SYLLABUS 2022

Basic Pathological Sciences

Table of Contents

About the Basic Pathological Sciences Examination

The Basic Pathological Sciences (BPS) examination is designed to ensure that all doctors undertaking the RCPA training program can demonstrate at an early stage of training that they have adequate foundation knowledge of pathology.

The BPS examination is not an entry requirement for the RCPA training program nor is it a prerequisite for sitting the Part I examination, but a pass in this examination (or exemption) must be achieved before proceeding to sit the Part II examination.

The BPS examination may be taken before commencement of training and is open to registered trainees. Prevocational doctors or medical students who have had pathology included within their studies may also attempt the examination prior to registering with the College. This helps with preparation for training and enables trainees to proceed more rapidly with specific discipline training in pathology. It also provides an opportunity to demonstrate commitment to a career in pathology.

The list of examination topics (syllabus) was approved by the RCPA Board of Education and Assessment in 2021 and reflects knowledge that appears in current, authoritative texts as well as newer knowledge that may not yet appear in textbooks.

The syllabus covers the basic mechanisms of disease that trainees need to understand so they are equipped to train in their chosen discipline and to understand pathology disciplines other than their own chosen field. For example, the microbiology trainee needs to understand the mechanisms of Systemic Inflammatory Response Syndrome or what a septic infarct looks like; the chemical pathology trainee needs to know about the anatomical pathology changes seen in metabolic syndrome; the anatomical pathology trainee needs to understand why certain antibodies used in routine diagnosis are relevant, hematology trainees need to understand the tissue changes seen in inflammation and infection, and the genetic pathology trainee needs to understand how enzyme deficiencies may lead to morphological changes, and so on.

The current syllabus is primarily based on **the first 11 chapters** of Robbins and Cotran Pathologic Basis of Disease, by Vinay Kumar, Abul K. Abbas, and Jon C. Aster (editors), 10th Edition, 2020, Elsevier (including the online version). Supplementary references have been included which explain details more clearly than the textbook, contain diagrams that help explain basic concepts or cover research design. As much as possible these references are from Open Access journals but for copyright reasons the actual articles cannot be placed on the College website.

Section 1: The cell as a unit of health and disease

1.1 The genome and epigenome

Genomic and epigenomic sciences

- Genome organization, including repetitive DNA, transposons, gene regulatory regions, pseudogenes, etc.
- Noncoding DNA- classes
    - DNA variants – SNP: what they are and significance in disease, e.g. drug sensitivity
- Histone organisation
- Micro-RNA and long noncoding RNA
- Mitochondrial genome (structure and function)
- Chromatin structure and function; higher-order chromatin folding and fractal packaging

Gene editing

1.2 Cellular housekeeping, cellular metabolism and mitochondrial function

- Cell components and their functions, includes cytoskeleton, membrane transport, cell-cell interactions, mitochondria etc

1.2 Cellular activation

- Types of cell signalling
- Concepts around cell receptors, types and how they are important in health and disease including tyrosine kinases, Notch family, Wnt
- Signal transduction pathways
- Transcription factors

1.4 Growth factors

- EGFR: mutations in various malignancies
- TGFα: involvement in regeneration and repair
- HGF: c-met not only involved in carcinogenesis but also in myocardial infarction
- PDGF: Role in malignancies
- VEGF: Antibody therapy and diagnosis in tumours; angiogenesis, may cause preeclampsia
- FGF: Involvement in organogenesis and may also interact with CD20 affecting Rituxumab therapy
- TGFß: A key role in neoplasia, chronic inflammation and keloids
- Ras and mutations: How mutated KRAS is permanently turned on leading to cell proliferation

1.5 Extracellular matrix

- Components, forms and roles
    - Fibrous structural proteins
        - Collagen
        - Elastin
    - Proteoglycans and hyaluronic acid: not passive but involved in cell growth and remodelling
    - Glycosaminoglycans and their families
    - Cell adhesive glycoproteins
        - Fibronectins: Role in wound healing
        - Laminin

- Integrins: Postulated role in viral infection and neoplasia

1.6 Maintaining cell populations

- Cell cycle diagram
- Regulators of cell cycle

1.7 Stem cells

- Types
- Tissue stem cells (Adult stem cells) – where located
  - Bone marrow
  - Liver
  - Brain
  - Skin
  - Intestine
  - Mediators of regeneration

Supplementary references

Micro-RNA review
O'Brien J, Hayder H, Zayed Y, Peng C. Overview of MicroRNA Biogenesis, Mechanisms of Actions, and Circulation. Front Endocrinol (Lausanne). 2018 Aug 3;9:402.

Mitochondria review
Galluzzi L, Kepp O, Kroemer G. Mitochondria: master regulators of danger signalling. Nat Rev Mol Cell Biol. 2012 Dec;13(12):780-8.

PDGF review
Farooqi AA, Siddik ZH. Platelet-derived growth factor (PDGF) signalling in cancer: rapidly emerging signalling landscape. Cell Biochem Funct. 2015;33(5):257-265.

VEGF review
Kong DH, Kim MR, Jang JH, Na HJ, Lee S. A Review of Anti-Angiogenic Targets for Monoclonal Antibody Cancer Therapy. Int J Mol Sci. 2017;18(8):1786.

RAS review
Simanshu DK, Nissley DV, McCormick F. RAS Proteins and Their Regulators in Human Disease. Cell. 2017 Jun 29;170(1):17-33.

TGF review
Akhurst RJ, Hata A. Targeting the TGFβ signalling pathway in disease. Nat Rev Drug Discov. 2012 Oct;11(10):790-811.

Section 2: Cell injury, cell death and adaptions

2.1 Causes of cell injury

- Oxygen deprivation
- Physical agents
- Chemical agents and drugs
- Infectious agents
- Immunologic reactions
- Genetic abnormalities
- Nutritional imbalances

2.2 How cells respond to injury

- Reversible Cell Injury
- Cell Death
    - Necrosis: why different tissues have different types of necrosis
    - Necroptosis: An emerging concept and proposed to be important in SIRS, AMS,
    - Apoptosis: causes, mechanisms and morphologic and biochemical changes
    - Other mechanisms of cell Death
    - Autophagy

2.3 Mechanisms of Cell Injury

- General mechanisms of cell Injury and Intracellular targets of injurious stimuli
- Mitochondrial damage
- Membrane damage
- Damage to DNA
- Oxidative stress: accumulation of oxygen-derived free radicals
- Generation of free radicals
- Removal of free radicals
- Pathologic effects of free radicals
- Disturbance in calcium homeostasis
- Endoplasmic reticulum stress: the unfolded protein response
    - Loss of function
    - Gain of toxic function
    - Infectious misfolding

2.4 Examples of Cell Injury and Death

- Hypoxia and Ischemia: why ischemia can lead to cell death
- Mechanisms of Ischemic Cell Injury
- Ischemia-Reperfusion Injury: why a consequence of some therapies
- Chemical (Toxic) Injury

2.5 Adaptations of Cellular Growth and Differentiation

- Physiological versus pathological adaptation
- Hypertrophy
- Hyperplasia
- Atrophy: causes and effects
- Metaplasia

2.6 Intracellular Accumulations

- Lipids
- Steatosis (Fatty Change)
- Cholesterol and cholesterol esters
- Proteins
- Hyaline Change
- Glycogen
- Pigments: exogenous and endogenous

2.7 Pathologic Calcification

- Dystrophic calcification
- Metastatic calcification

2.8 Cellular Aging

- Telomeres
- Oxidative damage
- Calorie restriction

Supplementary references

Apoptosis and Necrosis
Guicciardi ME, Malhi H, Mott JL, Gores GJ. Apoptosis and necrosis in the liver. Compr Physiol. 2013 Apr;3(2):977-1010.

Autophagy
Khandia R, Dadar M, Munjal A, Dhama K, Karthik K, Tiwari R, Yatoo MI, Iqbal HMN, Singh KP, Joshi SK, Chaicumpa W. A Comprehensive Review of Autophagy and Its Various Roles in Infectious, Non-Infectious, and Lifestyle Diseases: Current Knowledge and Prospects for Disease Prevention, Novel Drug Design, and Therapy. Cells. 2019;8(7):674.

Calcification
New SE, Aikawa E. Molecular imaging insights into early inflammatory stages of arterial and aortic valve calcification. Circ Res. 2011 May 27;108(11):1381-91.

Necroptosis review
Linkermann A, Green DR. Necroptosis. N Engl J Med. 2014 Jan 30;370(5):455-65.

Telomeres
Srinivas N, Rachakonda S, Kumar R. Telomeres and Telomere Length: A General Overview. Cancers (Basel). 2020 Feb 28;12(3):558.

Section 3: Inflammation and repair

3.1 Stimuli (causes) for acute inflammation

3.2 The vascular phase

- Flow calibre: how to explain cardinal signs
- Vascular permeability
- Responses of lymphatic vessels and lymph nodes

3.3 The cellular phase

- Getting cells to the area: Why CD31 and CD99 are useful antibodies
- Getting cells to identify microbes and dead tissues
- Chemotaxis of leukocytes

3.4 Removal of the agent

- Phagocytosis: Key antibacterial mechanism
- Engulfment
- Role of Neutrophil Extracellular Traps (NETS): Role in pathogenesis of systemic lupus erythematosus (SLE)
- Getting cells to the area: Role of complement and adhesion molecules
- Getting cells to identify microbes and dead tissues: Role of pathogen recognition mechanisms
- Leukocyte abnormalities: How these may lead to bacterial infection
- Role of the platelet in inflammation
- Termination of the acute inflammatory response
- The myeloperoxidase (MPO) system: Understanding deficiencies and role in infections
- Role of macrophage
    - One of the key cells involved in acute and chronic inflammation
    - Understand the different roles played by different types of macrophages (M1, M2)

3.5 Morphologic Patterns of Acute Inflammation

- Serous inflammation
- Fibrinous inflammation
- Purulent (suppurative) inflammation and abscess
- Ulcers

3.6 Mediators – cell derived

- Vasoactive: key mediators in the inflammatory process
    - Vasoactive amines: Histamine and serotonin
    - Arachidonic acid metabolites
    - Cytokines and chemokines
    - Complement system
    - Other mediators of inflammation

3.7 Mediators – plasma derived

- Complement : Use in renal biopsies
- Coagulation and kinins: Role in Disseminated Intravascular Coagulation (DIC) and sepsis

3.8 Sterile inflammation and the inflammasome

- Role in nonalcoholic fatty liver disease (NAFLD), gout, silicosis

3.9 Chronic inflammation

- Causes
- Features: The ability to distinguish between acute and chronic
- Role of the macrophage: Importance in innate immunity and antigen presentation
- Macrophage activation: Role in obesity and insulin resistance
- How granulomas form: The good and bad of granulomatous inflammation

3.10 Systemic effects

- Fever
- Acute phase reactants: Involvement in the development of amyloidosis

3.11 Angiogenesis

- Role of VEGF: How it works in antibody directed therapy for a number of diseases such as macular degeneration
- Role of Notch signaling pathway
- Stimulation by angiopoietin: Contrasting role of Ang1 and Ang2 and role in sepsis and endothelial dysfunction (see below).

3.12 Wound healing

- Formation of blood clot: a key component in preventing undue haemorrhage
- Formation of granulation tissue
- Cell proliferation and collagen deposition
- Remodelling
- Factors that influence tissue repair

3.13 Pathological aspects of repair

- Too much
- Too little

3.14 Fibrosis

Supplementary references

Angiogenesis

Lugano R, Ramachandran M, Dimberg A. Tumor angiogenesis: causes, consequences, challenges and opportunities. Cell Mol Life Sci. 2020 May;77(9):1745-70.

Akil A, Gutiérrez-García AK, Guenter R, Rose JB, Beck AW, Chen H, Ren B. Notch Signaling in Vascular Endothelial Cells, Angiogenesis, and Tumor Progression: An Update and Prospective. Front Cell Dev Biol. 2021 Feb 16;9:642352.

Macrophage role in obesity

Wu H, Ballantyne CM. Metabolic Inflammation and Insulin Resistance in Obesity.
Circ Res. 2020 May 22;126(11):1549-1564.

Inflammasome review
Zheng, D., Liwinski, T. & Elinav, E. Inflammasome activation and regulation: toward a better understanding of complex mechanisms. Cell Discov 2020 6, 36

Neutrophil review
Rosales C. Neutrophil: A Cell with Many Roles in Inflammation or Several Cell Types? Front Physiol. 2018 Feb 20;9:113.

Section 4: Haemodynamic disorders: thromboembolic disease and shock

4.1 Oedema and effusions - 5 categories (2% of Australians died of heart failure)

- Increased hydrostatic
- Decreased plasma oncotic
- Sodium and water retention
- Lymphatic obstruction
- Inflammation
- Types of exudates and effusions

4.2 Haemorrhage

- Haematoma formation: Correlation of clinical appearances with pathological changes
- Petechiae formation: Correlation of clinical appearances with pathological changes
- Purpura causes
    - Correlation of clinical appearances with pathological changes
    - Relation to immune dysfunction and inflammation
- Ecchymosis: Correlation of clinical appearances with pathological changes
- Breakdown of blood

4.3 Haemostasis

- Vasoconstriction
- Primary haemostasis
- Secondary haemostasis

4.4 Platelets

- Receptors
- α granules: components and role in inflammation and thrombosis
- ß granules: components and role in inflammation and thrombosis
- Adhesion: components and role in inflammation and thrombosis
- Secretion: components and role in inflammation and thrombosis
- Aggregations

4.5 Coagulation cascade

- Role of fibrin
- Role of thrombin
- Role of factor XII: inhibiting factor XII may reduce sepsis induced inflammation and injury

4.6 Thrombosis

Factors leading to thrombosis

- Endothelial injury: key initiator in atherosclerosis, sepsis and DIC
- Stasis of blood
- Hypercoagulability of blood
- Primary: Leiden mutation: common mutation in Australia
    - Prothrombin gene mutation: common mutation in Australia
    - Homocysteine: role in atherosclerosis
- Secondary: Drugs
    - Cancer
    - Heparin-Induced Thrombocytopenia (HIT) syndrome
    - Antiphospholipid: role in systemic diseases, e.g. SLE

Fate of thrombus

4.7 Fibrinolytic pathway

- Evidence of fibrinolytic dysfunction in metabolic syndrome

4.8 Disseminated Intravascular Coagulation (DIC)

4.9 Emboli – types

- Thromboemboli: 4% of deaths in Australia
- Fat and marrow
- Air
- Amniotic fluid
- Septic
- Systemic embolism

4.10 Infarct - Red and white

- Correlate gross appearances with pathology

4.11 Shock – Mechanisms

- Septic: 12% of all admissions to Australian and New Zealand ICU are due to severe sepsis with a mortality of 60%
    - Systemic inflammatory response syndrome (SIRS) (pro-inflammatory)
    - Compensatory Anti-inflammatory response syndrome (CARS) (anti-inflammatory)
    - Mixed antagonist response syndrome (MARS)
    - Immunopathogenic
    - Coagulation disorders in sepsis: How sepsis is able to activate the coagulation cascade. Review of therapies attempted to try and modulate this

Supplementary references

Coagulation and neutrophils (including NET)
Zucoloto AZ, Jenne CN. Platelet-Neutrophil Interplay: Insights Into Neutrophil Extracellular Trap (NET)-Driven Coagulation in Infection. Front Cardiovasc Med. 2019 Jun 20;6:85.

Sepsis
Iskander KN, Osuchowski MF, Stearns-Kurosawa DJ, Kurosawa S, Stepien D, Valentine C, Remick DG. Sepsis: multiple abnormalities, heterogeneous responses and evolving understanding. Physiol Rev. 2013 Jul;93(3):1247-88.

Section 5: Genetic disorders

5.1 Mutation

- Point mutation in coding sequence
- Missense versus nonsense, e.g. HbA to HbS
- Mutation within non-coding sequences
- Deletions and insertions
- Trinucleotide repeats

5.2 Single gene

- Types
    - Autosomal dominant – loss of function
    - Gain of function
    - Autosomal recessive
    - X-linked
- Result in
    - Enzyme defects
        - Increased substrate
        - Decreased end product
        - Decreased inactivation of tissue damage
    - Defects in receptors
    - Alteration in structure/function
    - Adverse reaction to drugs

5.3 Structural abnormalities

- Number
    - Aneuploidy
    - Trisomy: common congenital pathology (T21, 18, 13)
    - Mosaicism
- Structure
    - Deletions
    - Ring
    - Inversion
    - Isochromosome
    - Translocation

5.4 Non-classical inheritance

- Trinucleotide
- Mitochondrial
- Genomic imprinting
- Gonadal mosaicism

5.5 Diagnostic Methods and Indications for Testing

- Laboratory Considerations
- Indications for analysis of inherited genetic alterations
- Indications for analysis of acquired genetic alterations
- PCR and detection of DNA sequence alterations
- Molecular analysis of genomic alterations
    - Fluorescence In Situ Hybridization (FISH)

    - Cytogenomic array technology
- Polymorphic markers and molecular diagnosis
- Epigenetic alterations
- RNA analysis
- Next-Generation Sequencing (NGS)
    - Bioinformatics
    - Clinical applications of next-generation DNA sequencing
- Advantages and disadvantages of each methodology

Supplementary reference

Molecular genetics and genomics

Coleman WB, Tsongalis GJ (Eds). Diagnostic molecular pathology: a guide to applied molecular testing. London, UK: Academic Press, Elsevier, 2017.

Section 6: Diseases of the immune system

6.1 Innate immunity

- Epithelial barrier – skin, gastrointestinal tract, respiratory
- Neutrophils and macrophages
- Dendritic cells
    - Peripheral
    - Follicular
- Natural killer (NK) cells
- Complement
    - Understand how complement deficiency may lead to bacterial infections or associated conditions
    - Understanding downstream effects of complement
    - Understand the role of complement in development of atherosclerosis
- Pathogen-associated molecular patterns (PAMP): role in infection and autoimmunity
- Damage-associated molecular patterns (DAMP): role in infection and autoimmunity
- Toll-like receptors (TLR): role in infection and autoimmunity

6.2 Adaptive immunity

- Humoral: B-cells and Ig
- Structure of lymph nodes and spleen
- Cellular: T-cells (CD4 and CD8)
    - TCR: structure and use of antibodies to detect components
    - Rearrangement: role in assessment of T-cell neoplasia

6.3 Major Histocompatibility Complex Molecules (MHC)

- Class I versus Class II: How one triggers CD4 and the other CD8.
- Role of HLA

6.4 T-cell subsets

- Th1
- Th2
- Th17
    - IL-17 functions in inflammation, a host defence and autoimmunity.
    - How IL-17 stimulates cytokines and chemokines and functions as antimicrobial.
- Tgamma-delta: allows a quick triggering of the immune response system
- Treg

6.5 Hypersensitivity reactions

- Type I – Immediate: A (Atopy/Anaphylaxis)
- Type II – Antibody-mediated: C (Complement/Cyt2toxic)
- Type III – Immune complex: I (Immune complex)
- Type IV – T-cell mediated: D (Delayed Type – purified protein derivative [PPD])

6.6 Tolerance

- Central: how escape may lead to auto-immune disease
- Peripheral: role of co-stimulatory molecules such as CD28 and CTLA-4, and development of anergy, apoptosis or suppression

6.7 Autoimmunity disease

- Systemic Lupus Erythematosus (SLE)
- Rheumatoid Arthritis Scleroderma
- Polyarteritis Nodosa and other vasculitides
- IgG4 related disease

6.8 Transplant rejection

- Mechanisms of recognition and rejection of allografts
- Morphology of rejection: acute and chronic

6.9 Acquired Immunodeficiency Syndrome (AIDS)

- Epidemiology, pathogenesis and natural history of HIV infection

6.10 Amyloidosis – types

- Mechanism of development
- Why patients with rheumatoid arthritis can develop Aa amyloidosis

Supplementary references

Innate immunity
Gasteiger G, D'Osualdo A, Schubert DA, Weber A, Bruscia EM, Hartl D. Cellular Innate Immunity: An Old Game with New Players. J Innate Immun. 2017;9(2):111-125.

Human immunology and immunotherapy
Varadé, J., Magadán, S. & González-Fernández, Á. Human immunology and immunotherapy: main achievements and challenges. Cell Mol Immunol 2021 18, 805–828.

Tolerance
Klein L, Kyewski B, Allen PM, Hogquist KA. Positive and negative selection of the T cell repertoire: what thymocytes see (and don't see). Nat Rev Immunol. 2014 Jun;14(6):377-91.

Section 7: Neoplasia

7.1 Nomenclature

- Benign versus malignant
  - Metaplasia, dysplasia, and carcinoma In situ
- Hamartoma: understanding of terminology
- Choristoma: understanding of terminology
- Dysplasia: understanding of terminology

7.2 Determination of rates of growth

7.3 Cancer stem cells and tumour initiating cells (see - Section 1)

7.4 Metastasis

- Seeding of body cavities
- Lymphatic spread
- Haematogenous spread

7.5 Geographic and environmental factors

- Mechanism of cell induced damage by occupational factors such as:
  - Arsenic
  - Asbestos
  - Benzene
  - Cadmium
  - Chromium
  - Nickel
  - Radon
  - Vinyl chloride
  - Radiation

7.6 Genetic predisposition

- Autosomal dominant
- Defective DNA repair

7.7 Non-hereditary

- Chronic inflammation
- Microbial carcinogenesis : eg viral hepatitis, helicobacter pylori

7.8 Molecular basis

Self-sufficiency that drives proliferation

- Proto-oncogenes and oncogenes
- Growth factors
- Signal transducers
- Alterations in non-receptors e.g. Tyrosine kinase, nMYC
- Transcription factors
- BRAF: Presence in some tumours and use of monoclonal therapy (BRAF monoclonal) as well as diagnosis in histopathology

Insensitivity to growth-inhibition

- Cannot apply the brakes
- Some examples:
    - p53: use in diagnostic pathology and interaction with oncogenic viruses
    - RB: role in development of some tumours
    - Cyclins: diagnostic role in some lesions such as mantle cell lymphoma
    - APC/ß catenin: role in development of some tumours
    - INK4: role in HPV associated disorders and diagnosis
    - TGFß: role in development of some tumours
    - PTEN: may be lost in some tumours
    - NF1 and NF2: role in development of tumours in neurofibromatosis (NF) syndromes
    - SMAD2, SMAD4: role in colonic and pancreatic carcinoma
    - VHL: role in renal cell carcinoma

Evasion of apoptosis

- Bcl-2
    - Viruses such as EBV have bcl-2 homologues
    - Use of Bcl-2 in immunohistochemistry
- Death pathway (CD95)

Limitless replication (immortality)

- Telomeres: mechanism of action of telomeres in development of cell proliferation

Sustained angiogenesis and vascular changes

- VEGF: use of monoclonal therapy for these tumours
- Hypoxia
- P53
- bFGF

Ability to invade and metastasise

- Invasion of extracellular matrix
- Cell dissociation
- Degradation of basement membrane
- Change in attachment to extracellular matrix

Evasion of the host immune response (see below)

Defects in repair

- ATM: how mutation prevents cell arrest
- BRCA1: involvement in different cancers

7.9 Dysregulation of cancer associated genes

- Chromosomal changes
- Gene amplification
- Epigenetics

7.10 Microbial carcinogenesis

- HTLV1
- HBV: the many pathways in which HBV and HCV are involved in carcinogenesis
- HCV
- H pylori

- EBV: how LMP1 of EBV is able to stimulate cell proliferation and survival

7.11 Host defences

- Changes in tumour antigens
- Tumour immunity including CTLA-4 and PD-1
- Product of mutated genes that are recognized by Class I MHC and Class II
- Overexpressed cellular proteins (i.e. structurally normal)
    - Tyrosinase and melanin
    - Cancer-testis antigen: use in diagnosis and immunotherapy
    - Antigens produced by oncogenic viruses
    - Oncofetal antigens
    - Altered cell-surface glycolipids/glycoproteins: the concept of post-translational modification e.g. sialylation in development of malignancies
    - Ganglioside GD1, GD2: used in monoclonal therapy
    - Mucins – Ca125, CA19-9, MUC1: diagnostic role in neoplasia

7.12 Clinical aspects

- Local and humoral
- Cancer cachexia including Warburg effect
- Paraneoplastic:
    - Hypercalcaemia
    - Neuromyopathic
    - Hypertrophic osteoarthropathy: understand some of the proposed mechanisms
    - Migratory thrombophlebitis: activation of Factor X by mucin from tumours increased tissue factor
- Grading and staging of neoplasms

7.13 Laboratory diagnosis

- Histology
- Immunohistochemistry
- Flow cytometry
- Molecular profiling
- Tumour markers

Supplementary references

BRAF review
Zaman A, Wu W, Bivona TG. Targeting Oncogenic BRAF: Past, Present, and Future. Cancers (Basel). 2019 Aug 16;11(8):1197.

PD-1
Sharpe, A., Pauken, K. The diverse functions of the PD1 inhibitory pathway. Nat Rev Immunol 2018;18: 153–67

Section 8: Infectious diseases

8.1 Categories of infectious agents

- Prions
- Viruses (including SARS-CoV-2)
- Bacteria: difference between Gram +ve and -ve
- Fungi and cell wall component
- Protozoa
    - Intracellular
    - Extracellular

8.2 Route of entry and protective mechanisms

- Skin
    - Breaks in skin – burns, diabetes, trauma
    - Enzymes released by organism e.g. schistosomiasis
- Gastrointestinal tract defences
    - Mucus in stomach: how overcome by organisms such as Giardia attach to epithelium
    - Pancreatic enzymes: overcome by Cryptosporidia taken up by enterocyte
    - Defensins: overcome by pore formation by *E histolytica*
    - Normal flora
    - IgA
- Respiratory pathogen strategies:
    - Overcome mucociliary: Influenza cleaves surfactant protein
    - Avoid detection by alveolar macrophages
        - Paralyse cilia: B. pertussis
        - Ciliostasis: Pseudomonas
        - Invade after epithelium lost: Strep/Staph
- Urogenital
    - *N gonorrhoeae* and *E coli* have adherence
- Protective role of mucosa in viral infection: how viruses evade these mechanism

8.3 How infectious agents cause disease

- Directly
- Release toxin
- Induce host immune response

8.4 Viral pathogenicity

- HIV: gp 120 binds CD4, CXCR4(T-cell)
- EBV: gp350 – binds CR2 on B cells and integrins
- JCV: Cell type restricted. Only replicates in oligodendrocytes
- Rhinovirus: Temperature sensitive

8.5 How viruses kill

- Prevent DNA/RNA replication: Polio
- Inhibit DNA, degrade RNA: HSV
- Increased apoptosis: HIV
- Increased caspases
    - Antiviral immune response: Hepatitis B
    - Transformation of infected cells: See neoplasia.

8.6 How bacteria and fungi kill

- Biofilms: important aspect of bacterial endocarditis, artificial joint infection and cystic fibrosis
- Adherence to host cells
    - Strep pyogenes: (Adhesins) Protein F binds to surface of host cells via fibronectin
    - *E. coli*: cause urinary tract infection by binding to urothelial cells
    - *N. gonorrhoeae*: pili mediate attachment
- Intracellular inhibition of host proteins: Shigella and *E. coli*
- Mechanism of cell damage in anthrax
- Mechanism of disease formation in syphilis
- Blocks fusion of lysosome with phagosome: *M tuberculosis*
- Escape from phagolysosome and actin polymerization: *Listeria monocytogenes*
- Capsule and enzyme properties and switching by fungi
- Distinction between yeasts and moulds
- Toxin
    - Exotoxin
        - LPS induces cytokines and chemokines
        - Binds to CD14 and TLR4
        - If excessive may lead to disseminated intravascular coagulation
    - Endotoxin
    - Enzymes: *S. aureus* destroys keratinocytes
    - Alter intercellular signalling: *B. anthrax* and *V. cholera*
    - Neurotoxin: *C. botulism, C. tetani*
    - Superantigens stimulate T cells polyclonally: *S. aureus, S. pyogenes* toxic shock syndrome

8.7 Specific viral pathogens

- Measles
    - Receptor CD46
    - Hallmarks: Lung giant cells
- Mumps
    - Site of replication (lymph node and salivary gland): to explain clinical symptoms
- Polio
    - Receptor unique to humans CD155
    - Percentage that develop symptoms
- West Nile Virus/ Viral Hemorrhagic Fever
    - Replication sites and spread Pathogenesis of a vector disease
- Zika virus
    - Cause of microcephaly
- Dengue
    - Mechanism of infection and reaction: emerging pathogen in Australasian region
- Herpes Simplex Virus (HSV)
    - Replication sites
    - How evade cytotoxic T lymphocytes (inhibit MHC1): mechanism of immune evasion
- Varicella-Zoster Virus (VZV)
    - Similar to HSV in mucus membranes
    - Morphology of infection
- Cytomegalovirus (CMV)
    - Latent infection of monocytes
    - Mechanism of immune evasion: decreases MHC I and II, evade NK cells

- Epstein-Barr Virus (EBV)
  - Role of EBNA1, 2
  - Role of LMP1
  - Role of LMP2
  - Morphology of infectious mononucleosis
- CORONAVIRUSES (including MERS, SARS and SARS-CoV-2)
  - Receptors ACE2, DPP4
  - Organ tropism
  - Types of vaccine strategies

8.8 Malaria

- Important infectious agent in Asia Pacific Region; Australia's leading role in development of a vaccine
  - Mechanism of replication
  - Role of glycophorin
  - Role of thrombospondin

8.9 Special Techniques for diagnosing infectious agents

Supplementary references

Prion disease
Baiardi S, Rossi M, Capellari S, Parchi P. Recent advances in the histo-molecular pathology of human prion disease. Brain Pathol. 2019 Mar;29(2):278-300.

Toxic shock
Low DE. Toxic shock syndrome: major advances in pathogenesis, but not treatment. Crit Care Clin. 2013 Jul;29(3):651-75.

H pylori update
Franceschi F, Zuccalà G, Roccarina D, Gasbarrini A. Clinical effects of Helicobacter pylori outside the stomach. Nat Rev Gastroenterol Hepatol. 2014 Apr;11(4):234-42.

Coronaviruses
Chathappady House NN, Palissery S, Sebastian H. Corona Viruses: A Review on SARS, MERS and COVID-19. Microbiol Insights. 2021 Mar 19;14:11786361211002481.

Zika virus
Baud D, Gubler DJ, Schaub B, Lanteri MC, Musso D. An update on Zika virus infection. Lancet. 2017 Nov 4;390(10107):2099-2109.

.

Section 9: Environmental and nutritional disorders

9.1 Xenobiotic metabolism

9.2 Phase I and II reactions and cytochrome P450 enzymes (CYP)

- Phase I reactions and CYP induction: understand difference between the two
- Phase II reactions

9.3 Environmental pollution: out door and indoor

- Ozone
- Particulate matter
- Carbon monoxide: a common cause of disease in humans
- Formaldehyde: a common laboratory agent

9.4 Metals

- Lead: mechanism of cell damage
- Mercury
- Arsenic
- Cadmium

9.5 Occupational health risk

- Organic solvents eg: Chloroform: conversion to phosgene and toxicity
- Polycyclic hydrocarbon: presence in PM2.5 and interaction with DNA
- Organochloride
- Dioxin

9.6 Tobacco and role in

- Lung carcinoma
- Atherosclerosis: see atherosclerosis
- Other diseases eg fetal growth, type 2 diabetes

9.7 Alcohol and other medications

- Alcohol
    - Metabolism
    - Microsomal ethanol oxidizing system (MEOS)
    - Catalase
    - CYP2E1
    - Effects on organs
- Acetaminophen: mechanism of cell damage. A common cause of poisoning in Australia
- Cocaine: mechanism of action
- Heroin: mechanism of action
- Amphetamine
- Marijuana
- Morphological changes to pharmaceutical medications

9.8 Burns

- Shock: mechanism
- Sepsis: mechanism
- Respiratory insufficiency: mechanism

9.9 Ionizing radiation

- Direct and indirect effects of DNA damage
    - Cell death
    - Teratogenesis
    - Carcinogenesis

9.10 Protein energy malnutrition

- Dietary
- Cachexia
- Severe acute malnutrition (SAM): Kwashiorkor vs marasmus

9.11 Vitamin A and role in

- Infection: stimulation of RIG-I
- RARα: immune modulation

9.12 Vitamin D and role in

- Disease as a result of deficiency or excess
- Immune system

9.13 Vitamin C

- Results of deficiency: antioxidant mechanism

9.14 Obesity

- Leptin versus ghrelin: role in metabolic syndrome
- Adiponectin

9.15 Climate change

- Role in disease

Supplementary references

Vitamin D review

Chun RF, Liu PT, Modlin RL, Adams JS, Hewison M. Impact of vitamin D on immune function: lessons learned from genome-wide analysis. Front Physiol. 2014 Apr 21;5:151.

Climate change

Hess J, Boodram LG, Paz S, Stewart Ibarra AM, Wasserheit JN, Lowe R. Strengthening the global response to climate change and infectious disease threats. BMJ. 2020 Oct 26;371:m3081.

Section 10: Diseases of infancy and childhood

10.1 Definitions of congenital anomalies

- Malformations
- Disruptions
- Deformations
- Malformation syndrome
- Sequence
- Agenesis
- Hypoplasia

10.2 Causes of anomalies

- Genetic
- Environmental
- Pathogenesis regarding to timing

10.3 Specific abnormalities

- Prematurity with necrotizing enterocolitis
- Fetal hydrops: immune and nonimmune
- Sudden infant death syndrome

10.4 Inborn errors of metabolism and other genetic disorders

- Phenylketonuria
- Galactosemia
- Cystic fibrosis

Section 11: Blood vessels

11.1 Endothelial cells

- Contents: use of vWF antibodies and CD31 antibodies
  - Endothelial activation: beneficial but danger in sepsis (too much of a good thing)
- Expressing new inducible properties
- Endothelial dysfunction
- Impairment of vasoactivity
- Thrombogenic
  - Vascular smooth muscle
- Ability to proliferate
- Ability to produce extracellular matrix
- Ability of migrate under influence of certain factors such as PDGF, FGF, nitrous oxide and IFN.

11.2 Response to injury

- Intimal thickening
  - Smooth muscle growth
  - Increased matrix

11.3 Hypertension

- Essential
  - Multifactorial
  - Genetic
  - Decreased Na excretion
- Secondary
  - Renovascular
  - Hyperaldosteronism

11.4 Atherosclerosis

- Constitutional risk factors
  - Age
  - Gender
  - Genetics
- Modifiable
  - Hypertension
  - Diabetes mellitus
  - Inflammation
  - Hypercholesterolaemia
  - Metabolic
  - Lipoprotein a
  - Factors affecting haemostasis

11.5 Pathogenesis of atherosclerosis

- Endothelial injury
  - hypertension, hyperlipidaemia, nicotine, homocysteine, infection, haemodynamic
- Lipids
  - Increased oxygen free radicals
  - Increased nitric oxide
  - Oxidized low density lipoproteins

        - Ingested by macrophages
        - Release of growth factors by endothelial cells
        - Toxic to endothelial cells -> dysfunction
    - Inflammation
        - Macrophages activated increase WBC adhesion
        - Increased T-lymphocyte
        - Increased cytokines
        - Increased complement activation

11.6 Consequences of atherosclerosis

- Stenosis
- Thrombus
- Infarction
- Acute plaque changes
    - Rupture
    - Erosion
    - Haemorrhage
    - Aneurysm

11.7 Vasculitis

- Infectious causes
- Non-infectious causes

Supplementary references

Atherosclerosis review
Bergheanu SC, Bodde MC, Jukema JW. Pathophysiology and treatment of atherosclerosis : Current view and future perspective on lipoprotein modification treatment. Neth Heart J. 2017 Apr;25(4):231-42.

Oxidative stress and vascular disease
Kim YW, Byzova TV. Oxidative stress in angiogenesis and vascular disease. Blood. 2014 Jan 0;123(5):625-31.

Section 12: Research concepts

12.1 Research

- Definition
- Research vs audit
- Planning
    - Null hypothesis
    - Literature review
    - Ethics approval
- Evidence based medicine: levels of evidence

12.2 Research designs

- Naturalistic
- Observational
- Case control
- Cohort
- Cross sectional/prevalence
- Experimental
- Intervention
- Randomized control trial
- Meta-analysis
- Systematic review

12.3 Research methods

- Quantitative
- Qualitative
- Mixed methods
- Single/double blind

12.4 Data

- Variables: dependent and independent
- Categorical (nominal), ordinal, ratio (interval, continuous)
- Control
- Bias and confounding
- Error – random, systematic
- Type 1 error
- Type 2 error
- p value
- Validity
- Reliability

12.5 Measurement

- Accuracy
- Precision
- Frequency distribution (polygon)
- Central tendency: mean, median, mode
- Dispersion: range, standard deviation
- Confidence interval
- Standard error of the mean

- Z-score

12.6 Tests

- Sensitivity
- Specificity
- True/false positive/negative

Supplementary references

Glasser SP (Ed.). Essentials of Clinical Research (2nd edition). Springer International Publishing, Switzerland, 2014

Schulz KF and Grimes DA. Essential Concepts in Clinical Research: Randomised Controlled Trials and Observational Epidemiology (2nd edition). Elsevier, 2019.

https://research.library.gsu.edu/c.php?g=115595&p=755213 (accessed 12/9/2021)

Section 13: Error reduction and prevention

13.1 Error

- Definitions
  - Error
  - Quality control
  - Quality assurance

13.2 Preanalytical errors

- Definition and types
  - Incorrect clinician test selection
  - Lost specimen or incorrect specimen transport
  - Patient and specimen misidentification
  - Inadequate or incorrect specimen
  - Inadequate or incorrect specimen description
- Error Management

13.3 Analytical errors

- Definition and types
  - Work habits- eg. specimen processing, preparation
  - Clinical history
  - Diagnostic criteria
    - False positives/ false negatives
    - Misclassification
    - Misinformation
  - Competence- continuing professional development
- Error Management -case review; multidisciplinary team review

13.4 Post analytical errors

- Definition and types
  - Transcription error
  - Transmission error
  - Tracking reports
  - Clinician misinterpretation of the test results, and clinical action based on that interpretation.
- Error Management – quality systems – NATA accreditation

Supplementary references

https://link.springer.com/book/10.1007%2F978-1-4939-2339-7

https://journalofethics.ama-assn.org/article/error-disclosure-pathology-and-laboratory-medicine-review-literature/2016-08