BSc / MSc Degree Examinations 2018-9

Department:
Biology

Title of Exam:
Understanding health and disease

Time Allowed:
1.5 hours

Allocation of Marks:
Total marks available: 60
Section A: Short answer questions = total 30 marks
Section B: Essay question = total 30 marks

Instructions for Candidates:
Answer all of the short questions
Answer one of the essay questions. Either Essay A OR Essay B.

Do not write on this booklet before the exam begins
Do not turn over this page until instructed to do so by an invigilator
1. R120G is a mutation resulting in hypertrophic cardiomyopathy. An experimental study on mice with the R120G mutation was performed and the results are shown below. Explain the data and identify a link between the 2 pieces of data. 

   (3 marks)

   The reduction in PCr/ATP ratio in part A shows the heart is energy deficient (1). An increase in TUNEL positive cells in part B reflects an increased apoptotic cell death (1). Both are related to the mitochondria so suggest mitochondrial dysfunction (1).

   Module learning outcome 1: Explain the genetic, molecular and cellular mechanisms of exemplar human diseases. Module learning outcome 3: Identify and explain appropriate scientific techniques and experimental approaches, and describe strategies for post-genomic biomedical research

2. Describe one piece of evidence for energy depletion as a cause of cardiac hypertrophy. 

   (2 marks)

   A number of answers possible. The examples described in the lecture included: Experimental knock-out of a metabolic gene (1) e.g. CD36/ GLUT4 (1) induces hypertrophy or Patients with a metabolic disease (1) e.g. mitochondrial disease (1) often present with cardiac hypertrophy or HCM patients, also with a mutation in a mitochondrial protein (1), present with more severe (1) hypertrophy.

   Module learning outcome 1: Explain the genetic, molecular and cellular mechanisms of exemplar human diseases.
3. Explain the role of macrophages in the development of an atherosclerotic plaque. (3 marks)

Macrophages oxidise LDLs to oxLDLs (1). Macrophages phagocytose oxLDLs to form foam cells (1) which recruit leucocytes (via secretion of pro-inflammatory cytokines) which contribute to inflammation and the formation of a necrotic core (1).

Module learning outcome 1: Explain the genetic, molecular and cellular mechanisms of exemplar human diseases.

4. Patients with Glanzmans' thrombasthenia have mutations in gene encoding for glycoprotein (GP) IIb or IIIa that reduce the expression and/or function of the protein. Why does this cause bleeding? (2 marks)

GPIIb/IIIa are initially expressed in an inactive state and change confirmation in the initial stages of platelet activation, which allows them to bind to fibrinogen (outside-in signalling). (1 mark)

After binding to fibrinogen, GPIIb/IIIa signalling into the platelet (outside-in signalling), promoting the changes in platelet shape and stimulating granule release which further drives platelet aggregation. GT patients exhibit dysfunctional platelet aggregation that can lead to excessive bleeding. (1 mark)

Module learning outcome 1: Explain the genetic, molecular and cellular mechanisms of exemplar human diseases.

5. A new diagnostic test for infection with hepatitis B virus that involves measuring the amount of antibody in a blood sample was compared to the gold standard. The results are given in the table below. Calculate and interpret the sensitivity and negative predictive value for this test. (2 marks)

Sens = 129/177 = 0.728: 73% of truly infected people will test positive (1)

NPV = 1257/1305 = 0.963: 96% of people with negative test results will truly be free of infection (1)
<table>
<thead>
<tr>
<th></th>
<th>Gold standard</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>New test</td>
<td>129</td>
<td>116</td>
</tr>
<tr>
<td>Positive</td>
<td>177</td>
<td>1373</td>
</tr>
<tr>
<td>Negative</td>
<td>48</td>
<td>1257</td>
</tr>
</tbody>
</table>

Module learning outcome 2: Discuss the application of epidemiological findings to public health and the control of human disease.

6. Increased alcohol consumption is associated with an increased risk of coronary vascular disease (CVD). Explain what is meant by the following statement: Sex is a confounder of this association. (3 marks)

Sex is associated with alcohol consumption (1)

Sex is associated with CVD risk (1)

Accounting or adjusting for sex for changes the association between alcohol consumption and CVD (1)

Module learning outcome 2: Discuss the application of epidemiological findings to public health and the control of human disease.

7. Relative risk and attributable risk are two ways to compare the incidence of disease between groups of people with differing exposures. Explain how these two measures differ in how they are calculated and how they are used. (3 marks)

Relative risk is the ratio of the incidence rates between the groups and attributable risk is the difference in the incidence rates between the two groups (1)

Relative risk is used to quantify the strength of an association: it describes how much the baseline risk of disease is changed when you have the exposure and can be used to identify risk factors for intervention (1)

Attributable risk is used to quantify the burden disease associated an exposure: it describes how many additional cases of a disease occur because of the exposure
and can therefore be used to predict the potential impact of removing the exposure. It can be used to prioritise risk factors for intervention (1)

Module learning outcome 2: Discuss the application of epidemiological findings to public health and the control of human disease.

8. Define what is meant by Primary Prevention and give an example. (2)

Primary prevention is a program that aims to stop the population from being exposed to a risk factor or change the exposure to the risk factor before the initiation of the disease process (1)

Examples include: (1 mark)
Vaccination, smoking cessation, healthy eating advice, fluoridation of water, folate supplementation of cereals

Module learning outcome 2: Discuss the application of epidemiological findings to public health and the control of human disease.

9. Below is a schematic of the amino acid arrangement in the distinctive coiled quaternary structure of the rod domain of Myosin heavy chain β protein.

![Amino Acid Arrangement](image)

a) Label the hydrophobic residues (2 Marks)
b) Label the non-polar residues (1 Mark)

A&D are hydrophobic (2 marks one for each), BCEFG are non-polar (1 mark)

c) What would the possible consequence of a non-conservative amino acid change at position a or d be? Explain your answer. (7 Marks)

A non-conservative change would lead to a hydrophobic residue being changed for an uncharged residue (1) The hydrophobicity of these residues is important as it leads to the two coils preferentially interacting with each other very strongly (1) This makes the quaternary structure of two myosin molecules wrapped around each other very stable (1). Replacing a hydrophobic residue here would probably lead to a weaker association in this part of the tail (1). This would have knock on effects on protein stability (1) and therefore the contractility of the actin-myosin complex (1) potentially leading to an increased risk of HCM (1).
Essay A

Explain how reperfusion can worsen cardiac injury following a period of ischaemia

After a period of ischaemia, it is important that blood flow is reintroduced quickly to prevent the negative effects of ischaemia such as excessive cell death. Reperfusion can help initiate healing, for example, the activation of matrix metalloproteinases degrade the existing damaged extracellular matrix, and infiltration of inflammatory cells such as neutrophils and macrophages phagocytose damaged or dead cells. Immune cells release cytokines such as TGFbeta which is known to initiate fibrosis. Fibrosis provides structural support, but when excessive it can contribute to cardiac stiffness and diastolic dysfunction. Reperfusion is also associated with increased ROS production which can be damaging to cellular organelles and increase cell death.

Apoptosis is known to increase during reperfusion (to a greater extent compared with ischaemia). In particular, apoptosis increases in areas remote to the infarct site which contributes to infarct expansion and global cardiac modelling.

The MPTP (mitochondrial permeability transition pore) plays a key role in triggering apoptosis in reperfusion. The MPTP is a pore in the inner mitochondrial membrane. When open, it acts as a non-selective pore, therefore, fluid and small molecules can enter the mitochondria dissipating the membrane potential (therefore reducing ATP synthesis), causing mitochondrial swelling and rupture. This results in the release of pro-apoptotic proteins which trigger a cascade of events resulting in cell death. During ischaemia, the pore remains closed as opening is inhibited by low pH. In reperfusion, with the onset of oxidative phosphorylation, pH is restored and MPTP opening is encouraged by high calcium and increased levels of ROS.

Good answers will be supported by experimental examples.
Describe how single cell genomics can be used in the diagnosis and treatment of disease, as well as fundamental research into disease mechanisms.

Answers should mention the utility of single cell genomics in cell lineage tracing and assessing the heterogeneity and clonal evolution of cancer cells and the implications of this on resistance to certain treatments. There is also the potential to provide direct read out of allele burden in haematological malignancies which will have an impact on staging and treatment selection for these.

Studying the epigenomes and transcriptomes of cells is allowing us to obtain a far more granular picture of what constitutes a cell type, beyond less descriptive colony forming assays, or cell type determination based on location. For example, new neuronal, intestinal and lung cell subtypes have been determined. These cells may well contribute to disease progression in novel and potentially important ways, for example the CFTR pulmonary ionocyte. They have the potential to shed a lot of light on the fundamental mechanisms behind the progression of certain diseases. Extra credit will be given for pertinent and precise examples covered both within the lectures as well as in the wider literature.

Module learning outcome 3: Identify and explain appropriate scientific techniques and experimental approaches, and describe strategies for post-genomic biomedical research.