individuals • Positive titres of less than 1:160 are present in up to 20% of the healthy population, especially the elderly. Anti-Ro (SS-A) and anti-La (SS-B) Anti-Ro Sjögren's syndrome (50–70%) SLE with cutaneous involvement (30%) anti-Ro can cross the placenta and cause neonatal lupus in babies. Anti-Smith (Anti-Sm) very specific marker for SLE (99%) sensitivity (20%) not associated with disease activity. Anti-nuclear ribonucleoprotein (anti-nRNP) also known as anti-U1RNP highly associated with mixed connective tissue disease. SLE (30 – 40%) Anti-double stranded DNA (anti-dsDNA) very specific marker for SLE, (nearly 100%). sensitivity (85%). Correlate with disease activity in SLE. also linked with lupus nephritis. Anti-histone drug induced lupus (75–95%) idiopathic SLE (75%) Unlike anti-dsDNA, these antibodies do not fix complement. anti-glycoprotein210 (anti-gp210) and anti-nucleoporin 62 (anti-p62) primary biliary cirrhosis (PBC) (25–30%). Anti-centromere limited cutaneous systemic sclerosis, also known as CREST syndrome, primary biliary cirrhosis Thyroid autoantibodies (microsomal and thyroglobulin) Hashimoto's thyroiditis (70-90% microsomal: 75-95% thyroglobulin) Pernicious anaemia (55% microsomal) Anti-Scl-70 diffuse cutaneous scleroderma (40%), limited cutaneous involvement (10%). SLE (5%) The antigenic target of anti-Scl-70 antibodies is topoisomerase I Antireticulin Coeliac disease (37%) Crohn's disease (24%) Gastric parietal cell antibody Pernicious anaemia (>90%) Atrophic gastritis(60%) Autoimmune thyroid disease (33%)

Marker Associated condition Anti-mitochondrial antibody Primary biliary cirrhosis (60-94%) Anti-smooth muscle antibody Chronic active hepatitis (40-90%) Primary biliary cirrhosis (30-70%) Idiopathic cirrhosis (25-30%) Viral infections (80%) Anti-sp100 primary biliary cirrhosis (PBC) (20–30%). very specific marker of the disease. Anti-PM-Scl polymyositis/systemic sclerosis (PM/SSc) overlap syndrome (50%). Anti-Hu small-cell lung cancer, neuroblastoma and prostatic cancer Intrinsic factor antibodies pernicious anaemia, and hence (subacute combined degeneration of the spinal cord) secondary to vitamin B12 deficiency Anti-Ri neuroblastoma (children) and fallopian or breast cancer (adults), resulting in paraneoplastic opsoclonus myoclonus ataxia (POMA). Anti-Yo gynaecological tumours and breast cancer, Anti-Tr Hodgkin's disease, resulting in cerebellar degeneration. Anti-Ta (Ma2) testicular tumours, and can lead to limbic or brain stem encephalomyelitis. Anti-endomysial / gliadin / transglutaminase coeliac disease, and related vitamin B-1 deficiency may lead to Wernicke's encephalopathy and Korsakoff's psychosis Tissue transglutaminase antibody ('tTGA') & Endomysial antibody ('EMA') The most accurate blood tests for coeliac disease double-stranded DNA (ds-DNA) AntidsDNA highly specific for SLE. Antibodies that bind single-stranded denatured DNA (ssDNA) present in 90% of patients with SLE, but also in drug-induced lupus and other connective tissue disorders. Anti-Jo Polymyositis Rheumatoid factor Rheumatoid arthritis, Sjogren’s (90%), SLE (30%) 5% of normal population The only two auto-antibodies which have a role in monitoring disease activity (there is correlation between levels and disease activity)

1. Anti-ds DNA antibodies in systemic lupus erythematosus (SLE)
2. Circulating anti-neutrophil cytoplasmic antibody (cANCA) in Wegener's granulomatosis.

Basic sciences Immunology Interleukins Definition • Interleukin are a group of signaling proteins expressed by leukocytes that regulate immune response as well as cellular proliferation and differentiation. Production • The majority of interleukins are synthesized by helper CD4 T lymphocytes, as well as through monocytes, macrophages, and endothelial cells. Function • The function of the immune system depends in a large part on interleukins, • They promote the development and differentiation of T and B lymphocytes, and hematopoietic cells. Overview of interleukins Cytokine Main sources Functions IL-1 Macrophages Acute inflammation Induces fever IL-2 Th1 cells Stimulates growth and differentiation of T cell response IL-3 Activated T helper cells Stimulates differentiation and proliferation of myeloid progenitor cells IL-4 Th2 cells Stimulates proliferation and differentiation of B cells (Stimulates switching to IgE and IgG.) IL-5 Th2 cells Stimulates proliferation and differentiation of B cells (Stimulates switching to IgA.) Stimulate production of eosinophils IL-6 Macrophages, Th2 cells Stimulates differentiation of B cells Induces fever stimulates production of acute phase proteins. IL-8 Macrophages Neutrophil chemotaxis IL-10 Th2 cells Inhibits Th1 cytokine production Also known as human cytokine synthesis inhibitory factor and is an 'anti-inflammatory' cytokine IL-12 Dendritic cells, macrophages, B cells Activates NK cells. stimulates differentiation of naive T cells into Th1 cells Other cytokines Cytokine Main sources Functions Tumour necrosis factor-α Macrophages Induces fever Neutrophil chemotaxis Interferon-γ

Th1 cells Activates macrophages Both cytokine overexpression and underexpression can be pathogenic: Production of IL-1, IL-6 and TNF due to endotoxin stimulation of macrophages following Gram-negative infection → Septic shock Chagas' disease (Trypanosoma cruzi infection) → reduced expression of IL-2 receptor → marked immune suppression.

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Mnemonic Hot T-Bone stEAk IL-1: fever (Hot) IL-2: stimulates T lymphocytes IL-3: stimulates Bone marrow IL-4: stimulates IgE IL-5: stimulates IgA Interleukin 1 (IL-1) • Produced by macrophages and monocytes • Action Endogenous pyrogen (one of the mediators of shock in sepsis): promotes Fever (Along with IL-6 and TNF, it acts on the hypothalamus causing pyrexia) Vasodilation → edema Adhesion and diapedesis of inflammatory cells via cytokines, e.g. WBCs Co-stimulator of T cell and B cell proliferation. (Stimulation of acute phase response) Hematopoietic growth factor Stimulates proliferation of granulocytes in the bone marrow and lymphocytes in the spleen Inhibits hematopoiesis Induces expression of adhesion molecules in the endothelium Promotes differentiation of Th17 cells involved in autoimmunity Also known as osteoclast-activating factor: Dysregulation of IL- 1 in cartilage leads to damage and osteoarthritis. Play a role in the formation of the atherosclerotic plaque The uptake of oxidized low-density lipoproteins (LDL) by vascular endothelial cells results in →IL-1 expression →stimulates the production of plateletderived growth factor. Interleukin-2 (IL-2) • Produced by Th1 cells (mainly CD4+ cells) • Functions Stimulates proliferation and differentiation of T cells (helper, cytotoxic, regulatory T cells, and natural killer cells) Activates macrophages IL-2 is part of the body's natural response to microbial infection, and in discriminating between foreign ("non-self") and "self". there is some evidence that IL-2 may be involved in itchy psoriasis • Therapeutic use High-dose interleukin-2 can produce a high rate of response and durable remissions in patients with metastatic renal cancer. IL-2 analog (aldesleukin): metastatic melanoma and renal cell carcinoma IL-2 antagonists (e.g., basiliximab): prevention of renal transplant rejection

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Interferon Overview • Interferons (IFN) are cytokines released by the body in response to viral infections and neoplasia. • Are a part of the innate immune system • Have antiviral, antimicrobial, and antiproliferative properties • Used in the treatment of chronic infections (hepatitis B and C, chronic granulomatous diseases), immune-mediated diseases (multiple sclerosis), and even tumors (leukemia, Kaposi sarcoma) • They are classified according to cellular origin and the type of receptor they bind to. • IFN-alpha and IFN-beta bind to type 1 receptors whilst IFN-gamma binds only to type 2 receptors. Types • IFN-alpha Produced by leucocytes Function: Antiviral action (Inhibits viral protein synthesis by activating ribonuclease L) Therapeutic use: Hepatitis B & C, Kaposi's sarcoma, metastatic renal cell cancer, hairy cell leukaemia • IFN-beta Produced by fibroblasts Function: Antiviral action Therapeutic use: Multiple sclerosis → Reduces the frequency of exacerbations in patients with relapsing-remitting MS • IFN-gamma (γ) The only

member of the type II class of interferons Produced by Th1 cell Function Activates macrophages to increase phagocytosis Activates the expression of Class II major histocompatibility complex (MHC) molecules Weaker antiviral action Therapeutic use Chronic granulomatous diseases (e.g., leprosy, leishmaniasis, toxoplasmosis) Side effects of interferon • Flu-like symptoms (fever, chills) • Depression • Myopathy • Neutropenia • Interferon-induced autoimmunity Interferon-γ is responsible for activating macrophages To remember the use of interferon-γ, think “Interferon gamma for granulomatous diseases!”

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What is the MOA of Toxic Shock Syndrome Toxin (TSST-1) from Staphylococcus aureus? • Bringing of MHC II and T-cell receptors in proximity to outside of the antigen binding site, thereby causing overwhelming release of IFN-gamma and IL-2 The relation between IL-12 and IFN-gamma: How do IFN-gamma levels change in IL-12 Receptor Deficiency? Decrease IL-12 →Th1 cell activation →release IFN-gamma →activates macrophages. No IL-12 action = no IFN-gamma release from Th1 cells

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Tumour necrosis factor (TNF) Overview • Tumour necrosis factor (TNF) is a pro-inflammatory cytokine with multiple roles in the immune system • TNF is secreted mainly by macrophages • Act mainly in a paracrine fashion Function • Activates macrophages and neutrophils, acts as co-stimulator for T cell activation • Increased acute phase proteins • Similar properties to IL-1 , induced pyrexia • TNF is important in the pathogenesis of rheumatoid arthritis. TNF blockers (e.g. infliximab, etanercept) are now licensed for treatment of severe rheumatoid • A key cytokine in the pathogenesis of multi-organ failure , a Key mediator of bodies response to Gram negative septicaemia. High concentrations of TNF induce shock-like symptoms • Exerts an interferon-like effect against viruses • Enhanced HLA class I expression • Anti-tumour effect (e.g. phospholipase activation) • TNF-alpha binds to both the p55 and p75 receptor. These receptors can induce apoptosis. It also cause activation of NFkB • Endothelial effects include increase expression of selectins and increased production of platelet activating factor, IL-1 and prostaglandins • Promotes the proliferation of fibroblasts and their production of protease and collagenase. • the prolonged exposure to low concentrations of TNF can result in cachexia, a wasting syndrome. This can be found, for example, in cancer patients. • Raised levels lead to increased insulin resistance TNF blockers • Used to treat IBD, rheumatoid arthritis, ankylosing spondylitis and psoriasis. • Examples Infliximab: monoclonal antibody, IV administration Etanercept: fusion protein that mimics the inhibitory effects of naturally occurring soluble TNF receptors, subcutaneous administration Adalimumab: monoclonal antibody, subcutaneous administration • Adverse effects of TNF blockers reactivation of latent tuberculosis demyelination

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• Contraindications of usage of TNF- alpha antagonist Active infection Active TB MS (Multiple sclerosis) Heart failure (NYHA grade 3-4). Pregnancy and Breast feeding

Nitric oxide (NO) Overview • It is formed from L-arginine and oxygen by nitric oxide synthetase (NOS). • An inducible form of NOS has been shown to be present in macrophages. • Nitric oxide has a very short half-life (seconds), being inactivated by oxygen free radicals • Nitric oxide generates cyclic guanosine monophosphate (cGMP) as the second messenger • Can freely diffuse across cell membranes, so NO can act as an intracellular and extracellular signaling molecule Effects • Acts on guanylate cyclase leading to raised intracellular cGMP levels and therefore decreasing Ca2+ levels • Causes smooth muscle relaxation and subsequent dilation of blood vessels • Inhibits platelet aggregation Clinical relevance • Underproduction of NO is implicated in hypertrophic pyloric stenosis • Lack of NO is thought to promote atherosclerosis • In sepsis increased levels of NO contribute to septic shock • Organic nitrates (metabolism produces NO) is widely used to treat cardiovascular disease (e.g. angina, heart failure) • Sildenafil is thought to potentiate the action of NO on penile smooth muscle and is used in the treatment of erectile dysfunctions • N2O, also known as 'laughing gas', is often used in obstetrics and trauma for pain relief Nitric oxide (NO) Has a half-life of only a few seconds. It is not stored by the body but is synthesized as a result of activation. Nitrate drugs stimulate the formation and release of NO. Relaxation of smooth muscle cells in vessel walls leads to the dilation of coronary arteries, pulmonary arteries, and peripheral veins. Peripheral vasodilation leads to a decrease in cardiac preload.

Endothelin-1 (ET-1) • A 21-amino-acid polypeptide • Endothelin-1 is a potent vasoconstrictor that is encoded by the EDN1 gene and produced by vascular endothelial cells. • It is a highly potent vasoconstrictor and plays a part in the modulation of vascular tone • It may have a role in diseases such as Raynaud's phenomenon • Its levels increase when the endothelium is stressed, for example in trauma or oxidative stress • Clinical significance Long term ET-1 exposure has been associated with hypertrophic cardiomyopathy. Endothelin-1 receptor antagonists (Bosentan) are used in the treatment of pulmonary hypertension. Inhibition of these receptors prevents pulmonary vasculature constriction and thus decreases pulmonary vascular resistance.

Kinins Overview • Kinins are mostly produced at inflamed or injured tissue of the body • kinins are potent vasoactive basic peptides involved in the inflammatory response • Their activation leads to release of chemotactic cytokines Functions • increase vascular permeability • cause vasodilation, pain, and the contraction of smooth muscle • stimulate arachidonic acid metabolism

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Erythrocyte sedimentation rate (ESR) Overview • The ESR is a non-specific marker of inflammation and depends on both the size, shape and number of red blood cells and the concentration of plasma proteins such as fibrinogen, alpha2-globulins and gamma globulins Causes of a high ESR • temporal arteritis • myeloma • other connective tissue disorders e.g. systemic lupus erythematosus • other malignancies • infection • other factors which raise ESR: increasing age, female sex, anaemia Causes of a low ESR • polycythaemia • afibrinogenaemia/ hypofibrinogenaemia

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Leukocyte alkaline phosphatase Raised in Low in • Myelofibrosis • Leukemoid reactions • Polycythemia rubra vera • Infections • Steroids, Cushing's syndrome • Pregnancy, oral contraceptive pill • Chronic myeloid leukemia • Pernicious anemia • Paroxysmal nocturnal hemoglobinuria • Infectious mononucleosis

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Thymus Embryology: Thymus epithelium arises from the 3rd pharyngeal pouch (endoderm). Function: Maturation and differentiation of T lymphocytes Location: The thymus is a gland composed of two identical lobes, located in the superior anterior superior mediastinum, in front of the heart and behind the sternum. Clinical significance • Thymic hypoplasia or aplasia: DiGeorge syndrome, SCID • Thymoma: tumor of thymic epithelial cells: Seen in myasthenia gravis, pure red cell aplasia, immunodeficiency with thymoma Thymic cortex and medulla • The cortex is the area of the thymus that is dense and full of immature T cells. • The medulla is the area of the Thymus that is pale and full of mature T cells

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B cells (B lymphocytes) Origin: Originate and mature in the bone marrow Function • Major component of the adaptive immune system: The humoral immune response of the adaptive immune system mainly consists of B cells and antibodies. • After activation, B cells differentiate into plasma cells that produce and secrete antibodies Surface proteins • B cells express numerous proteins on their surface: CD19, CD20 , CD21 (used by EBV), and CD40 MHC II IgG B7 Plasma cells T cells = Thymus B cells = Bone marrow The Thymus arises from the Third pharyngeal pouch

• Plasma cells are fully differentiated cells from B-cells and hence lack these features (i.e. they lack surface-bound IgG and MHC class II and cannot undergo somatic hypermutation or isotype switching). • plasma cells do not have surface-bound IgG (unlike B-cells). • plasma cells cannot undergo somatic hypermutation (unlike B-cells). • plasma cells cannot undergo isotype switching (unlike B-cells). B lymphocytes VS T lymphocytes B lymphocytes T lymphocytes Site of production bone marrow. germinal centre of lymph nodes and spleen. produced in the bone marrow but mature in the thymus Paracortical region of lymph nodes and spleen. Functions Humoral immunity antibody production (immunoglobulins) control of pyogenic bacteria prevention of blood-borne infections. neutralization of toxins. % of total lymphocytes: 12% mainly fixed.

T cells (T lymphocytes) Origin • Originate from lymphoid progenitor cells in the bone marrow and mature in the thymus. Distribution • T lymphocytes compose the majority of circulating lymphocytes in plasma. • Lymph nodes: The paracortical areas contain T cells and accessory cells. B cells are found within the cortex in follicles, which have central areas known as germinal centres. The medulla contains large blood vessels and sinuses, and medullary cords that contain plasma cells secreting antibody. Function • A major component of the adaptive immune response •

Essential for cell-mediated immunity T lymphocytes are involved in cell-mediated acquired immune responses, whereas B lymphocytes are involved in humoral immunity and produce immunoglobulins. Mechanism of action • T cells recognise antigen only when presented by (self) MHC molecules on an antigen presenting cell (Co-operation with other cell types is required for T cell recognition of antigen) • Patients with HIV have a deficiency of T-cells (CD4 T-cell lymphocytes)
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Cell-mediated immunity; protection against intracellular organisms, protozoa and fungi; graft rejection; control of neoplasms. 70-80% (the majority of circulating lymphocytes in plasma). mainly circulating; long-lived memory cells.

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T cell subtypes • T cells are largely divided into cytotoxic T cells (CD8+), T helper cells (CD4+), and regulatory T cells. What is the predominant site in the lymph node that contains T cells? Paracortex T-Helper cells (CD4+) • Activated via antigen presentation by MHC class II receptors • There are two major subsets of T-Helper cells: Th1 involved in the cell mediated response and delayed (type IV) hypersensitivity Immune response to intracellular pathogens (viruses, intracellular bacteria) secrete IFN-gamma, IL-2, IL-3 Th2 involved in mediating humoral (antibody) immunity e.g. stimulating production of IgE in asthma Immune response to extracellular pathogens (bacteria, parasites) secrete IL-4, IL-5, IL-6, IL-10, IL-13 • An increase in the Th1:Th2 ratio is associated with a reduction in the risk of allergic/hypersensitivity reactions. MRCP-part-1-Jan- 2018 exam: What is most commonly secreted agent by T-helper cells subset 2 (Th2 cells) ? Interleukin 4 CD8 proteins on the surface of cytotoxic T cells interact with MHC I receptors, while CD4 proteins on the surface of T-helper cells interact with MHC II receptors. Rule of 8: MHC I x CD 8 = 8. MHC II x CD 4 = 8.

Primary immunodeficiency Disorders may be classified according to which component of the immune system they affect. Neutrophil disorders Disorder Underlying defect Notes Caused by a failure of intracellular killing (no respiratory burst). Causes recurrent pneumonias and abscesses, particularly due to catalase-positive bacteria (e.g. Staphylococcus aureus and fungi (e.g. Aspergillus) Negative nitroblue-tetrazolium test Screening is by the nitroblue tetrazolium (NBT) test Abnormal dihydrorhodamine flow cytometry test Chronic granulomatous disease Lack of NADPH oxidase reduces ability of phagocytes to produce reactive oxygen species ChediakHigashi syndrome Microtubule polymerization defect which leads to a decrease in phagocytosis Affected children have 'partial albinism' and peripheral neuropathy. Recurrent bacterial infections are seen Giant granules in neutrophils and platelets Leukocyte adhesion deficiency Defect of LFA-1 integrin (CD18) protein on neutrophils Recurrent bacterial infections. Delay in umbilical cord sloughing may be seen Absence of neutrophils/pus at sites of infection B-cell disorders Disorder Underlying defect Notes Common variable immunodeficiency CVID Many varying causes Hypogammaglobulinemia is seen. May predispose to autoimmune disorders and lymphona Bruton's (x-linked) congenital

agammaglobulinaemia Defect in Bruton's tyrosine kinase (BTK) gene that leads to a severe block in B cell development Selective immunoglobulin A deficiency Maturation defect in B cells Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

X-linked recessive. Recurrent bacterial infections are seen Absence of B-cells with reduce immunoglogulins of all classes • Most common primary antibody deficiency. • Recurrent sinus and respiratory infections • Associated with coeliac disease and may cause false negative coeliac antibody screen

Chapter 15

Basic sciences Immunology T-cell disorders Disorder Underlying defect Notes DiGeorge syndrome 22q11.2 deletion, failure to develop 3rd and 4th pharyngeal pouches Combined B- and T-cell disorders Combined B- and T-cell disorders: SCID WAS ataxic (SCID, Wiskott-Aldrich syndrome, ataxic telangiectasia) Disorder Underlying defect Notes Most common (Xlinked) due to defect in the common gamma chain, a protein used in the receptors for IL-2 and other interleukins. Other causes include adenosine deaminase deficiency Severe combined immunodeficiency Ataxia telangiectasia Defect in DNA repair enzymes Wiskott-Aldrich syndrome Defect in WAS gene X-linked recessive. Features include recurrent bacterial infections, eczema, thrombocytopaenia. Low IgM levels Increased risk of autoimmune disorders and malignancy

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Selective IgA deficiency The history of mucosal infections (sinus and gastrointestinal) and the family history of immune cytopenia and coeliac disease are suggestive of selective IgA deficiency. Definition • Most common primary immunodeficiency that is characterized by a near or total absence of serum and secretory IgA Features Notes & Notes for MRCP
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Common features include congenital heart disease (e.g. tetralogy of Fallot), learning difficulties, hypocalcaemia, recurrent viral/fungal diseases, cleft palate Recurrent infections due to viruses, bacteria and fungi. Reduced T-cell receptor excision circles Stem cell transplantation may be successful • Autosomal recessive. • Features include:

1. cerebellar ataxia,
2.

telangiectasia (spider angiomas), 3. recurrent chest infections 4. and 10% risk of developing malignancy, lymphoma or leukaemia

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• Often asymptomatic • Recurrent infections May manifest with sinusitis or respiratory infections (S. pneumoniae, H. influenzae) Chronic diarrhea, partially due to elevated susceptibility to parasitic infection (e.g. by Giardia lamblia) • Associated with autoimmune diseases (e.g., gluten-sensitive enteropathy, inflammatory bowel disease, immune thrombocytopenia) and atopy 10-fold increased risk of coeliac disease Pernicious anaemia and hence gastric carcinoma ↑

Adverse reactions to blood products Patients with selective IgA deficiency should be tested for the presence of anti-IgA antibodies prior to transfusion with blood products. • Anaphylactic reaction to products containing IgA (e.g., intravenous immunoglobulin) • Associated with IgG2 deficiency They are more likely than the general population to have an IgG2 deficiency, leading to recurrent bacterial infections The possibility of IgG2 deficiency should always be investigated in IgAdeficient individuals with a history of recurrent bacterial infections, but Staphylococcus aureus is the exception Diagnosis • low serum IgA level, with normal IgG and IgM levels • False-positive pregnancy tests Treatment • No specific treatment • Prophylactic antibiotics • Intravenous infusion of IgA is not recommended because of the risk of anaphylactic reactions (caused by the production of anti-IgA antibodies).

IgG subclass deficiency Overview • A decrease of one of IgG subclass (IgG1, IgG2, IgG3 or IgG4) in a patient whose total IgG concentration is normal. IgG1 deficiency • Almost always presents as hypogammaglobulinemia, since IgG1 normally makes up about 70 percent of total IgG. Therefore, only those patients with IgG1 deficiency with normal total IgG should be diagnosed with selective IgG1 deficiency. lgG2 deficiency • More common in children • Infections with Streptococcus pneumoniae, Haemophilus influenzae type b, and Neisseria meningitidis are characteristic, since IgG2 comprises most of the antibody response against To prevent transfusion reactions, IgA-deficient patients must be given washed blood products without IgA or obtain blood from an IgA-deficient donor. The Six A's of selective IgA deficiency: Asymptomatic, Airway infections, Anaphylaxis to IgA-containing products, Autoimmune diseases, Atopy

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polysaccharide capsular antigens → multiple presentations with otitis media and respiratory tract infections. • If these patients are vaccinated with Pneumovax, they are still unable to mount a response to S. pneumoniae antigens lgG3 deficiency • More common in adults. • Infections with Moraxella catarrhalis and S. pyogenes are typical → frequent chronic sinusitis IgG4 deficiency • May or may not be associated with symptomatic sinopulmonary infections.

Isolated IgD deficiency • IgD are surface receptors of B lymphocytes • No specific signs or symptoms • increased viral respiratory tract infections, IgE deficiency leads to both viral and parasitic infections • IgA, IgG and IgM levels are entirely normal • Isolated IgD deficiency has been identified amongst people of Basque origin, hence the link to northern Spain • Not require any specific treatment

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Common variable immunodeficiency (CVID) Definition • primary immunodeficiency with low serum levels of all immunoglobulins despite phenotypically normal B cells Epidemiology • The most common clinically significant primary immunodeficiency is CVID. IgA deficiency is more common, but most are asymptomatic. • Sex: ♀ = ♂ • Onset: present later than other B cell defects (usually 20–35 years of age) Pathophysiology • Most cases are sporadic with no known family history (No

clear pattern of inheritance) • B cells are phenotypically normal but are unable to differentiate into Ig-producing cells,(Bcell dysfunction) resulting in low immunoglobulins of all classes. Features • Recurrent pyogenic respiratory infections, e.g., sinopulmonary infections (in rare cases, enteroviral meningitis) • Associated with a high risk of lymphoma, gastric cancer, bronchiectasis, and autoimmune disorders (e.g., rheumatoid arthritis, autoimmune hemolytic anemia, immune thrombocytopenia, vitiligo) Investigations • Quantitative immunoglobulin levels: low levels of IgG, IgA, and IgM • Decreased number of plasma cells • Flow cytometry shows subsets of normal B and T cells • Poor response to immunizations

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Treatment • Intravenous immunoglobulin (IVIG) replacement therapy (first line), the best option to prevent recurrent chest infections. • Prophylactic antibiotics CVID →B-cell Cannot differentiate into plasma cells →low immunoglobulins but normal or decreased B cells. Bruton's → Pre-B lymphocytes are increased because there's a maturation defect. MRCP-part-1-May-2018 H/O recurrent Giardia lamblia diarrhea and multiple upper respiratory infections since birth. serum analysis reveals normal levels of mature B lymphocytes. What other finding on serum analysis predisposes the patient to recurrent diarrheal infections? Deficiency in IgA The patient has common variable immunodeficiency disorder (CVID) IgA prevent the binding of pathogens to the epithelial cells; thus, preventing protozoa like Giardia lamblia from causing inflammation. Its absence, therefore, leads to the increased likelihood of repeat infection of the GI mucosa

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Bruton's agammaglobulinemia (X-linked agammaglobulinemia) Pathophysiology • X-linked recessive disease caused by a mutations in the gene coding for Bruton tyrosine kinase (BTK) leads to complete deficiency of B lymphocytes • The most common genetic event is a missense mutation (substitution in one amino acid in a protein). Epidemiology: occurs mainly in boys Features • Symptoms develop between 3 and 6 months of age when maternal IgG levels in fetal serum start to decrease. • Hypoplasia of lymphoid tissue (e.g., tonsils, lymph nodes) • Recurrent, severe, pyogenic infections (e.g., pneumonia, otitis media), especially with encapsulated bacteria (S. pneumoniae, N. meningitidis, and H. influenzae) • Hepatitis virus and enterovirus (e.g., Coxsackie virus) infections Diagnosis • Flow cytometry Absent or low levels of B cells (marked by CD19, CD20, and CD21) Normal or high T cells • Low immunoglobulins of all classes • Absent lymphoid tissue, i.e., no germinal centers and primary follicles Treatment • IV immunoglobulins • Prophylactic antibiotics Live vaccines (e.g., MMR) are contraindicated in patients with Bruton agammaglobulinemia.

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Severe combined immunodeficiency disease (SCID) Overview • Numerous genetic mutations → Combined B- and T-cell disorder → immunodeficiency • X-linked recessive mutations → defective IL-2R gamma chain receptor linked to JAK3 (most common SCID mutation) • Autosomal recessive → Adenosine deaminase deficiency (it aid in breakdown of deoxyadenosine, which is a breakdown

product of DNA) → Accumulation of toxic metabolites (deoxyadenosine and dATP) (Deoxyadenosine is toxic to lymphocytes, thus accumulation of this leads to apoptosis of lymphocytes) Features (usually manifests in the first year of life) • Recurrent infections • Diarrhea • Dermatitis • Failure to thrive • Lymph nodes and tonsils may be absent Diagnosis • Flow cytometry: absent T cells , abnormal function of B-cells • CXR: absent thymic shadow • Lymph node biopsy: absent germinal centers • ↓ Lymphocyte count (< 3000/µL) Treatment • Bone marrow transplantation (the best initial curative treatment) Prognosis • Without intervention, SCID usually results in severe infection and death in children by age 2 years.

DiGeorge syndrome Definition • A syndrome characterized by defective development of the third and fourth pharyngeal pouches leading to hypoplastic thymus and parathyroids Pathophysiology • Autosomal dominant; microdeletion at chromosome 22 → Abnormal development of the third and fourth pharyngeal pouches →thymic aplasia and defective parathyroid → T-cell deficiency and dysfunction → primary immunodeficiency The thymus arises from the 3rdpharyngeal pouch, the parathyroid glands receive contribution from both 3rd and 4th pouches. • It is an example of a microdeletion syndrome. Features • Thymus aplasia/hypoplasia → Recurrent infections (viral/fungal/PCP pneumonia) due to Tcell deficiency • Parathyroid gland hypoplasia → hypocalcaemic tetany SCID is due to either a deficiency in IL-2R gamma chain (most common, X-linked) or deficiency in adenosine deaminase (autosomal recessive)

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