The Royal College of Pathologists
Pathology: the science behind the cure

FRCPath Part 1 examination

Immunology: First paper

Tuesday 24 September 2019

Candidates must answer FOUR questions ONLY

Time allowed: Three hours

Question 1

a) Write short notes on B lymphocyte development in the bone marrow and in lymphoid tissue. Include information on the factors necessary for B cell survival. You may use diagrams to illustrate your answer. (*Two thirds of marks for this question)*

b) Outline the phenotypic abnormalities seen in peripheral blood B cells populations in the following diseases (*one third of marks for this question)*:

i) Common Variable Immunodeficiency

ii) X-linked Hyper-IgM Syndrome

iii) B-Chronic Lymphocytic Leukaemia

Question 2

a) Briefly describe how mutations in the following genes give rise to autoimmune disease: *(Half of marks for this question)*

i) Fas

ii) FOXp3

iii) AIRE

b) Describe the immunological mechanisms involved in desensitisation to hymenoptera venoms. *(Half of marks for this question)*

Question 3

a) Describe the development, cellular characteristics and effector functions of eosinophils. What are the pathologic consequences of prolonged tissue eosinophilia? *(Half of marks for this question)*

b) Describe the mechanism of antigen processing and presentation by a virally-infected cell to a CD8 cytotoxic T cell. You may use a diagram to illustrate your answer. *(Half of marks for this question)*

Question 4

a) What is a Toll receptor (TLR)? Classify the TLR receptors and their ligands? What signalling pathways are activated when TLR receptors are activated? Give two examples of diseases caused by defects in the TLR pathway. You may use diagrams to illustrate your answer. *(Half of marks for this question)*

b) What is an inflammasome? Outline how an inflammasome is activated and consequences of such activation. Outline the molecular defects in inherited diseases where inflammasomes has been found to play a critical role in pathogenesis? You may use a table or diagram in your answer. *(Half of marks for this question)*

Question 5

a) Briefly describe the effector functions and mediators of the following CD4 T lymphocyte subsets:

i) Th1 cell

ii) Th2 cell

iii) Th17 cell

List the cytokines and principal transcription factors that induce differentiation of CD4 T cells into these subtypes. You may use a table. *(Two thirds of marks for this question)*

b) What prevents the immune system from responding to and destroying tumour cells in malignant disease? Name the key molecules involved in this pathway that are therapeutic targets?

c) Give 2 examples of monoclonal antibodies used in these pathways for the treatment of cancer, and the type of cancer for which they have been successfully used.

d) What are the major adverse immunological effects of such therapies?

(One third of marks for these questions)

The Royal College of Pathologists
Pathology: the science behind the cure

FRCPath Part 1 examination

Immunology: First paper

Tuesday 26 March 2019

Candidates must answer FOUR questions ONLY

Time allowed: Three hours

Question 1

a) Describe the immunological mechanisms leading to the generation of specific IgE to insect venom. In your answers, please cover antigen processing, interaction of B and T cells, and B cell events that lead to IgE production. (15 marks)

b)

i) List the key changes that have been observed in lymphocytes, antibodies and cytokine expression as a result of sub-cutaneous allergen immunotherapy. (7.5 marks)

ii) What are the currently proposed mechanisms, explaining the effectiveness of allergen immunotherapy, based on these observations? (7.5 marks)

Question 2

a) The complement system can be triggered by three separate mechanisms. Draw an annotated diagram illustrating activation and propagation of these pathways. (There is no need to include the regulatory mechanisms) (9 marks)

b) CD4+ Helper T-cells can be differentiated into several subsets; Th1, Th2, Th17 and T-Reg . In a table list the following:

i) Cytokines and transcription factors responsible for this differentiation
ii) Effector functions of these T-cells
iii) List <u>one</u> disease that can develop as a result of a defect in each of these subsets (21 marks)

Question 3

a) Describe the biochemical steps of the respiratory burst that result in intracellular killing of microbes within neutrophils (You may illustrate your answer with an annotated diagram). Briefly describe the diseases associated with genetic defects in this pathway. (15marks)

b)

i) Describe with an annotated diagram the immunological pathway involved in host defence against mycobacteria with reference to types of cells and cytokines involved (5 marks)

ii) What is mendelian susceptibility to mycobacterial disease (MSMD)? List three categories of defects that can lead to MSMD. (5 marks)

iii) List laboratory investigations that would be useful in identifying potential causes of susceptibility to disseminated non-tuberculous mycobacterial disease in a 40 year old man. (5 marks)

Question 4

a) What is meant by the term “cluster of differentiation (CD) molecule”? Briefly outline the stages of B cell development up to the mature naïve B cell, using the expression of characteristic CD molecules and other surface antigens. List the biological function of these where this is known. (You do not need to discuss immunoglobulin gene rearrangement in your answer). (15 marks)

b) What is meant by the term immunoglobulin class switching? Briefly outline the cells, signals and molecular events involved in this process. Illustrate your answer with four examples of the failure of these processes in human inherited disease. (15 marks)

Question 5

a) Classify the immunological mechanisms of rejection of a solid organ transplant. (15 marks)

b) Outline the principles underlying the use of checkpoint inhibitors in current clinical use for treatment of malignancies. What are the main immunological mediated adverse effects associated with their use. (15 marks)

The Royal College of Pathologists
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Part 1 examination

Immunology: First Paper

Tuesday 25 September 2018

Candidates must answer FOUR questions

Time allowed: 3 hours

Use of annotated diagrams and appropriate tables to support your answers are encouraged

1.

a) Compare and contrast phenotypical and functional features of neutrophils and macrophages. Name the main cytokines produced by these cells and their role in the inflammatory response. You may draw a table to help you structure your answer. (1/3 marks)
b) Write short notes on toll like receptors (TLRs) and their ligands in humans. You may draw a diagram to illustrate signalling pathways. (1/3 marks)

c) Briefly describe how TLR agonists can be used in clinical practice and give at least one example. (1/3 marks)

2.

a) Describe the process leading to mast cell activation / degranulation by IgE (type I hypersensitivity reaction). (1/4 marks)

b) Describe how mast cells can be activated independent of IgE? (1/4 marks)

c) How does the release of mast cell mediators following activation/degranulation result in anaphylaxis? (1/4 marks)

d) Compare and contrast the differences and similarities between mast cells and basophils. You may draw a table to help you structure your answer (1/4 marks)

3.

a) Describe the mechanisms leading to generation of antibody diversity in the bone marrow and lymphoid tissue. (1/3 marks)

b) Compare and contrast peripheral blood immunophenotyping in patients with

i) B-Chronic Lymphocytic Leukaemia and
ii) Common Variable Immunodeficiency (CVID)
(1/3 marks)

c) Give 3 examples of genetic conditions that lead to a susceptibility to Epstein-Barr virus (EBV). Include the molecular mechanisms of disease and inheritance patterns. (1/3 marks)

4.

a) Write short notes on checkpoint inhibitors. Give an example of a therapeutic checkpoint inhibitor in clinical use. (1/3 marks)

b) Briefly describe the stages in T cell development in the thymus, and describe the mechanisms that lead to self- tolerance. Give an example of a genetic defect that leads to failure of central tolerance. (1/3 marks)

c) Explain the terms direct and indirect allo-recognition in the context of organ transplantation. Briefly explain the mechanisms involved in, and clinical presentation of, hyper-acute graft rejection? (1/3 marks)

5.

a) Describe antigen presentation to T cells (1/4 marks)
b) What molecules are involved in T cell costimulation? (1/4 marks)
c) What are the clinical features of genetic defects affecting these molecules? Give 3 examples. (1/4 marks)
d) Describe the clinical utility of biological agents that target co-stimulation. (1/4 marks)

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Part 1 examination

Immunology: First paper

Tuesday 20 March 2018

Candidates must answer FOUR questions

Time allowed: 3 hours

Question 1

a) Describe with an illustration the structure of an immunoglobulin G (IgG) molecule (25%)

b) Write short notes to describe the process of immunoglobulin gene rearrangement in the generation of antibody diversity at the antigen binding site. You may use diagrams to illustrate your answer. (50%)

c) Give 2 examples of how defects in this process lead to immunodeficiency (25%).

Question 2

a) Outline the aetiological factors that predispose to IgE-mediated allergic disease. In your answer include: (80%)

(i) Genetic risk factors
(ii) Immunological pathways involved
(iii) Principal modulating environmental influences
(iv) Structure of putative allergens.

b) Briefly outline the immunological processes that occur during desensitisation (subcutaneous immunotherapy) to grass pollen. You may use an annotated diagram. (20%)

Question 3

a) For the cytokine, Interferon gamma, write short notes to outline: (50%)

(i) Production
(ii) Function
(iii) An example of one genetic or acquired defect of the cytokine (or its receptor) and the associated clinical features

b) Outline the mechanisms of peripheral T cell tolerance. Briefly illustrate how this knowledge has helped in the development of immunotherapy for melanoma. (50%)

Question 4

a) Describe the factors required for the development of Th17 T cells. Describe their effector role in host defence. Briefly outline the phenotype and mechanism of **three** human diseases associated with Th17 deficiencies. (50%)

b) Describe the activation and control of the alternate pathway of complement activation (you may use annotated diagrams to illustrate your answer) (25%)

c) Outline the clinical features, mechanisms and the expected patterns in C3, C4, CH50, and AP50 in three primary or acquired defects of the alternate complement pathway.(you may use a tabulated format for this answer).
(25%)

Question 5

a) Compare and contrast the key features of recognition receptors in the innate (pattern recognition receptors) and adaptive immune systems. You may wish to use a tabulated format to answer this question. (25%)

b) Outline the ligands and molecular signalling pathways relevant to Toll-like receptors. You may wish to use annotated diagrams. Outline 3 defects in pattern recognition pathways that are known to result in human disease)? (75%)

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Part 1 examination

Immunology: First paper

Tuesday 26 September 2017

Candidates must answer FOUR questions only

Time allowed: three hours

Marks are distributed equally between the parts of the question **EXCEPT WHERE INDICATED**

Question 1

a) Describe the genetic factors, environmental factors and immunological processes that lead to the development of coeliac disease and outline how knowledge of these can assist in the diagnosis of coeliac disease.

b) Describe the cellular, cytokine and molecular pathways involved in the generation of a specific IgE response to wasp venom. You may use diagrams to illustrate your answer.

Question 2

c) Briefly describe how mutations in the following genes give rise to autoimmune disease:

iv) Fas
v) FOXp3
vi) AIRE

b) Describe the mechanism of antigen processing and presentation by a virally-infected cell to a CD8 cytotoxic T cell. You may use a diagram to illustrate your answer.

Question 3

a) Write short notes to describe the process of immunoglobulin gene rearrangement in the generation of antibody diversity at the antigen binding site. You may use diagrams to illustrate your answer. Give 2 examples of how defects in this process lead to immunodeficiency.

b) Briefly describe the stages of antigen-dependent B cell maturation. You make use a diagram to illustrate your answer.

c) Outline the phenotypic abnormalities seen in peripheral blood B cell populations in the following diseases:

i) X-Linked Agammaglobulinaemia
ii) Common Variable Immunodeficiency
iii) Hyper IgM Syndrome
iv) Chronic Lymphocytic Leukaemia

Question 4

a) Describe the primary defect(s) and the pathophysiology of each of the following diseases:

i) Hereditary angioedema types 1 and 2
ii) Atypical Haemolytic Uraemic syndrome

b) Briefly describe the effector functions and mediators of the following CD4 T lymphocyte subsets:

i) Th1 cell
ii) Th2 cell
iii) Th17 cell

List the cytokines and transcription factors that induce differentiation of CD4 T cells into these T-cell subtypes

Question 5

a) List the genetic mutations (including inheritance patterns and relative frequency) that cause Chronic Granulomatous Disease. Describe the pathway affected by these mutations and the immunological mechanism leading to disease. **(1/3 of marks for this part)**

b) Briefly outline the mechanisms by which T helper-1 cells are important in the control of human mycobacterial infection. Illustrate your answer with 4 recognised defects in this pathway. **(2/3 of marks for this part)**

The Royal College of Pathologists
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Part 1 examination

Immunology: First paper

Tuesday 21 March 2017

Candidates must answer FOUR questions ONLY
You may use tables or diagrams to illustrate your answers.

Time allowed: Three hours

Question 1

a) Explain how neutrophils recognise pathogens.

b) How do neutrophils kill bacteria? You may use diagrams to illustrate your answer.

c) Give examples of inherited conditions that lead to defective killing by neutrophils.

d) Describe how phagocytes clear apoptotic cells.

Question 2

c) Write short notes on B lymphocyte development in the bone marrow and in lymphoid tissue. Include information on the factors necessary for B cell survival. You may use diagrams to illustrate your answer. (*Two thirds of marks for this question)*

d) Describe the typical immunophenotypic features of peripheral B cells in:

i) X-linked Agammaglobulinaemia.
ii) CD40L (CD154) deficiency.
iii) B-Chronic Lymphocytic Leukaemia.

(*One third of marks for this question)*

Question 3

a) Describe the mechanisms of Toll like receptor stimulation. Include information on TLR ligands and intracellular pathways. You may use diagrams to illustrate your answer.

b) What is the inflammasome? Describe how the inflammasome is activated and the resultant effects.

c) Describe the molecular defects in inherited diseases where the inflammasome has been found to play a critical role in pathogenesis? You may use a table or diagram in your answer.

Question 4

a) Describe the development, cellular characteristics and effector functions of eosinophils. What are the pathologic consequences of prolonged tissue eosinophilia? (*Half of marks for this question)*

b) Describe the immunological mechanisms involved in desensitisation to hymenoptera venoms. (*Half of marks for this question*)

Question 5

Question 5a

i) What features distinguish innate lymphoid cells from conventional T- and B-lymphocytes?

ii) How would you classify the major subsets of innate lymphoid cells? For each, describe briefly the relevant transcription factors they express, the main tissue location(s), and principal immunological functions. You may use a table in your answer.

(*Two thirds of marks for this question)*

Question 5b

i) What do you understand by immune checkpoint pathways in relation to cancer? Name the key molecules involved in this pathway that are therapeutic targets?

iii) Give 2 examples of monoclonal antibodies used in these pathways for the treatment of cancer, and the type of cancer for which they have been successfully used.

iii) What is the major adverse immunological effect of such therapies?

(*One third of marks for this question*)