L2 – Human Body

Describe and demonstrate the anatomical position of the human body

Erect, arms at side, face palms and toes forward

Comparative = on all fours

Define the anatomical reference lines and planes

Coronal plane (ear to ear)

Sagital plane (back to chest)

Horizontal/Transverse plane (up and down)

Define terms used to denote relative position

Anterior = front of coronal

Posterior = back of coronal

Lateral = Away from sagittal

Medial = towards sagittal

Superior = above horizontal

Inferior = below horizontal

Comparative = Dorsal (to back)

Cranial Rostral (head) < ^ > Caudal (to pelvis)

Ventral (to belly)

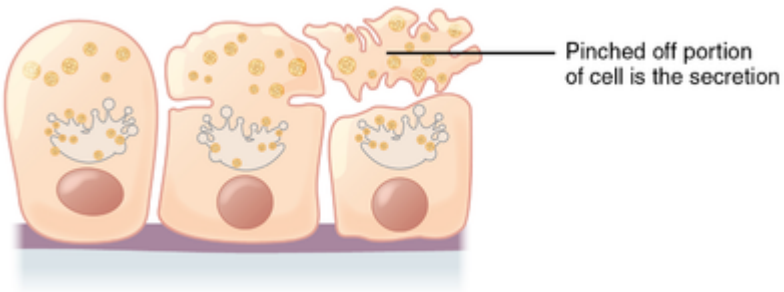
Limbs (Left):

Arm: Proximal (superior)

Ulnar (medial) < ^ > Radial (lateral)

Distal (inferior)

Leg: Proximal (superior)



Endocrine = Hormones directly into blood stream

- Paracrine = R close by
- Autocrine = R on that cell

Carcinoma = epithelial cell origin; 45yo, >90% of tumors

L5 Histology 2

Describe the major characteristics of the 3 other basic tissues

Describe morphological and functional feature of different types of CT

Note: Edema occurs when water is retained in CT (can palpate or see); Hydrostatic and osmotic pressure are different

Cells (6)

- Fibroblasts: most common (active); synthesizes extracellular matrix, healing and scar formation. Damage below basement membrane = scarring because CT has been touched; Retired/quiescent called fibrocytes;
- Macrophage: Phagocyte, inflam/immune response. Fr bone marrow
- Mast Cell: histamine, inflam/immune response. Fr bone marrow
- Plasma Cell: antibodies; dark cytoplasm, lots of RER for proteins(aB)
- Adipose Cells: fat storage
- Leukocytes: Diapedesis (migration) in inflam response

Fibres (3)

- Collagen fibers: structural (comes from fibroblasts)
- Reticular fibers: collagen 3; needs special staining
- Elastic fibers: resist pulling

Ground Substances (3)

- Glycosaminoglycan (GAGs): polysacc and hyaluronic acid
- Proteoglycans : protein + gags; dermatan-, chrodroitin-, keratin-, heparin-sulfate

- Glycoproteins: Proteins + carbohydrates; fibronectin, lamini

Cartilage (3)

- Hyaline: perichondrium top; no BV; Collagen 2, proteoglycans,, chondronectin
    - Synchondrosis Joint
    - Embryonic skeleton
    - Trachea
    - Articular surfaces of joints
- Elastic: Collagen 2, elastic fibres
    - External ear, Eustachian tube (middle ear to pharynx), epiglottis (divides GI from resp in throat)
- Fibro: collagen 1; dense CT
    - Symphysis joint
    - Intervertebral discs, symphysis pubis, sternoclav, temporomandibular, menisci of knees, certain tendons (muscle to bone) and ligaments (bone to bone)

Bone

- Long bones
    - Epiphysis (ends)
    - Metaphysis (in between)
    - Diaphysis (Shaft)
- Compact outside
- Cancellous inside
- Marrow and Trabeculae (microscopic small beams; bone cells)
- Cells
    - Osteoprogenitors -> osteoblasts -> osteocytes (retired, in lacuna)
        - Osteoid becomes mineralized
    - Osteoclasts: Big, lots of nuclei, reabsorb bone
- Extracellular matrix: collagen 1, proteoglycans, glycoproteins
- Mineralization: of extracellular matrix by Hydroxyapatite crystals (Ca and P) $Ca_{10}(PO_4)_6(OH)_2$
- Function: Support, protect, store (Ca and P)
- Osteon / Haversian System
    - Vertical (parallel) = harversian canals
    - Perp = Volkmann canals
    - Lamella = concentric circles
    - Lacuna = small space containing One osteocyte
    - Canaliculi = canals that connect to BV from main canals
    - Periosteum = Outside ‘cement’
- Conditions
    - Paget’s: uncontrolled blast/clast = larger disorganized bones; fractures
    - Osteoporosis: clasts > blasts = fractures and compression
    - Rickets: insufficient Ca (or Vit D for Ca abs) during growth

- Intermediate mesoderm: Sagittal stripe down either side of paraxial mesoderm; flanks gut, Kidneys (mesonephros = 1st kidney), ureters, gonads and reproductive ducts, adrenal cortex (Primary retroperitoneal organs if they stay there)
- Lateral (plate) mesoderm:
    - Mesothelium (lining of body cavities, 2 sides)
    - Splanchnic (visceral) mesoderm: Muscle and CT of perimative gut; Heart myocardium and endocardium
    - Somatic (parietal) Mesoderm: CT of anterolateral body walls and limbs, Appendicular skeleton

Endoderm – Epithelial derivatives of the primitive gut; a lot grows out of it

- Alimentary system: Pharynx, Alimentary canal, Accessory glands (Liver and Pancreas)
- Respiratory system: Larynx trachea, bronchi, lungs
- Urinary and genital systems: Urinary bladder, urethra, vagina and prostate
- Derivatives of pharyngeal pouches: Middle ear, tonsils, thymus, thyroid and parathyroid

L7 Body Cavities

Define the 3 main body cavities

Cranial – brain, meninges (dura, arachnoid and pia mater between skull and brain), pituitary and pineal glands

Thoracic – heart; ribcage, sternum, thoracic vertebrae; diaphragm is the base; cupula pleurae is the top (near neck)

Abdominopelvic – liver; diaphragm = roof, anterolateral abdomen wall, posterior abdomen wall, pelvic diaphragm = floor.

Describe the positions of the pleural and pericardial cavities, and mediastinum within the thoracic cavity

Pleural Cavities: R and L, Pleura and Lungs; Lungs covered in Pleural lining

Middle divider = Mediastinum: Pericardial cavity, Pericardium and Heart

Trachea, esophagus and great vessels

Describe in general terms pulmonary and systemic circulation, and lymphatic drainage

R Atrium > R ventricle > Pulmonary artery > Lungs > Pulmonary vein > L atrium > L ventricle > Aorta

Coronary arteries supply heart with blood

Explain the significance of vascular anastomoses and portal systems

Normal Anastomoses

- Artery-artery: Collateral circulation (backup plan for heart and brain, but variation in the population so different susceptibility to ischemia and infarctions)
- Vein-vein: alt drainage paths
- Arteriole-venule: regulation of blood flow, ie: skin and intestines

Pathological anastomoses: due to trauma or disease; congenital, acquired or enlargement of existing anastomoses

Hepatic Portal circulation

- Venous blood from gut > hepatic portal > liver for processing
- Connection without dilution (mixing with the rest of systemic circulation)
- Functional significance
- Other portal vessels can be arteriolar (glomerular arterioles)

Define the primary and secondary lymphoid organs in structural and functional terms

Primary = where lymphocytes originate: Thymus and Bone Marrow

Secondary = where you can find lymphocytes; usually in recognition to pathogens: Lymph nodes, spleen (dense, encapsulated) or non-encapsulated (loose) = MALT, GALT, BALT (mucosa, gut, bronchus associated lymphoid tissue)

Lymph node = organ associated

Accumulation of lymphocytes = not a node

Lymph Node

- Afferent lymph vessels
- Lymphoid nodule
- Cortex (meaty stuff) Outer and inner
- Trabecula (ingrowths)
- Capsule (outside)

Outline the processes by which genes are transcribed and translated in eukaryotes

Semi-conservative process

Leading strand: Primer + dna polymerase; helicase unwinds

Lagging strand needs okazaki fragments and many primers

RNA

- 2’ hydroxyl on the sugar
- U replaces T
- mRNA = protein (<5%)
- rRNA = protein synthesis on ribosomes
- tRNA = adaptors between mRNA and AA
- miRNA = regulators, block expression by blocking mRNA translation
- siRNA = block gene expression at mRNA degradation and chromatin

RNA polymerase reads antisense strand and makes RNA 5’ to 3’

Eukaryotes transcription

- 5’ capping
- 3’ poly A tail
- RNA splicing to remove introns
- Differential splicing to allow for more mRNA combos

Prokaryotes it’s just DNA -> RNA

Translation

- mRNA interacts with ribosome
- tRNA with matching anticodon brings AA
- AA is attached to growing peptide chain and removed from tRNA
- Genetic code is degenerate but not ambiguous
- UAA, UAG, UGA are stop, AUG = Met (start)
- Bacterial ribosome is slightly different

Describe the various levels at which gene expression can be regulated

Initiation of transcription (Most important)

Capping, elongation, and splicing

Cleavage, poly A, and termination

Export of mRNA

- Acquired: infection, nutritional, chemical, physical, etc
- Single etiologic agent (ie: HFE gene in hemochromatosis, single mutation, less common)
- Multifactorial (ie: atherosclerosis; much more common)

Pathogenesis = sequence of events that occurs in response of cells/tissues to the etiologic agent

Morphological changes

- Structural changes in cells/tissues characteristic of the disease
    - Tools: physical exam, gross exam, LM (tissue, including stains and immunochem), TEM (cellular)
- Molecular changes
    - DNA, RNA, Chromosomal, amplifications, deletions, mutations
    - Tools: Karyotypes, PCR, SNP chips, cDNA microarray, array CGH (comparative genomic hybridization), Whole genome seq

Clinical manifestations

- Symptoms (ie: chest pain) and signs (ie: jaundice)
- Caused by underlying abnormalities in cells/tissues

Understand common adaptations and responses to cell injury: hypertrophy, hyperplasia, atrophy, metaplasia

Response = Adaptations, or cell death

- Other pathology = inflammation and neoplasia (next lectures)

Homeostasis = steady state, normal

Adaptations = reversible structural/functional changes in response to injury/stress

- New SS, cell/tissue survives

Cell death = irreversible injury; necrosis or apoptosis

Adaptations

- Hypertrophy
    - Increased cell size, due to increased cellular protein
    - Physiologic = uterus during pregnancy
    - Pathologic = cardiomyopathy
- Hyperplasia
    - Increase in # of cells in an organ/tissue
    - Typically results in increased tissue/organ mass
    - Physiological: Hormonal (breast prolif at puberty) or Compensatory (partial hepatectomy, liver regenerates)
    - Pathological: warts

- Necrosis (any cause)
- Foreign bodies
- Immune reactions

Components

- Altered vasculature => increased blood flow
- Structural changes in microvasculature => plasma proteins and leukocytes leave circulation (edema)
- Emigration of leukocytes from microcirculation -> accumulation in focus of injury -> activation to eliminate offending agent

Leukocytes adhere and pass through endothelial wall

Exudate edema = increased permeability of BV -> high [proteins] in extravascular fluid

Transudate edema = Increase hydrostatic pressure; fluid leakage; fluid with low protein content

Leukocytes: Neutrophils and macrophages mostly; ingest and destroy bacteria, produce GF and aid repair. Rolling > adhesion (via chemokines) > penetration

- Phagocytosis = eat stuff
- Degranulation = send out ROS and lysosomal enz
- NETs = send out nuclear components

4 Types of morphological patterns with all the above general features)

- Serous inflammation
    - Exudation of cell-poor fluid (clear)
        - Not many leukocytes; typically not from microbes
        - Fluid in body cavities (effusion) or blisters from burn/virus
- Fibrinous inflammation
    - Large Vascular leaks, or there is a local pro-coagulant stimulus
    - Usually in linings of body cavities (meninges (brain), pericardium, pleura)
- Purulent (suppurative) inflammation/ Abscess
    - Puss
    - Many neutrophils, debris of cells, and edema fluid
    - May lead to enclosure of neutrophils = abbess
    - Bacterial pathogens
- Ulcer = local deficit on surface of organ/tissue from shedding of inflamed tissue

Outcomes

- Resolution = short term, minimal damage
- Abscess formation
- Scarring or fibrosis = healing by replacement with CT. In tissues not capable of regen/extensive fibrin exudation
- Progression to chronic inflame (persistence of agent, or interference with normal healing)

Navigate the 4 levels of protein structure in a variety of pictorial formats, providing examples of structural diversity and its role in various protein functions.

Genome > proteome > metabolome

Primary structure

- Linear polymer of AA
- Ionized at physiological pH
- 20 common AA; each have different side chain
- Differ by polarity (hydrophobic and polar) and ionizability (acidic and basic)
- Peptide bond (cis or trans)
- Proteomics (Mass spec or NMR)

Secondary structure = regular arrangements of residues in close proximity

- A-helix and B-sheet
- H-bond interactions
- Diseases like Alzheimer's and prions

Tertiary = 3D arrangement of a single polypeptide

- Cysteine = disulfide bonds

Quaternary = number and arrangement of multiple subunits

Post-translational modifications

- Phosphorylation
    - Transfer of PO3 from ATP to OH groups of some AA (Ser/Thr or Tyr)
    - Catalysed by Kinase, removed by Phosphatase
    - Regulation of metabolism and signal transduction
- Glycosylation
    - Attachment of complex carbohydrate groups to AA (Ser or Asn)
    - Secreted, extracellular, or lumen proteins
    - Affects stability, targeting, recognition
- Proteolysis
    - Enzymatic cleavage of polypeptide chain at specific sites
    - Activation of other proteases
    - Synthesis of peptide hormones (ie: insulin)

Protein stability and denaturation

- Orientation of membrane lipids and proteins is maintained from point of synthesis

Secretory = ER > Golgi > lysosome, exterior, or vesiscle

Endocytic = Exterior > early endosome > late endosome > sometimes lysosome

Retrieval = Exterior, endosome or vesicle > golgi > ER

Outline the major cytoskeletal components and their roles in maintaining cell shape and movement

Microtubules = alpha beta dimers to form a hollow tube

- Largest diameters
- Bound to GDP
- Hydrolize to GTP => Polarize (Gives info)
- + and - end
- Anchored at - end to centrosome for example, grow and shrink at + end
- Carry things through cells
- Allow separation of chromosomes through mitosis
- Anticancer drugs can inhibit MT function (ie: taxol)

Actin

- Smallest
- Formed by reversible polymerization of G-actin (globular)
- Polymerizes to form F-actin (fibrous)
- Usually 50/50
- Also polar, - and + end
- Polymerise as ATP bound
- Hydrolyze to ADP => treadmill (gives info)
- Can push things in a certain direction

IF

- Usually insoluble fibrous proteins
- Polymerization usually controlled by Phos and de-phos
- So less info than others

Actin in motility

- Stress fibre = Contractile bundle; point of attachment to extracellular matrix; point of contraction
- Cell cortex = Gell/mesh that gives rigidity and structure to plasma mem
- Filopodium = tight parallel bundle; sends out finger to push cell forward

Actomyosin = contractions:

- Myosin head on actin (rigor)

Explain basic concepts related to cellular metabolism and energy transformation, including free energy, equilibrium, anabolic and catabolic

Catabolic pathways

- Destroys -> provides building blocks
- Carbs, fat, proteins -> CO2, H2O, NH3
- Oxidative process
- Generates reduced cofactors (NAD+ and FAD -> NADH and FADH)
- Yields energy (ATP)

Anabolic pathways

- Builds
- Uses ATP and the reduced cofactors (NADH, FADH)
- Reductive process; requires energy
- AA, sugars, N-bases, fatty acids -> Proteins, polysaccharides, nucleic acids, lipids

Free energy: energy intake (food) = expenditure + weight gain/loss

- G measured in calories
- Spontaneous if deltaG <0
    - Due to release in heat (delta H – enthalpy) or increase in disorder (delta S – entropy)
- Standard free energy = Delta G* (all same [])
- In Actual body, the reaction depends on DG (so DG* and the [])
- Unfavorable (endergonic) rxn can proceed if its coupled with a favourable (exergonic) rxn

List the main energy stores at the cellular and whole body levels and describe in general terms how their breakdown (oxidation) leads to generation of ATP

Storage: glycogen (animals), starch (plants), triacylglycerols (fat*) and protein

Transport: Glucose, fatty acids, glycerol, AA

Energy Release: pyruvate, Acetyl CoA; breakdown coupled to ATP synthesis

We get our energy from the oxidation of glucose, FA, or other fuel molecules

- Coenzymes get reduced from NAD+ to NADH
- NADH subsequently reoxidized to NAD+ in the e-transport chain, which is coupled to ATP synthesis by oxidative phosphorylation (in mitochondrion)

ATP

Discuss how diagnostic and screening tests are used to support clinical decision making

Tests clinically useful to avoid harm

Sensitivity and specificity are properties of the test

PPV and NPV are properties of both the population and the test

- 2 populations with different disease prevalence = different PV

Most useful when it meets criteria

- Condition can be detected preclinically
- Highly accurate
- Minimal harm from false + and false –
- Early intervention can actually make a difference
- Feasible and affordable

L28 Virtual EBP

Identify several steps and sources of information involved in the process of clinical reasoning

Clinical guideline = systematically developed statement to ASSIST practitioner and patient decisions about APPROPRIATE health care for specific clinical circumstances

Aim = improve patient outcomes; without constraining practitioner or producing "cook-book" medicine

Resources: Cochrane collab/database, systematic review, EBM

EBM = current best evidence; mathematical estimates of the benefit: harm ratio

System 1 reasoning = Pattern recognition (fast, efficient, experience driven; don't have much yet)

System 2 reasoning = effortful, organized, slow and exhaustive

- Malignant features (above)
- Reporting
    - Benign (-‘ve for malignancy)
    - Abnormal/atypical
    - Suspicious for malignancy
    - Positive for malignancy
    - No diagnosis; ie: if you didn’t get any cells because lesion was too thick

Core needle biopsy

- Small tissue sampled from lesion
- Often guided by mammography or US
- Tissue architecture present
- Longer to process
- Can do special stains, immunohistochemistry and molecular analysis
- 25-30% of CNB are malignant (compared to 10% of all lumps)

Briefly discuss the issue of limited sampling in tissue biopsies

Surgical margin is very important; determines if you got all the cancer out of there.

Can determine: Architecture, tumor grade (differentiation), nuclear atypia, and mitotic activity

- Can’t determine tumor stage

Proper sampling and staining = info about prognosis, if they need more surgery, what drugs will work, and if full body chemo is necessary

Identify one example of a molecular screening test for an inherited cancer syndrome

Immunohistochemistry Biomarker tests; see if tumor cells have these R on the outside

- Estrogen receptor
- Progesterone receptor
- HER2
- Can get negative, equivocal (can’t tell) or positive
- Prognosis and predictive significance

Fluorescence in situ hybridization

- Targets actual genes
- Uses a control gene, see if the ratio of Her2 genes is > control

HNPCC/Lynch Syndrome

    - Metaplasia
- Injury
    - Reversible
    - Irreversible
        - Apoptosis
        - Necrosis
            - Reduced O2
            - Chemical injury
            - Infection
- Intracellular accumulations
- Cellular aging

Granulation tissue

Dense fibrosis = a lot of collagen (pink)

Shrunken lumen

Atherosclerosis = major cause of MI; fibrosis and some calcification

Thrombosis blocking coronary artery

Hypertrophy = bigger myocytes, wide, some have 2 nuclei

Discuss the features assessed on a tumor biopsy

Tumor type (ductal, lobular), grade, size, margins, Lymphatic invasion, precursor lesions, presence of any metastases to lymph nodes, biomarker profile (ER, PR, HER2)

Architecture, nuclear atypia, tumor grade, mitotic activity

And features of a malignant tumor (above)

Can't determine stage

TNM

Acknowledge morphologic subtypes and varied differentiation in tumors

Variety how a tumor behaves

Different morphology and differentiation patterns

Crowding

Gland fusing (adenocarcinoma)

Rhabdoid cells = nucleus off to the side