

Outline of the MIMS lecture course

Important note. This information is provided at the beginning of the year for your guidance and that of your supervisors. It is not intended to be a comprehensive list of contents. Lecturers will all issue their own handouts, and may vary the topics and the order in which they are presented.

Michaelmas Term - Metabolism in Health and Disease

Dr Yeo PROLOGUE: DIABETES (2)

The aim of the Prologue is to illustrate the molecular basis of medicine, to anticipate the main topics covered in the first term's lectures and to introduce terminology, within the context of diabetes as a common metabolic disease.

Lecture 1

Case studies, illustrating typical presentation of diabetes.

Definition of diabetes in terms of hyperglycaemia; diagnosis by glucose tolerance test.

Classification, causes and treatment of type 1 (juvenile) and type 2 (maturity onset) diabetes; other forms of diabetes; diabetes in animals.

Historical perspective on Banting and Best and the discovery of insulin.

Acute manifestation of diabetes as a metabolic problem reflecting lack of insulin action.

Long term complications of diabetes resulting from chronic hyperglycaemia

Statistics on prevalence of diabetes and obesity and cost implications for health care.

Lecture 2

Structure of insulin, as an example of a small protein.

Carbohydrates and lipids as fuels; metabolic pathways for their oxidation.

Introduction to regulation of metabolic pathways by cellular energy charge or hormonal signals ; allosteric regulation and covalent modification of enzymes.

Insulin biosynthesis and secretion.

Actions of insulin on carbohydrate, lipid and protein metabolism.

Insulin receptors and glucose transporters as examples of membrane proteins.

Introduction to mechanism of insulin action & signalling via protein kinase cascades.

Obesity, insulin resistance and type 2 diabetes; why is insulin action impaired by obesity?

Prof E. D. Laue and Dr McCafferty BIOLOGICAL MACROMOLECULES, PROTEIN STRUCTURE AND ENZYME CATALYSIS (6)

After an introduction to macromolecules, the lectures concern understanding of the structure of proteins and how structure leads function. We will focus particularly on enzymes, seeing how they catalyse reactions and how this activity is controlled. We will study examples of the structures of medically relevant enzymes and see how knowledge of their structure and function helps to develop inhibitors that act as drug molecules.

Lecture 1. Introduction of macromolecules. (Prof E. D. Laue)

Lectures 2-3. Structure and function. (Dr McCafferty)

A case study - development of HIV protease inhibitors.
An introduction to biological macromolecules.
Methods for studying macromolecules.
The levels of protein structure.
The structure of a protein is determined by the amino acid sequence.
The amino acids and peptide bond formation.
Prediction of function from sequence information.
Bond formation in the development of protein structure.
How proteins fold.
The role of prosthetic groups and cofactors.
Case study - how protein structure leads to function in haemoglobin.

Lectures 4-6. Enzyme function and control. (Dr McCafferty)

Catalysis of a reaction by transition state stabilisation.
How the structure of an enzyme active site causes catalysis.
Michaelis-Menten kinetics.
Classification and characterisation of enzymes.
Irreversible inhibitors and nerve gas.
Reversible competitive and non-competitive inhibitors.
Alteration of activity by covalent modification (frequently phosphorylation) and its reversal.
Allosteric control and conformational change.
Cooperativity of multimeric enzymes.
Design of enzyme inhibitors as drug molecules.

Dr. R. W. Broadhurst, Prof. P. Leadlay. BIOENERGETICS AND METABOLISM (8)

Mitochondrial respiration and oxidative phosphorylation

ATP couples exergonic catabolism to endergonic anabolism.
How oxidation is coupled to phosphorylation by mitochondria.
Overview of the electron-transport chain.
Some comments on individual redox cofactors.
Experimental background to the ordering of the electron-transport chain.
Structure and function of the complexes of the electron-transport chain.
How the proton motive force drives the ATP synthase to make ATP.
How the proton motive force drives transport in and out of mitochondria.

The metabolic fates of glucose and fat after feeding

Importance of blood glucose concentration and insulin.
Compartments of fuel economies of gut, liver, muscle, adipose tissue, brain.
Uptake of glucose and its conversion to fuel stores.
Glycolysis.
Formation of acetyl-CoA from pyruvate.
Biosynthesis of fatty acids from acetyl-CoA.
Biosynthesis of triacylglycerols ('fat').
Digestion of dietary fat: formation and fate of chylomicrons.
Role of other lipoproteins in transferring triacylglycerol from liver to adipose tissue.

The fuelling of muscle contraction by carbohydrate and lipids

Mobilisation of glycogen: glycogenolysis.

Fates of pyruvate: reduction to lactate (anaerobic) and oxidation to CO₂ (aerobic)
Mobilisation of triacylglycerol: lipolysis.
Fatty acid transport to muscle and β -oxidation to acetyl-CoA.
Citric acid cycle and oxidation of acetyl-CoA to complete carbohydrate and fat oxidation.
Formation and use of ketone bodies.

Control of fuel storage and oxidation

The interplay of insulin and the catabolic hormones glucagon and adrenaline.
Principles of metabolic control.
Control of glycogen synthesis and breakdown.
Control of fatty acid and triacylglycerol synthesis.
Interplay of short-term acute control and longer term adaptive control.
Control of lipolysis in adipose tissue.
Control of glycolysis and citric acid cycle.
Amphibolic role of citric acid cycle.

Fasting and gluconeogenesis; aspects of amino acid metabolism

Fuel needs of brain and how met in fasting by liver making glucose and ketone bodies.
Amino acids in gluconeogenesis and ketogenesis.
Control of gluconeogenesis.
Ketosis and diabetes.
Overview of metabolic roles of amino acids and of amino acid catabolism.
The importance of aminotransferases and glutamate dehydrogenase.
The urea cycle.
Amino acids and the supply of methyl groups and other 'one-carbon' fragments for biosynthesis.

Dr Pereira – NUTRITION (2)

Micronutrients I. Vitamins and trace elements.

Micronutrients II. Oxidative stress and phytochemicals.

Prof. Irvine MEMBRANE DYNAMICS AND CELLULAR SIGNALLING (5)

Lecture 1. Protein trafficking, secretion and endocytosis.

Secretion and endocytosis.
Importance of protein trafficking for maintenance and synthesis of intracellular structures.
The diabetes context: insulin synthesis and secretion.
Structure of the endoplasmic reticulum, Golgi apparatus and plasma membrane, emphasising their dynamic nature and interrelationship.
Secretion Concept of targeting sequences. Consideration of organelle-specific targeting, protein processing, role of cytoskeleton and motor proteins. Outline of molecular events in secretion.
Endocytosis Pinocytosis and endocytosis in coated pits leading to lysosomes or recycling to plasma membrane. Example of LDL receptors.

Lectures 2-5. Hormonal signalling

Recognition of water-soluble hormones by surface receptors generates a signal inside the cell. The lectures will give an understanding of the key elements of the nature of some of the signals, how they are generated and removed, and how the cell interprets them as a part of its function.

The three basic types of receptor, how they work and why: ligand-gated ion channels, G-protein coupled (7 transmembrane domain), and tyrosine kinase. The role of trimeric G-proteins in signal transduction, illustrated by control of adenylyl cyclase activity to produce the 2nd messenger cyclic AMP. Actions of cyclic AMP to illustrate protein phosphorylation as a transducing mechanism. Simple introduction to cyclic GMP and nitric oxide.

Hormonal activation of phosphoinositide hydrolysis and elevation of Ca^{2+} concentration by inositol trisphosphate.

Action of diacylglycerol to activate protein kinase C.

Phosphatidylinositol 3,4,5-trisphosphate as another lipid second messenger.

A brief outline of Ca^{2+} regulation and its importance as a 2nd messenger.

The operation of tyrosine kinase receptors, illustrated by the (typical) PDGF receptor and the insulin receptor.

Receptor families and the concept of more complex signal transduction cascades involving protein kinases. A complex signal transduction cascade exemplified by the pathway from the insulin receptor to the stimulation of glycogen synthesis.

Dr Yeo EPILOGUE (1)

The aim of the Epilogue is to draw together aspects of the term's lectures, as they relate to insulin structure and function and the causes of diabetes.

Mutations in glucokinase or the insulin receptor as rare causes of diabetes.

Central role of protein phosphorylation (tyrosine and serine) as a regulatory mechanism.

Glucose transporter isoforms: an example of horses for courses.

Causes of type 2 diabetes revisited: defective genes or foetal programming?

Prospects for novel diabetes therapies: where should we be looking?

Understanding the obesity epidemic: a major threat to public health.

A brief look at leptin and mechanisms regulating appetite and energy expenditure.

Lent Term. Macromolecules in Health and Disease

Dr T Littlewood. PROLOGUE: CANCER AS A MOLECULAR DISEASE (2)

The lectures provide a general introduction to cancer that requires minimal background knowledge.

Lecture 1. Cancer incidence and development

Cancers occur in many distinct forms but are characterised by common features.

Major human cancers: Incidence and mortality in the U.K. and worldwide.

Cancer defined.

The process of tumour development: vascularisation: metastasis.

Cancer primarily a disease of (somatic cell) genetic mutation.

Lecture 2. Cancer

Introduction to oncogenes: mechanisms of activation.

Tumour suppressor genes.

Inheritance of genetic predisposition to cancer.

Micro RNAs: oncogenes and tumour suppressors.

Dr F. Livesy ORGANISATION, REPLICATION AND REPAIR OF THE GENOME(5)

Lecture 1. Organisation of DNA in the genome

DNA is the genetic material.

Chemistry and structure of the DNA double helix.

Dimensions and scale of the DNA double helix.

How do you fit 2 metres of DNA into a 10 micron diameter nucleus?

Different levels of compaction.

Nucleosomes, nuclear scaffold, chromosomes.

Lecture 2. How DNA is replicated

The double helix as a template. Semiconservative replication.

DNA polymerases, requirement for substrates, primers and template.

Ensuring accuracy - proof reading.

Discontinuous replication and Okazaki fragments.

Origins of replication - the replication fork.

How genomes are replicated.

The problem of linear chromosomes and the solution – telomeres.

Centromeres.

Sequencing DNA – classical methods and massively parallel sequencing.

Polymerase chain reaction.

Lectures 3-4. Information content of DNA

What is a gene?

What is gene expression – cDNA libraries and microarrays?

The human and other genome projects – genomic libraries, sequencing and sequence assembly.

How many genes make a human?

Differing sizes of genomes.

Not all DNA encodes genes.

Junk DNA?

Repetitive DNA, microsatellites, hypervariability and fingerprints.

Mobile genetic elements.

Lecture 5. Change and constancy of DNA

DNA modifications and epigenetics.
Mutations and how they arise.
DNA damage and its consequences.
Mechanisms of DNA repair.
DNA repair and cancer.
How DNA rearrangements can be a good thing.

Dr Miska - TRANSCRIPTION, TRANSLATION AND CONTROL (5)

Lecture 1 Transcription in prokaryotes and its control

Course overview – The Central Dogma
What is a gene? What is mRNA?
Basic mechanism of RNA synthesis (transcription)
Regulation of transcription
The lac repressor and the catabolite activator protein (CAP)
Antibiotics that inhibit prokaryote transcription

Lecture 2 Transcription in eukaryotes and its control

RNA Polymerases
Eukaryotic promoters and upstream regulatory elements
Regulation of transcription
 Roles of chromatin
 Enhancers and response elements
 Tissue-specific and developmentally regulated transcription factors
Transcription factors and cancer – cFos/ c-Jun, p53

Lecture 3 Pre-mRNA processing - from pre-RNA to mature mRNA

'Polishing' pre-mRNA
 5' Capping
 Termination and polyadenylation
RNA splicing
 Alternative splicing
 Anomalous splicing and cancer – Wilms tumour
Making cDNA and genomic libraries

Lecture 4: Translation - Protein synthesis

Control of mRNA stability
Genetic code
 tRNA structure and charging with amino acids
Ribosomes and polysomes: structure and function
Initiation of translation

Lecture 5: Translation continued – Elongation, termination, degradation

Elongation
Control and termination of translation
Antibiotics that target the translational machinery
Protein degradation – the lysosome and the proteasome, ubiquitin.
Gene expression studies, arrays and cancer
MicroRNA, siRNA and RNAi

Prof. N. Coleman CONTROL OF PROLIFERATION AND DEATH IN CANCER CELLS (3)

Lecture 1. The clockwork of the cell cycle

Phases of the cell cycle: G₁, S, G₂, and G₀

Cyclins and cyclin-dependent kinases regulate cycle phase-transition.

Cyclin B and cdk1 (cdc2): the G₂-M transition.

Substrates of cdk1 in cytoskeleton, nuclear membrane and chromosomes.

APC/C (the anaphase-promoting complex): servant and master of cyclin B.

Events driven by other cyclin-dependent kinases.

Cyclin D and Rb (the retinoblastoma protein).

E2F-1 and G₁ progression.

The cyclin D/Rb/E2F pathway and carcinogenesis: action on cell proliferation and death.

Lecture 2. Controls of progression into and through the cell cycle

Extracellular signals that activate cell cycle entry: growth factors, tyrosine kinases, ras, the MAP kinase and PI3-kinase pathways.

The pre-replicative protein complex: constraints on inappropriate initiation of DNA replication.

Checkpoints at G₁-S transition, G₂-M transition and during spindle formation.

Activation of checkpoints: cytokines (e.g. TGFβ), injury, hypoxia.

p53 - guardian of the genome.

Cell cycle controls, checkpoints and carcinogenesis: mutations of p53, ras, MAP kinase pathway oncogenes.

Lecture 3. When checkpoints fail: apoptosis and carcinogenesis

Basic mechanisms of apoptosis.

Caspases and their substrates.

Signalling to the caspase cascade: mitochondrial and membrane receptor pathways.

The bcl-2 family.

Phenotype of cancer: the undead cell.

Many mutations are required for carcinogenesis.

Virus proteins, carcinogen-induced mutations, inheritance in cancer susceptibility.

Overall summary.

Dr McCafferty MOLECULAR RECOGNITION (2)

The aim of these lectures is to understand how molecules interact with one another within the cell. We will consider the basic principles of molecular recognition, focusing on examples from growth factor response pathways and antibody mediated recognition.

Lecture 1. Principles of molecular recognition

How the structure of a protein allows it to perform molecular recognition.

Bond formation in recognition.

Conformational changes and reversible covalent modification.

Protein recognition of specific DNA sequences.

Illustration of these principles by considering growth factor response pathways.

Lecture 2. Antibodies

Antibody structure and function.

How monoclonal antibodies are produced experimentally.

Use of monoclonal antibodies in cancer therapy.

Dr Crowther GENETICS IN HUMAN AND ANIMAL MEDICINE (5)

Lecture 1. Tracing genes and chromosomes

Problems of human genetics -small family sizes, long generation times.

Tracing the inheritance of single gene traits through pedigrees.

Autosomal and sex-linked inheritance , dominant and recessive alleles.

X-inactivation in female mammals.

Mitochondrial inheritance.

Lecture 2. Locating genes to chromosomes

Meiosis and gamete formation.

Independent segregation of genes on different chromosomes.

Linkage of genes on the same chromosome.

Lecture 3 Building chromosome “maps”

Genetic markers -tracing genes by changes to DNA or protein sequence.

Protein markers(blood groups, haemoglobins), and DNA based markers (microsatellites and SNPs).

Detecting linkage in pedigrees- The importance of linkage studies in human genetics. Finding and studying the genes which contribute to disease.

Lecture 4. How genetic variation and environment determine phenotype

Animal coat colour genes- combinations of alleles in several different genes give different phenotypes.

Multifactorial inheritance, where several genes co-operate to produce a phenotype.

The multifactorial basis of common mid-life diseases.

Why twins and affected sibs are important for these studies.

Lecture 5. Genes in populations

Relating phenotypes to allele frequencies- the Hardy –Weinberg equation.

Selection in action- Malaria and sickle cell haemoglobin.

Host pathogen interactions in bacterial and viral disease.

Evolution of multiple drug resistance.

Prof. N. Coleman. MESOLOGUE. CANCER THERAPY (1)

The lecture draws together the cancer theme so far developed, including therapeutic approaches, and looks forward to the final group of lectures on genetics. (That's why we have called it a mesologue, rather than an epilogue - in case you wondered.)

Easter Term. Macromolecules in Health and Disease, continued

Dr Sargent. GENETICS IN HUMAN AND ANIMAL MEDICINE, continued (4)

Lectures 6-9 Introduction to the study and understanding of genetic disease

Using karyotypic information to identify disease-causing genes.

Sex chromosome and autosomal anomalies.

FISH and array-based technology.

The impact of the genome projects and combining information from linkage studies and sequencing studies.

Genome sequencing strategies.

Genomic libraries.

cDNA libraries.

Analysing the candidate genes.

Types of disease-causing DNA mutation.

Methods of mutation screening, including DNA sequencing, PCR, Southern blotting, methods for assessing copy number loss and gain.